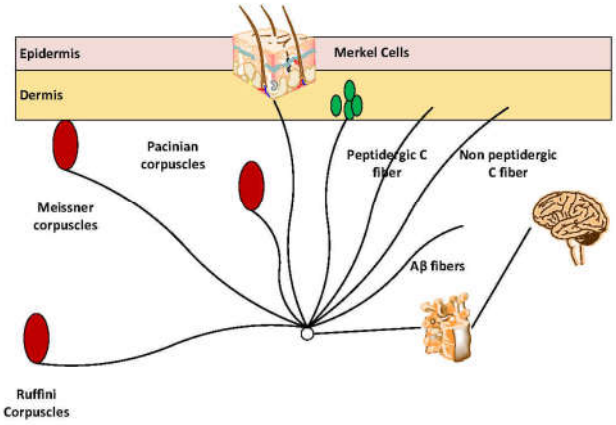

Itch, Cancer, and the Immune System

TGL 191 April 2022

ABSTRACT

This Note examines the issue of itch and its various classifications and in turn its relationship to various cancers. There are many classes of itch and some of the intractable forms are not so simply diagnosed. We examine these factors and discuss therapeutic options.

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1 INTRODUCTION

Pruritus or itching is a common complaint and in many cases can be mediated therapeutically. However, there are classes of itch which can become intractable and cause morbidity well in excess of pain. Sometimes the itch syndrome is a prodrome for cancers, or the sequella to cancer therapy. Studies in areas such as atopic dermatitis has opened the window to understanding some of the elements of cancer related pruritis. In this note we examine the current state of itch, cancer, the immune system, and possible therapeutics.

It must be understood, however, that this Note is a mix of scientific fact and conjecture. Many itch syndromes are still problematic and poorly understood. Furthermore, the treatment for many intractable itch syndromes have seen little scientific approaches not many truly scientific investigations. Thus the intent of this note is to blend what few facts we have at hand with conjecture based upon logical fact based extensions.

The Latin word prurio (verb) means either to *itch* or to *long for*. The term medically is pruritus. It is a modification of the Latin. However, one may also see pruritis, namely the ending indicating an inflammatory condition. The proper term is pruritus, namely a modification of the verb to itch and not an inflammatory condition of the itch, which may not make any medical sense[1]. For our purposes, we shall use "itch" since it is both understood and does not reflect the other meaning from the Latin, namely "to long for". It is clear that few if any "long for" chronic itching. In fact intractable itching is a symptom of many malignancies both before and after treatment. Our intent herein is to examine the current literature regarding such chronic and in fact intractable itching in the context of multiple malignancies.

Malignancies generate various significant responses from the immune system. At times they may be beneficial and at time they actually could be supporting of the tumor itself such as tumor associated macrophages and the like. But the immune system detects the tumor antigens and produces responses in the context of cytokines. These cytokines then can result in attacks on the nerves that result in itching and the itch is a systemic neurogenic itch. Its complexity can actually inform us of the malignancy as is the case of breast, pancreatic, liver and other cancers. Even melanomas are heralded by an itch in and around the growing lesion.

1.1 CATEGORIES

Very briefly there are at this time four major categories of itching. Namely:

Dermatogenic: This is the class of pruritus that the dermatologist see. Namely there is some form of skin lesion which in turn manages to irritate the nerves in the epidermis and dermis and thus result in classic itch. Poison ivy is a classic example.

[1] See Lehman

Neurogenic: This is a class where some internal reaction results in the nerves to be aggravated. It is a pruritic attack from the inside out as compared to the Dermatogenic type. The challenge is that we often do not know the driver and in addition it may be mitigated by the immune system.

Neuropathic: This a class where there is an actual neurologic disease or defect of some kind.

Psychogenic: This class is one of the most difficult. It is a result of some psychological stressor and in contrast to the Neurogenic where the cause is often below the pyramidal tract these class is well above the tract and is often a truly complicated psychologic complex.

As we shall see, it is possible that the itch syndrome may be an amalgam of several of these types simultaneously.

1.2 ELEMENTS

We examine several key elements. Namely:

Itching: What are the causes of itching and what type of itching syndromes are there. This may be a bit problematic since we really are just beginning to learn a great deal about the issue. Our concern is not about the classic dermatological itch syndromes, namely from the outside-in, but the neurogenic ones where we are on the inside-in. There is a complex neurogenic-immunogenic set of processes whereby the nerves resulting in the itch syndrome are aggravated by the results of processes driving the immune system.

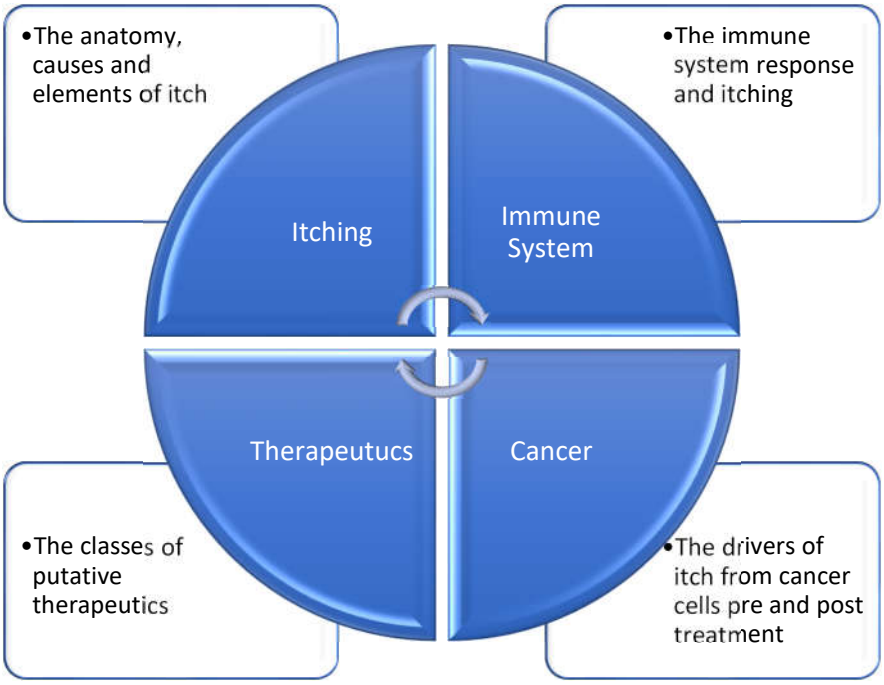
Immune System Interaction: Understanding some specific subtleties of the immune system may allow us to understand the drivers of the itch process. Our focus is based upon recent studies demonstrating the impact of certain cytokines that drive the itch. Unfortunately not all of the elements have been identified.

Cancer Related Itching: Itching has been a hallmark syndrome in many cancers, both before diagnosis and during treatment[2]. It is well known that itching can signal a lymphoma, polycythemia vera, gastrointestinal cancers, melanomas. In addition itching may be the result of various therapies such as chemo and targeted. The question then is; are there antigens generated that in turn are driving the immune system to produce cytokines that drive the nerve ending to create the itch syndrome. If so, then what are the details and the process?

Therapeutics: Itch therapeutics have to date been focused on the classic outside-in that the dermatologist is familiar with. The neurogenic itch syndrome, the one resulting often in the intractable itch is less well understood. There is a list of therapeutics that are an amalgam of more classic neurologic approaches such as gabapentin and doxepin, which may in some cases dull the effect but are at best secondary. We argue herein that based on current research a more targeted approach may be achieved using monoclonal antibodies to block certain receptors or neutralize certain antigens.

[2] https://blog.dana-farber.org/insight/2019/09/is-itching-a-sign-of-cancer/

We summarize out approach as shown in the following figure.



As Chen and Sun have recently noted:

Itch is defined as an unpleasant sensation that evokes a desire to scratch and consists of sensory, emotional, and motivational components.

Itch serves as an important protective mechanism that allows an animal to detect harmful substances invading the skin and remove them by scratching. The resultant scratching behavior, which is driven by strong emotional and motivational components, can sometimes induce a pleasant feeling, leading to an itch-scratch cycle.

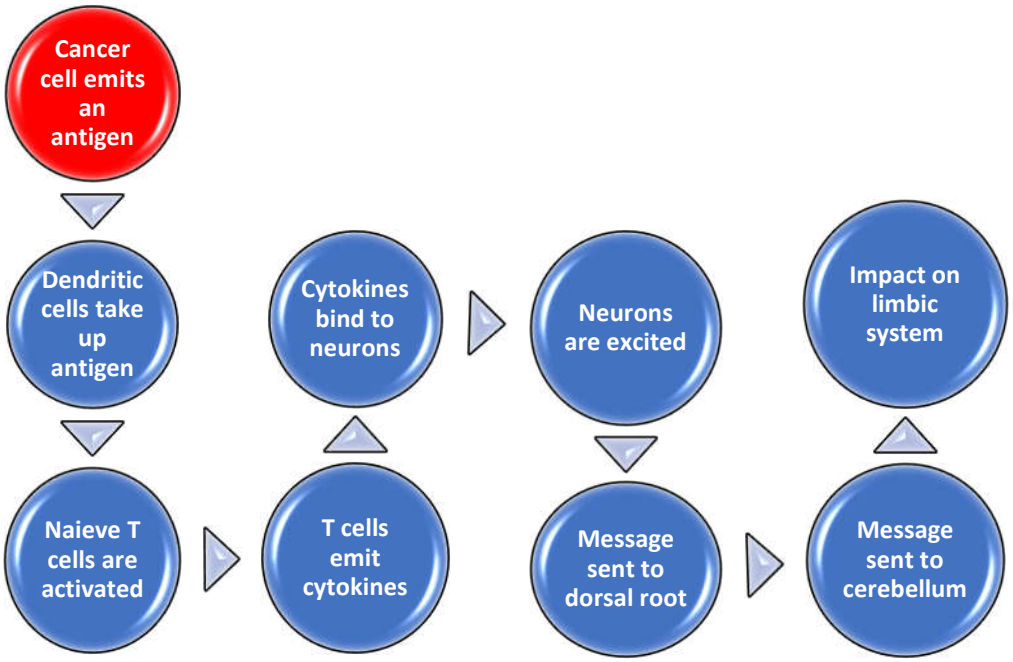
This itch-scratch cycle can result in serious skin damage for patients with chronic itch. Itch, like many other somatosensations, typically originates from the skin. The itch signals are relayed by peripheral sensory fibers to the spinal cord, where the information is processed by local interneurons before reaching the spinal projection neurons.

The spinal projection neurons then send the itch signals to the brain via the ascending pathways, and further processing of itch sensation occurs in multiple brain areas and circuits. Based on peripheral inputs, itch can be classified into mechanical and chemical itch. Chemical itch can be further classified into histamine-dependent and histamine-independent subclasses according to the response to antihistamine agents.

Progress has been made in deciphering the molecular and cellular mechanisms of itch in the peripheral nervous system. Several key receptors, including members of the Mas-related G-proteincoupled receptor (Mrgpr) and serotonin receptor families, were found to be important for detecting chemical itch signals. It was shown that MrgprA3 marks a group of itch-selective neurons in the dorsal root ganglia (DRG). In addition, transient receptor potential (TRP) channels have been shown to be recruited by histamine-dependent and histamine-independent itch pathways in the periphery for itch signal transduction. Consistently, mutation of the TRP channels causes pathological itch. More recently, it has been shown that sodium channels expressed in primary sensory neurons also play important roles in itch signal transmission. These developments on the peripheral mechanisms of itch have been discussed in several excellent reviews

1.3 PROCESS

The processes that is generally accepted for cancer related neurogenic pruritis may be presented as shown below. There are many steps yet to be fully understood.



Specifically:

1. Cancer cell emits an antigen: We know that many cancer cells emit antigen like substances which are collected by the immune system. The collection is usually done by M1 macrophages which then present the result to the immune system cells.
2. Also Dendritic cells take up antigen: Not only do we have macrophages but we can see dendritic cells collecting the antigens as well.
3. Naive T cells are activated: The immune system then kicks in with the naïve T cells getting activated. We demonstrate that process later.

4. T cells emit cytokines: T cells generally react via cytokines. There are a multiplicity of such cytokines and in many itch scenarios we see IL-31 being one of the most significant. We also have others.
5. Cytokines bind to neurons: The cytokines often then bind to receptors on the neurons in the skin. These are C neurons.
6. Neurons are excited: The cytokines than cause the neurons to be excited sending a message to the dorsal root ganglion.
7. Message sent to dorsal root: The DRG receives the message and it then proceeds up the spinal cord.
8. Message sent to cerebellum: The itch message arrives at the cerebellum and then to the cerebrum where it is processed.
9. Impact on limbic system: There is a putative impact on elements of the limbic system creating a putative limbic valence.

At each step there are some identified elements. Also at each step there is a putative therapeutic target. One can try to block the targeted Ag or the cytokine. Or at the extreme end one may try to block the neural paths at say the ganglions or the GABA pathways.

We examine all of the levels as shown above and attempt to create a holistic framework for understanding neurogenic itch as a system.

1.4 A CASE

It is worthwhile to consider a case of intractable itching and cancer. Let us consider a case where I have tried to apply the lessons learned herein. It is important that this is still a work in progress and we have attempted to place the patient's syndrome in the categories we have before us and then apply therapeutics accordingly.

The patient is an older female who initially presents with what appears to be a simple case of contact dermatitis. She alleges she was cutting shrubs and as a result her hairline has become inflamed with macules and papules almost acne like with a significant amount of itching. Thus the simple approach is the application of a clobetasol solution to the impacted area.

However the patient returns and the itching has gotten worse. Upon an examination it is observed that the patients has Paget's disease of the breast and axillary node enlargement as well as palpable lesions in the left breast. These two symptoms are still unconnected. The patient also has a high level of anxiety which has been observed in previous examinations.

The patient sees a surgeon and the path results along with imaging result in a Stage 3 breast cancer with no discernable mets. She is treated with paclitaxel, pertuzumab and trastuzumab for three months and the Paget's disappears the breast lesion shrinks as do the nodes. However the itching has become intractable. A dermatologist initially suggests triamcinolone, a milder steroid, which the patients uses daily. Limited relief is attained. The symptom appears mostly upon waking and just before bed, yet there may be symptoms at other times.

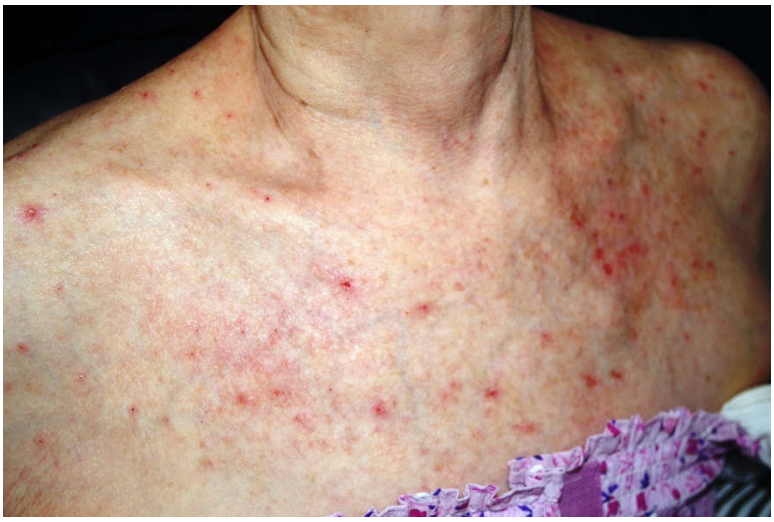
As second dermatologist at a major cancer center recommends doxepin crème and then doxepin tablets and neither seem to be effective.

The original attending suggests several H1 and H2 blockers and again no relief.

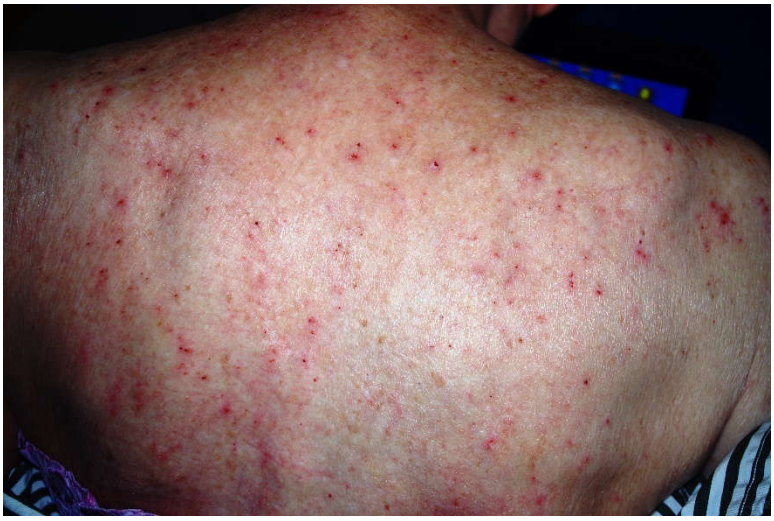
The patient undergoes surgery for removal of the residual lesion. Post-surgery the patient is on hydrocodone for pain relief and the itching appears somewhat abated. However, the patients is placed on gabapentin post removal from the opioid, with 300 mg doses titrated to 1200 per day with some relief.

The question then is, what was the cause of the itching and what remedy eliminated it?

In this patient we have a resultant surface erosoion resulting from manually itching the skin as shown below'



The back of the patient appears as shown below.



The excoriations are most likely due to the persistent itching of the surface creating a positive feedback in the itch complex. One may also question if the patient has significant depression resulting from the disease and its treatment.

In this case there does not appear to be any resulting lesions after surgery and targeted treatment and the areas most excoriated are those the patient persistently scratches. Treatment was begun with gabapentin and a loading to 1200 mg pd.

2 ITCHING

Itch can be generated from the outside-in and from the inside-in. Namely a dermatopathological condition can be driving the itch from the epidermis downward. In contrast, the nerves in the epidermis and dermis may be activated from internal drivers such as cytokines and other neural drivers. In some extreme cases the drivers may be very well in the brain itself. We first examine the anatomical elements as best understood and then delineate how itch classifications are presented.

From Cevikbas and Lerner we have a brief set of definitions:

i. *Neurogenic itch: induced by mediators but in the absence of neural damage. As the mediators of neurogenic itch are defined, it is likely that neurogenic itch will fall under pruritoceptive itch.*
ii. *Neuropathic itch: associated with damaged neurons, e.g., post-herpetic neuralgic itch or small fiber neuropathy.*
iii. *Pruritoceptive itch: itch associated with pruritogen activation of sensory fibers.*
iv. *Psychogenic itch: having a psychosomatic or psychiatric origin, e.g., delusions of parasitosis*

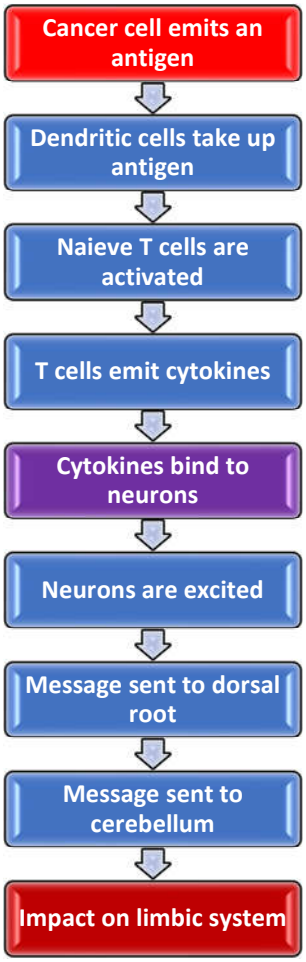
Lerner notes:

*In **systemic conditions** that are not necessarily considered inflammatory, such as **chronic liver and chronic kidney diseases**, itch can be intense but may not be associated with specific skin manifestations and neither the sensation of itch nor its location is uniform. Add to these the itches, **entirely not understood and for which no therapeutic approaches are regularly beneficial**, that result from the emerging use of immune checkpoint inhbitors to treat cancer. Next the neurogenic or neuropathic itches, including brachioradial pruritus and notalgia paresthetica, which may be associated with nerve compression rather than a conventional inflammatory component, and herpes zoster, which does. Finally, there are **psychogenic itches** associated with conditions ranging from depression or obsessions to delusions of parasitosis in which the entire process may be localized in the brain, raising the question whether targeting the periphery can have an impact. **Chronic itch is thus associated with a broad range of clinical entities that can arise in distinct anatomic locations**. Therapeutic approaches that restore homeostasis or interrupt the flow of immunologic or neurosensory information in the area may be of benefit for particular itches.*

2.1 PARADIGM

The paradigm we are focusing on attempts to integrate all elements holistically resulting in the itch characteristics. As we tried to note in the clinical example in the opening there may be a multifactorial itch syndrome. Dermatogenic may not be present initially but it may evolve as the itch response evolves. Moreover a psychogeneic elements may also be created as the itch may imprint itself in the limbic system. Finally a neuropathic element may also build on the

neurogenic where nerve endings and dorsal root ganglions become involved. We reiterate the mechanism below.



In this section we focus on the anatomy and each type separately. It must be remembered that all separate types may get blended as the chronic its persists. Thus the term "chronic pruritus of unknown origin" or CPUO may better be described as a multifactorial "genic" itch.

2.2 ANATOMY

The anatomical elements and interconnections that establish an itch response are somewhat complex. They start with the nerves in the skin when these nerves have been activated. The activation of the nerves are what we also focus on since most appear to focus solely on histamine driven itches. We argue herein that there is substantial evidence to assert that there are multiple drivers well beyond histamine.

As Wang and Kim have noted:

Cutaneous sensory nerves arise from cell bodies located in the dorsal root ganglia (DRG) and have diverse subtypes of nerve endings, named Ab, Ad, and C nerve fibers on the basis of the diameter and speed of transmission.

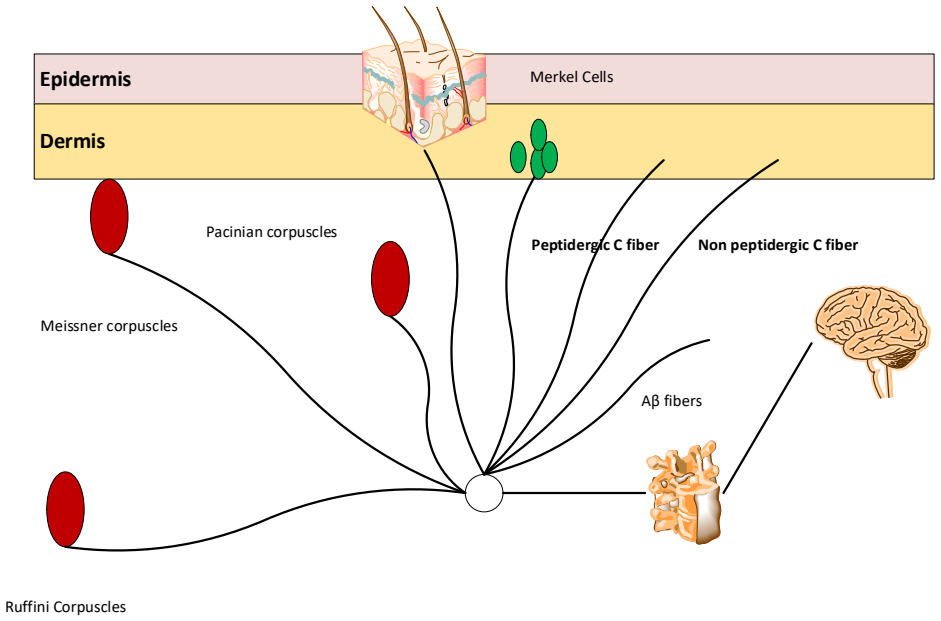
These nerve endings located throughout the dermis and epidermis mediate various sensations by encoding signals that relay pain, itch, temperature, pressure, position, and vibration. Both hairy and glabrous skin (e.g., skin of the palms and soles) are innervated by various different nerve fibers. Mechanoreceptors (e.g., Meissner corpuscles) allow glabrous skin to be specialized for discriminative touch with high spatial acuity.

Large encapsulated corpuscles such as Pacinian and Ruffini corpuscles are preferentially found in the dermis, whereas Meissner corpuscles are usually located in the dermal papillae.

Moderately myelinated Ad fibers are found throughout the dermis, whereas unmyelinated C fiber endings reach the epidermis. The vast majority of itch is thought be mediated by C fibers.

Pseudounipolar DRG neurons project centrally to the dorsal horn of the spinal cord, which then sends projection fibers to the brain.

We demonstrate these below.



In the above we can see a variety of nerve elements. The Ruffini, Meissner and Pacinian corpuscles deal with sensations of touch and temperature. Merkle cells are in the dermal layer. The C fibers and Aβ fibers provide sources for the itch syndrome. The C fibers in particular are itch related.

As Yosipovitch and Bernhard have noted as well:

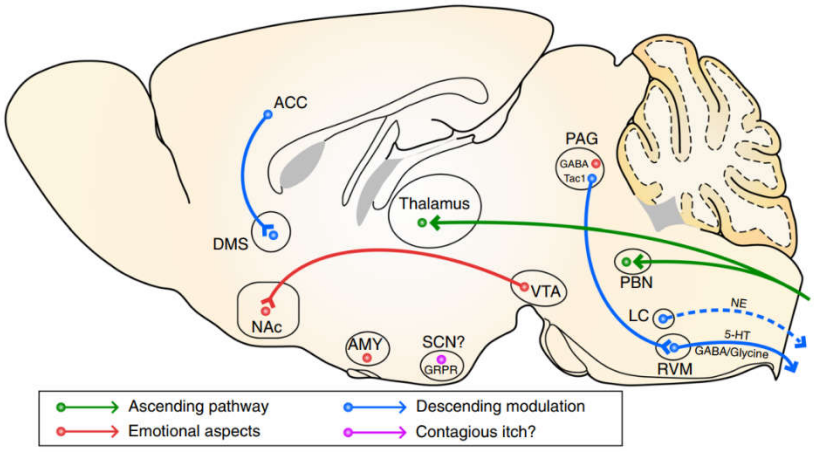
The mechanisms underlying the various types of chronic pruritus are complex. A number of mediators are involved in the itch sensation . The itch signal is transmitted mainly by small, itch-selective unmyelinated C fibers originating in the skin. Histamine-triggered neurons and nonhistaminergic neurons may be involved. They form a synapse with secondary neurons that cross over to the contralateral spinothalamic tract and ascend to multiple brain areas involved in sensation, evaluative processes, emotion, reward, and memory.

These areas overlap with those activated by pain.

Patients with chronic itch often have peripheral as well as central neural hypersensitization.

In this state, sensitized itch fibers overreact to noxious stimuli that usually inhibit itch, such as heat and scratching. Misinterpretation of nonnoxious stimuli also occurs: touch may be perceived as itch. It is not unusual for patients to report that just taking off or putting on their bedclothes triggers a bout of itching. Strange symptoms like this, combined with the extreme distress of chronic itch, sleep loss, and visits to many physicians, may lead to the erroneous diagnosis of psychogenic itch.

From Chen and Sun we have the putative neural pathways in the brain:



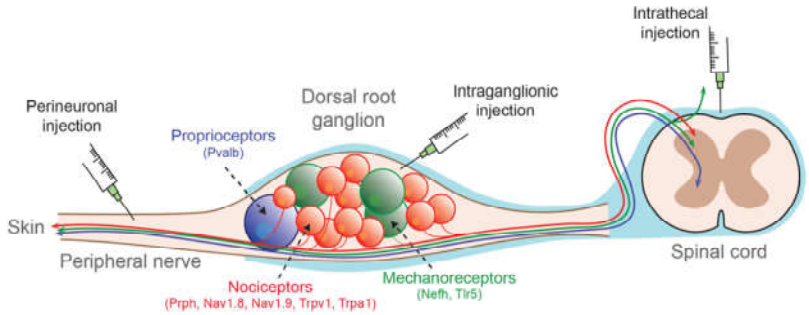
Understanding these cerebral pathways has also been useful in assessing therapeutic strategies.

From Berta et al:

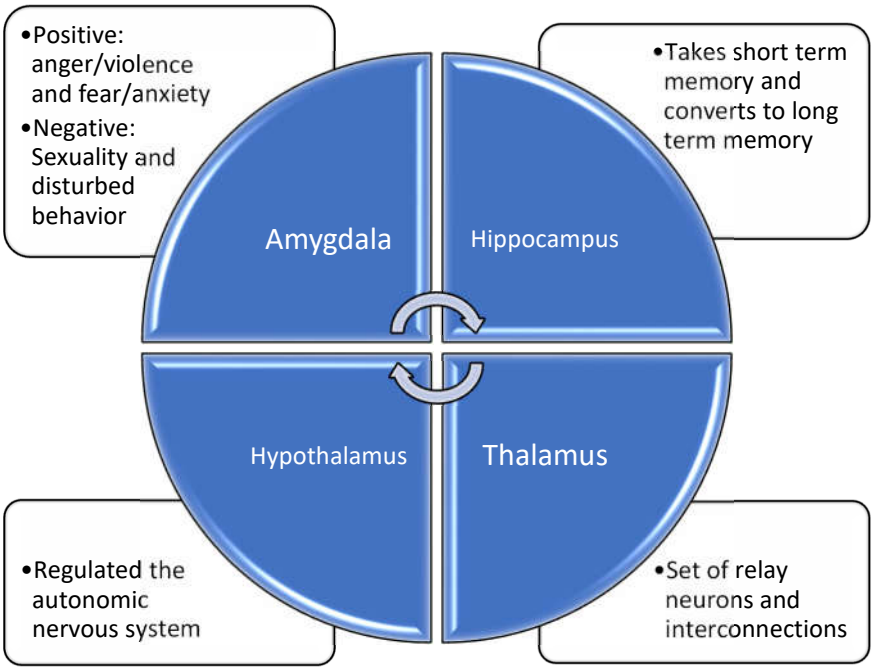
Morphological, electrophysiological, and molecular studies have supported the specificity theory that different populations of DRG neurons are responsible for distinct sensory modalities. Noxious stimuli, including mechanical, chemical, and thermal noxious stimuli, are sensed by nociceptors, characterized by the expression of the neurofilament peripherin (Prph), voltage-gated sodium channels Nav1.8 and Nav1.9, as well as transient receptor potential cation channels Trpv1 and Trpa1.

Low threshold mechanical stimuli such as light touch activate mechanoreceptors that specifically expressed neurofilament high (Nfh) and toll-like receptor 5 (Tlr5). Another type of DRG neuron is the proprioceptor that senses movement or vibration and it is generally characterized by the expression of parvalbumin (Pvalb).Information from DRG neuron subtypes arrives into different regions of the spinal cord and then is transmitted to the brain where the different stimuli are ultimately decoded. In chronic pain conditions DRG neurons undergo major cellular and molecular changes, which can be therapeutically targeted by using local drug delivery such as by peripheral nerve, intraganglionic, or intrathecal injections.

We show this below:



One area of interest in the itch syndrome is the limbic system. It was shown above that elements of the limbic system play a significant role in the itch process. We demonstrate below the elements of the limbic system and their putative roles.



As Melo et al note:

Substances that cause itch (pruritogens) are produced endogenously (histamine, kinins, neurotrophins, endothelin-1, bovine adreno medulla (BAM), proteases, cytokines or opioids), introduced from the environment (β alanine, Cowhage spicules from the bean plant Mucuna pruriens) or delivered as a medication (cloroquine, opioids)[3]. These agents produce itch by the activation of different cell types, including keratinocytes, mast cells or a specific subset of DRG[4] neurons.

Over the last decade, several receptors and transducers implicated in itch sensation have been identified, including histamine receptors, protease-activated-receptor-2 (PAR-2), members of the

***Mas-related G-protein coupled receptor family (MrgprD, MrgprC11)**, the **transient receptor potential vanilloid 1 (TRPV1)** channel or the **transient receptor potential ankyrin 1 (TRPA1) channel**.*

[3] See Reddy et al, Cowhage-Evoked Itch Is Mediated by a Novel Cysteine Protease: A Ligand of Protease-Activated Receptors, The Journal of Neuroscience, April 23, 2008.

[4] DRG, dorsal root ganglion. (From *γάγγλίον* Greek for tumor) See Berta et al. *The DRGs contain the cell bodies of primary sensory neurons including nociceptive neurons. After painful injuries, primary sensory neurons demonstrate maladaptive molecular changes in DRG cell bodies and in their axons. These changes result in hypersensitivity and hyperexcitability of sensory neurons (peripheral sensitization) and are crucial for the onset and maintenance of chronic pain. We discuss the following new strategies to target DRGs and primary sensory neurons as a means of alleviating chronic pain and minimizing side effects: inhibition of sensory neuron-expressing ion channels such as TRPA1, TRPV1, and Nav1.7, selective blockade of C- and Aβ-afferent fibers, gene therapy, and implantation of bone marrow stem cells.*

2.3 NEUROGENIC

Neurogenic itch is one wherein the neurons in the epidermis and dermis are activated from internal means such as via cytokines and the like. In many cases the neurogenic itch can be attributed to some underlying disorder or even medications being used. As Garibyan et al note:

Neurogenic and systemic itch result from disorders that affect organ systems other than the skin. These disorders include chronic renal failure, liver disease, hematologic, and lymphoproliferative conditions and malignancies. These itches are transmitted via the central nervous system, but there is no evidence of neural pathology. The administration of opioids in epidural anesthesia frequently results in itch. This observation has led to the hypothesis that neurogenic itch may result, at least in part, from a response to intraspinal endogenous opioids.

It follows that the administration of opioid antagonists might be expected to be at least partially effective in treating neurogenic itch. Recent advances in itch research have raised the possibility that itch-specific or itch-selective neurons in the spinal cord may provide targets for future therapies.

From Cheng at al:

Chronic itch is a common feature of most inflammatory skin disorders including allergic contact dermatitis (ACD), atopic dermatitis (AD), lichen planus, and prurigo nodularis. Although widely appreciated that inflammation causes itch, the molecular mechanisms driving this process has only come to light in the last decade.

It has been known for many decades that type 2 cytokines like IL-4 and IL-13 cause skin inflammation in AD. In addition to adaptive T helper type (Th2) cells, recent studies have revealed that innate immune cells like basophils and group 2 innate lymphoid cells (ILC2s) are major sources of type 2 cytokines and drivers of AD pathogenesis.

In terms of itch, IL-31, originally shown to be derived from adaptive Th2 cells is now a well-known effector cytokine and pruritogen that directly activates sensory neurons. Indeed, clinical trials are currently underway for the developmental of anti-IL-31 receptor antagonists to target AD associated itch

Abbas et al note:

Th2 cells activate defense mechanisms that use IgE antibodies, eosinophils, and mast cells to combat microbes. These reactions are important for the eradication of helminthic infections and perhaps also for elimination of other microbes in mucosal tissues.

They are central to the development of allergic diseases. Th2 cells are also thought to be important in tissue repair.

Th2 differentiation occurs in response to helminths and allergens and is dependent on the cytokine IL-4. Because the major cytokine that promotes Th2 development is IL-4 and this is a

product of Th2 cells, there has been some uncertainty about the source of IL-4 to initiate Th2 responses. The cytokine may be made by antigen-stimulated T cells, by mast cells, and possibly by group 2 innate lymphoid cells (ILC2; see Chapter 4), and other cells in the vicinity of the activated T cells. Other cytokines that may promote the development of Th2 cells include IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), all of which are produced by damaged epithelial and other cells and are involved in the activation of ILC2.

Cheng et al further note:

Upstream of the type 2 cellular immune response, epithelial cell-derived cytokines like ***thymic stromal lymphopoietin (TSLP)***[5] *and* ***IL-33 are known to be potent promoters of AD-associated inflammation.***

However, in addition to their proinflammatory roles, recent studies have implicated ***TSLP*** *and IL-33 as pruritogens in the context of AD and ACD in mice, respectively. In addition, the canonical effector type 2 cytokines IL-4 and IL-13, have also been shown to act directly on sensory neurons to modulate neuronal responsiveness to a variety of pruritogens. Thus, many cytokines previously thought to play key roles in promoting inflammation, have now been shown to promote distinct neuroimmune interactions in the setting of type 2 inflammation-associated itch. Future studies will be required to determine how these various pathways interact to promote various aspects of itch pathology.*

Importantly, various therapeutics including tezepelumab (anti-TSLP mAb), etokimab (anti-IL- 33 mAb), dupilumab (anti-IL-4/13 receptor mAb), lebrikizumab (anti-IL-13 mAb), and tralokinumab (anti-IL-13 mAb) are either available or in clinical development for AD. Although type 2 cytokines are known to signal through JAK1 in immune cells, given the ability of IL-4 and IL-13 to activate sensory neurons, it was also identified that neuronal JAK1 signaling is a critical component of itch in mice as well.

However, given the diversity of cytokines that are known to signal through JAK1, it remains unclear how many neuroimmune pathways, in addition to type 2 cytokines, are disrupted in this context.

Notwithstanding this, clinical studies have demonstrated that JAK inhibitors are effective in treating conditions such as chronic pruritus of unknown origin (CPUO), suggesting that JAK inhibitors may have broad anti-itch properties. In addition, JAK inhibitors such as abrocitinib, delgocitinib, and upadacitinib are also being evaluated for the treatment AD. Primary sensory

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[5] See NCBI https://www.ncbi.nlm.nih.gov/gene/85480 *This gene encodes a hemopoietic cytokine proposed to signal through a heterodimeric receptor complex composed of the thymic stromal lymphopoietin receptor and the IL-7R alpha chain. It mainly impacts myeloid cells and induces the release of T cell-attracting chemokines from monocytes and enhances the maturation of CD11c(+) dendritic cells. The protein promotes T helper type 2 (TH2) cell responses that are associated with immunity in various inflammatory diseases, including asthma, allergic inflammation and chronic obstructive pulmonary disease. The protein is therefore considered a potential therapeutic target for the treatment of such diseases. In addition, the shorter (predominant) isoform is an antimicrobial protein, displaying antibacterial and antifungal activity against B. cereus, E. coli, E. faecalis, S. mitis, S. epidermidis, and C. albicans*.

neurons, while mediating itch, can also communicate with immune cells to regulate skin inflammation.

A mouse model of ACD induced by the hapten squaric acid dibutylester (SADBE) demonstrated that, while itch and inflammation are frequently paired responses, they operate along different mechanistic pathways. In terms of chronic itch, the cation channels TRPV1 and TRPA1 expressed on primary sensory neurons were required for SADBE-induced pruritus.

Although both TRP channels were involved in itch signaling, and TPRA1 was the predominant itch mediator, TRPV1 played a critical role in protecting against SADBEinduced inflammation, which has been shown to be dependent on natural killer cells, T cells and B cells. Chemical ablation of TRPV1-positive sensory fibers with resiniferatoxin (RTX) increased skin edema in mice and genetic knockout of TRPV1 function enhanced dermal macrophage responses.

***Thus, in the context of ACD, it appears that bidirectional neuroimmune interactions can occur via distinct pathways that regulate itch via TRPA1 and cutaneous inflammation via TRPV1, respectively**.*

These differential responses emphasize that although persistent itch symptoms often follow skin inflammation, itch transduction can be independent of skin inflammation. This may explain why certain anti-inflammatory therapies fail to mitigate chronic itch in diseases such as CPUO, where persistent itch exists in the absence of overt inflammation.

2.4 NEUROPATHIC

Neuropathic itch results from actual damage to nerve elements or neural pathways. Unlike neurogenic where the driver is external to the neural system, in this case the damage and driver is internal to the neural system. As Garibyan et al note:

Because of the extensive nature of this topic, the present authors refer interested readers to the Neuropathic itch results from damage to central or peripheral sensory neurons, which leads to the firing of pruritic neurons without any cutaneous pruritogenic stimuli. Neuropathic itch can be caused by primary lesions or dysfunction at any point along the afferent pathway of the nervous system. As the location of the underlying neural damage can be located away from the actual itchy area, scratching a neuropathic itch is rarely effective.

Neuropathic itch is often accompanied by other sensory abnormalities such as paresthesia, hyperesthesia, or hypoesthesia. Patients whose neural damage causes both sensory loss as well as neuropathic itch can self-inflict lesions upon themselves via repetitive, painless scratching (9). Of note, many neurological diseases that cause neuropathic itch can also cause neuropathic pain. The mechanisms of neuropathic itch are poorly understood, but some hypotheses have been proposed.

One such hypothesis suggests that local nerve damage to pain- and itch transmitting C-fiber neurons could result in misfiring of itch-specific C-fibers.

In addition, the loss of C-fiber neurons and thus loss of afferent input to the central neurons can lead to uninhibited signaling of centrally located itch neurons, leading to the sensation of itch.

An example is hepatic itch from Bassari and Koea:

The pattern theory argues that itch, as well as other sensation, is generated by receptors and nerves that are not stimulus specific and the signals are decoded centrally.

Consistent with this theory is the observation that the itch pathway may be activated by pain producing stimuli such as capsaicin applied to the skin which will activate mechanically insensitive C-fibres involved in histamine related itch and different pruritogens may activate other neurological pathways. Cowhage are the barbed hairs of the tropical plant Macuna pruriens and their application to skin causes intense itch by stimulating mechanically responsive C-fibres rather than the mechanically insensitive fibres stimulated by the application of histamine.

Cowhage stimulated C-fibres innervate different neurons in the spinothalamic tract from histamine. These observations suggest that there are at least two separate itch pathways (histamine and cowhage). Consistent with this is the finding that experienced subjects report different characteristics of the two itch types. Histamine itch is described as "burning" while cowhage itch is described as "stinging". At cellular level histamine receptors types 1, 3 and 4 are important in the transmission of histamine stimulated itch.

Binding of histamine to these receptors activates phospholipase C, phospholipase A2 and transient receptor potential vanilloid 1(TPRV1) resulting in increased intracellular calcium in dorsal root ganglion cells. In contrast cowhage cleaves protease-activated receptor 2 (PAR2) that activates phospholipase C, TRPV1 and transient receptor potential ankyrin 1 (TRPA1) resulting in membrane depolarization

2.5 PSYCHOGENIC

Psychogenic itch is the most complicated of all. It is driven as a psychological response and its drivers are well withing the complexity of the central nervous system. As Garibyan et al note:

Psychogenic itch is associated with psychological abnormalities and is considered psychiatric in origin. It typically presents with excessive impulses to scratch or pick at otherwise normal skin. Psychogenic pruritus involves brain or psychiatric abnormalities that are not yet well defined, but multiple psychiatric diagnoses including depression, obsessive compulsive disorder, anxiety, somatoform disorders, mania, psychosis, and substance abuse have been associated with itch.

The incidence of patients in dermatology clinics with psychogenic itch is estimated to be 2% . Psychogenic itch is generally a diagnosis of exclusion and requires ruling out other causes of pruritus

The presence of psychogenic itch may be a part of the other three patterns evolving as the itch syndrome progresses. Thus even when one can suppress the other itch classes the psychogenic itch which has evolved may persist. This becomes a potentially confounder to the physician treating the patient.

2.6 DERMATOGENIC

Dermatogenic or Pruritoceptive itch is one driver from the epidermis or dermis inward. It is a classic dermatological problem and can be treated as such. Namely eliminating the dermatological issue eliminates the itch. As Garibyan et al note:

Pruritoceptive itch (or dermatogenic) is the type most frequently encountered by dermatologists. It is generated in the skin either through inflammation or skin damage, and is typically visualized by clinical examination. Age-related changes in the barrier function of the skin can also lead to pruritoceptive itch.

This type of itch accounts for the majority of the cases of clinical pruritus because everything from endogenous mediators and exogenous allergens that come into contact with the skin can induce pruritoceptive itch.

3 IMMUNE SYSTEM RELATIONSHIPS

We briefly review some key elements of the immune system which become critical to understanding the itch-cancer connection. This is not intended to be a dispositive review in detail but merely a focus on the key elements[6].

3.1 ANTIGENS

Simply stated, antigens (Ag) are substances that are not supposed to be in the body and can be recognized as such by the immune system. Many Ag are proteins or protein fragments and many other substances not normally recognized by the immune system such as polysaccharides. They may be polysaccharides, RNA or DNA fragments and the like. Cancer cells produce many Ag in their process of proliferating. We shall discuss these cancer related antigens later.

3.2 KEY IMMUNE CELLS

We first review some key immune cells.

3.2.1 Dendritic Cells

Dendritic cells are the scavengers of the immune system. From Abbas et al:

DCs are tissue-resident and circulating cells that detect the presence of microbes and initiate innate immune defense reactions, and they capture microbial proteins for display to T cells to initiate adaptive immune responses. These cells are named because of their long membranous projections, reminiscent of the dendrites of neurons.

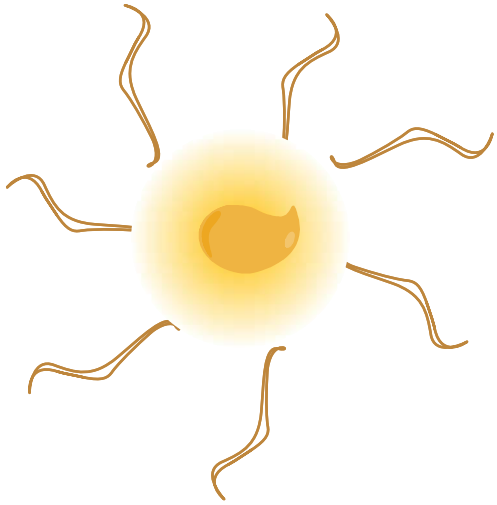
Most DCs are widely distributed in lymphoid tissues, mucosal epithelium, and organ parenchyma. The location of DCs in epithelia and tissues where microbes enter, their ability to capture antigens and take them to lymph nodes where naive T cells circulate, and their rapid responses to microbes all place these cells in a unique position in the immune system, serving as sentinels of infection that begin the rapid innate response but also link innate responses with the development of adaptive immune responses…

The DC collect Ag and roam about to ultimately present them to T cells and the like.

The dendritic cells are cells in the immune system which have branches, thus the dendron, and flow throughout the body collecting information on foreign invaders and presenting these to the immune cells. They present the antigens to the effector immune cells and start the immune process off against the invader. One of the first immunological approaches using the dendritic cells, DC, is its use on castrate resistant prostate cancer, and sipuleucel. We shall proceed to examine this approach in detail later.

[6] https://www.researchgate.net/publication/314090163_Cancer_Immunotherapy_A_Systems_Approach

The dendritic cells are named for the tree like or branched structure they look like as depicted below. (δενδρον)



As Sabado and Bhardwaj note:

Dendritic cells (DCs) are often called nature's adjuvants because of the way in which they help to initiate an immune response. Found throughout the body, the cells acquire and process antigens (the molecules recognized and bound by antibodies) from pathogens and tumors.

They then migrate to lymph nodes and activate T cells, which in turn induce protective immune responses. These properties have driven attempts to develop vaccines containing DCs loaded with tumour antigens, with the aim of inducing antitumor immune responses in patients with cancer.

But this strategy has fallen short of expectations… simply improving DC migration to lymph nodes dramatically enhances antitumor responses in humans and mice, pointing to a way to optimize the use of DC vaccines. There is a general consensus that DC vaccines can safely induce long-lasting antitumor immune responses. These vaccinations have produced encouraging, if modest, clinical results in some patients with advanced cancers. For instance, the vaccine sipuleucel-T (the only cell-based cancer vaccine approved for use in the United States) increases median survival times by four months in patients with prostate cancer.

But several factors might be limiting the efficacy of DC vaccines: the source and type of DCs used; the site and frequency of injection; and the ability of DCs to migrate to lymph nodes. Moreover, the injected DCs may not themselves directly instigate an immune response, but instead might act indirectly through DCs already present in the lymph node. Less than 5% of cells in a DC vaccine reach the lymph nodes.

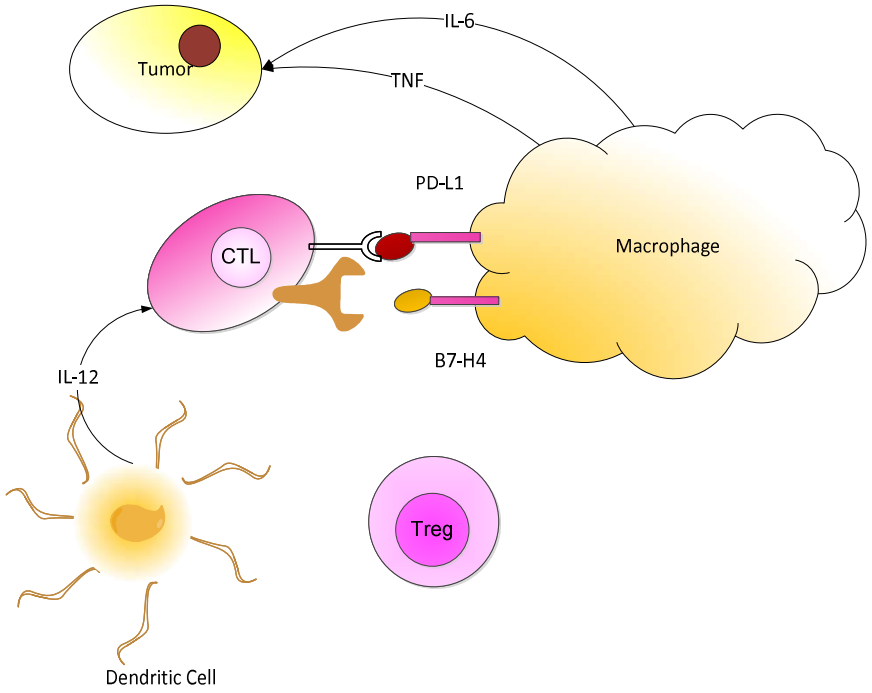
In mice, DC migration can be improved either by injecting activated DCs or by pre-conditioning the vaccination site in the skin with the inflammatory molecule TNF-α. Mitchell and colleagues therefore investigated whether pre-conditioning the DC vaccine site to generate local

inflammatory responses might enhance DC migration in humans. To do this, they used a tetanus/diphtheria (Td) toxoid vaccine.

Most people have been exposed to this toxoid during childhood vaccinations, and re-exposure activates a subset of T cells called memory CD4+ T cells that recognize only the Td antigen and mount a strong and rapid inflammatory immune response in its presence.

3.2.2 Macrophages

Macrophages are out collecting Ag as well. A typical example of a macrophage action is depicted in the Figure below where we see it presenting to a cytotoxic T cell, CTL, and also producing tumor necrosis factor as a result of that activation.



From Ruffelli and Coussens we have:

Macrophages are represented in all tissues by functionally and phenotypically distinct resident populations that are critical for development and homeostasis. Under nonpathological conditions, most resident macrophage populations derive from embryonic progenitors and are maintained through local proliferation. Exceptions to this include intestinal, dermal, and alveolar macrophages at barrier sites and macrophages in the adult heart that are replaced by circulating bone marrow-derived Ly6C+ inflammatory monocytes over a timescale of several weeks.

Under pathological conditions, there is evidence for both local proliferation and recruitment, with differences observed by tissue location and type of inflammatory insult….

For many solid tumor types, high densities of cells expressing macrophage-associated markers have generally been found to be associated with a poor clinical outcome. There are conflicting data for lung, stomach, prostate, and bone, where both positive and negative outcome associations have been reported, possibly related to the type/stage of cancer evaluated, or to the type of analysis performed. Some discrepancy may also reflect the use of different macrophage markers.

CD68, a glycoprotein predominantly resident in intracellular granules, represents a fairly specific marker for murine macrophages and, in combination with F4/80, identifies a majority of tumor-associated macrophages. In humans, however, CD68 expression is widespread and includes granulocytes, dendritic cells, fibroblasts, endothelial cells, and some lymphoid subsets…

3.2.3 Natural Killer Cells

NK cells are not normal T cells and they deviate from the T cell line earlier. They amount for between 5% to 10% of the circulating lymphocytes. They work by producing cytokines and are generally considered a part of the innate immune system. They are considered part of the innate immune system.

NK cells have both activation and inhibition receptors. They act in such a manner as to becoming active or inactive by a balancing of activation, it is a thresholding effect. The NK cells have two types of receptors reflective of the NK cells requirement to balance activating and inhibiting receptor-ligand responses. The Killer Activation Receptors, KAR, are receptors which have the ability to recognize what are termed "stress" associated molecules, namely the ones which tell the NK cell that the cell should be considered to be attacked. In contrast, there is a Killer Inhibition receptor, KIR, which examines the MHC I molecule on the presenting cell to see if it is self. If the number of KAR activations exceed the KAR ones, then the NK cell attacks the cell. We shall discuss this later in some detail.

NK cells have the ability to sense activation and inhibition based upon what receptors are active on the surface. The inhibition is driven by seeing MHC I receptors on the surface of the interacting cell. The MHC I tells the NK that this is self. However, when a KAR receptor is activated then the perceived cells contains something that needs to be dealt with. But the NK cell has a multiplicity of inhibitors and activators and it is a process of some form of majority voting that results in the NK acting or not. We shall discuss this in detail later.

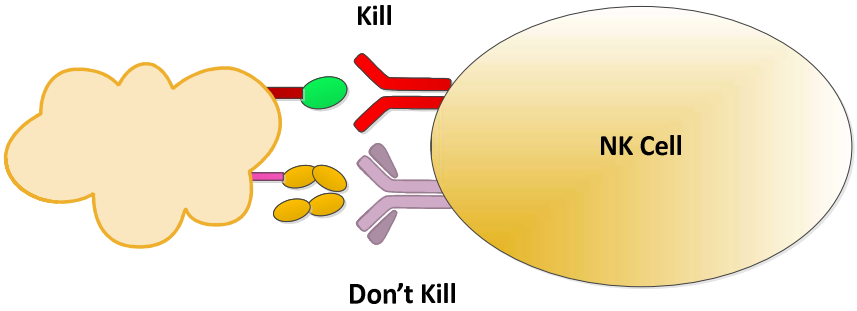
NK cells can be signaled by Interferons, TNF, IL-12 and IL-15. These have been used by researchers in attempts to activate the NK system.

The receptors are lechtin like or immunoglobulin like. The lechtin receptors bind proteins and not lechtins. The second receptors bind HLA-B and HLA-C.

There are inhibitory receptors which are immunoglobulin like such as ILT/LIR as well as KIR, called killer inhibitory receptors.

NK cells have activating and inhibiting ligands. Thus, an MHC-I represent a cell which is self and thus has an inhibitory reaction. A second receptor may reflect a viral infection and thus may activate. The actual activation is a balance between inhibition and activation. If the activation is strong enough then even though there may be an inhibitory self-recognition it may be overcome by the activating ligand. This may be a pathway for cancer management.

NK recognizes a marker on the surface and it decides to "kill" the cell. But it also recognizes the MHC I market as self and then does NOT Kill the cell. The MHC I acts as an inhibitor.



As Caligiuri notes:

Years ago, the histologic and functional definition of an NK cell was that of a large granular lymphocyte that could kill a target cell "naturally," that is, in a spontaneous fashion that did not require any priming and was not restricted by the target cell's expression of major histocompatibility complex (MHC) molecules. Experiments in mouse models of bone marrow graft rejection led to the proposal that NK cells would kill any target that lacked self–major histocompatibility complex (MHC) class I molecules (the "missing self" hypothesis). This extraordinary idea was developed before anyone knew what the NK cell was using to "see" its targets.

It is now clear that NK cells have a multitude of inhibitory and activating receptors that engage MHC class I molecules, MHC class I–like molecules, and molecules unrelated to MHC. Thus, NK cells are indeed restricted in what target cells they can engage by the expression of the target's MHC ligands, but in a very complex fashion that remains incompletely understood. Notably, orthologs of more recently discovered NK-cell receptor families cannot be found beyond mammals, suggesting that the composite modern day NK cell emerged well after T and B cells appeared to define the vertebrate adaptive immune system.

Furthermore, the complementary roles that NK and cytolytic T cells have in target recognition and host defense, and their similar mechanisms of cytolysis, suggest that these 2 cell types may have each evolved from a common ancestral cytolytic effector cell. Finally, a subset of human NK cells produce abundant cytokines with modest or no ability to lyse target cells. Thus, the older idea of an NK cell as an ancestral forerunner or as a cell defined by a simple function no

longer applies. The traditional cell surface phenotype defining human NK cells within the lymphocyte gate on the flow cytometric analyzer shows an absence of CD3 (thereby excluding T cells) and expression of CD56, the 140-kDa isoform of neural cell adhesion molecule (NCAM) found on NK cells and a minority of T cells.

In contrast, murine NK cells do not express CD56, and … that NKp46, a member of the highly conserved natural cytotoxicity receptor (NCR) family of NK-activating receptors, best defines NK cells across species. Nevertheless, under close examination NKp46 can be found on a small subset of human cytolytic T lymphocytes.

Conversely, some CD56CD3 cells have low-density expression or may even lack expression of NKp46; it will be interesting to determine the precise nature of these minority of cells. The search will no doubt continue for a sensitive and truly specific pan–NK-cell marker. Until this is found, the phenotypic definition of NK cells will continue to be determined by their expression of a unique combination of non– NK-restricted surface antigens.

He then goes on to describe what they do:

Thus far it has been fully appreciated that NK cells can secrete cytokines and chemokines that influence the host's immune response, and/or kill certain infected or transformed cells via perforin/granzyme or death receptor (egg, Fas, TRAIL)–related pathways.

Interferon gamma (IFN-) is considered the prototypic NK-cell cytokine, and its production by NK cells is known to shape the Th1 immune response, activate APCs to further up-regulate MHC class I expression, activate macrophage killing of obligate intracellular pathogens, and have antiproliferative effects on viral- and malignant-transformed cells. For many of these functions, it would make sense for NK cells to be in close proximity to APCs and T cells.

Indeed, the subset of NK cells that is the most potent producer of IFN- (i.e., CD56bright NK) is primarily located in the parafollicular T cell– and APC-rich region of SLT.21

As Pittari et al note:

The function of NK cells is governed by a set of germline- encoded activating or inhibitory receptors referred to as killer immunoglobulin-like receptors (KIRs). The extracellular domain determines which HLA class I molecule NK cells recognize, whereas the intracytoplasmic domain transmits either an activating or an inhibitory signal. KIRs are monomeric receptors with either 2 (KIR2D) or 3 (KIR3D) immunoglobulin-like domains, and are further subdivided into those with long (L) cytoplasmic tails (KIR2DL and KIR3DL) and short (S) cytoplasmic tails (KIR2DS and KIR3DS). Long-tail KIRs generate an inhibitory signal through the recruitment of the SH2-domain- containing tyrosine phosphatase 1 protein (SHP1). Short- tail KIRs possess truncated portions that transduce activating signals via tyrosine phosphatase of DAP12 and other proteins.

As Vivier et al note:

NK cells were originally described as cytolytic effector lymphocytes, which, unlike cytotoxic T cells, can directly induce the death of tumor cells and virus-infected cells in the absence of specific immunization; hence their name.

Subsequently, NK cells have been recognized as major producers of cytokines such as interferon-g (IFN-g) in many physiological and pathological conditions.

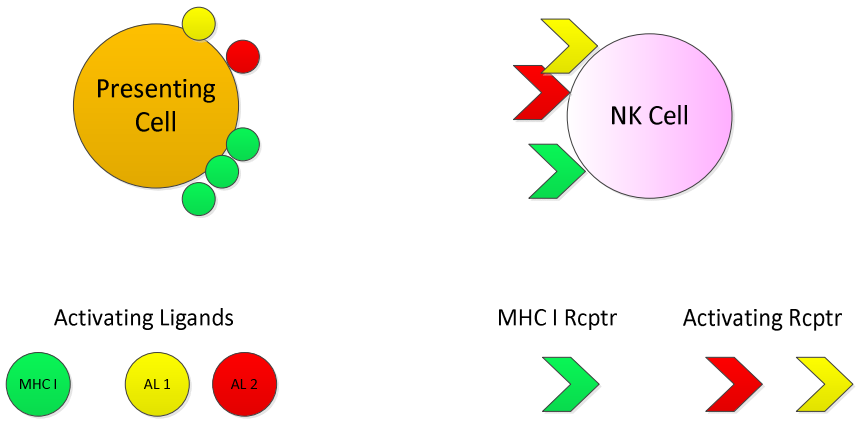
NK cells also produce an array of other cytokines, both proinflammatory and immunosuppressive, such as tumor necrosis factor–a (TNF-a) and interleukin (IL)–10, respectively, and growth factors such as GM-CSF (granulocyte macrophage colony-stimulating factor), G-CSF (granulocyte colony stimulating factor), and IL-3. NK cells also secrete many chemokines, including CCL2 (MCP-1), CCL3 (MIP1-a), CCL4 (MIP1-b), CCL5, XCL1 (lymphotactin), and CXCL8 (IL-8). Whereas the biological function of the growth factors secreted by NK cells remains to be clarified, their secretion of chemokines is key to their colocalization with other hematopoietic cells such as dendritic cells (DC) in areas of inflammation.

Furthermore, the production of IFN-g by NK cells helps to shape T cell responses in lymph nodes, possibly by a direct interaction between naïve T cells and NK cells migrating to secondary lymphoid compartments from inflamed peripheral tissues and by an indirect effect on DC.

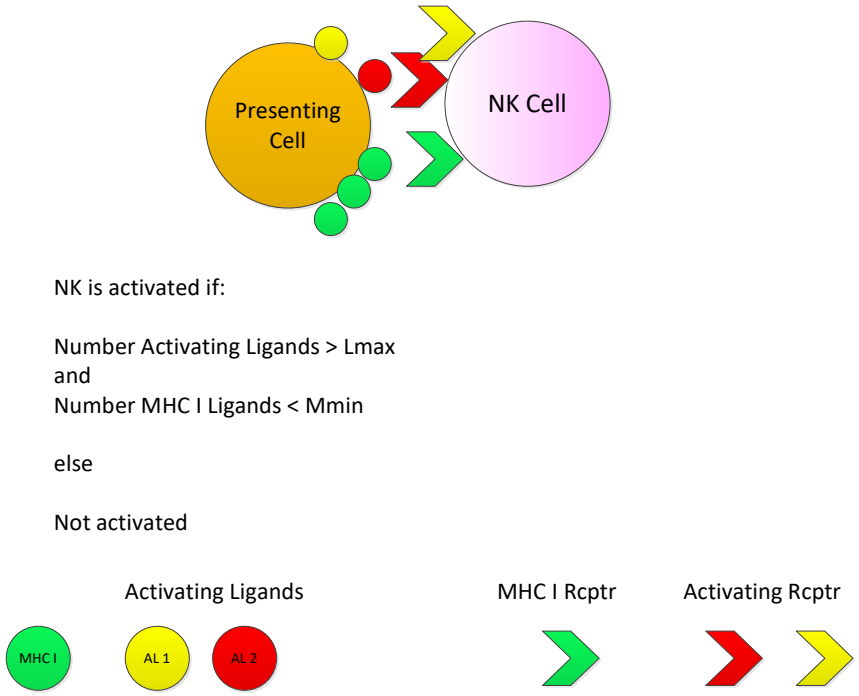
NK cell–mediated killing of target cells also impacts T cell responses, possibly by decreasing the antigenic load and/or because target cell debris might promote antigen cross-presentation to CD8+ cytotoxic T cells (Fig. 1). Although NK cells can positively or negatively influence host T and B cell immunity, depending on the nature of the antigenic challenge, the emerging notion is that NK cells are not only cytolytic effector cells against microbeinfected cells or tumor cells. Rather, NK cell– mediated cytotoxicity and cytokine production impact DC, macrophages, and neutrophils and endow NK cells with regulatory function affecting subsequent antigen-specific T and B cell responses.

Conversely, the "natural" effector function of NK cells has been revisited. NK cells require priming by various factors, such as IL- 15 presented by DC or macrophages , IL-12 or IL-18 , to achieve their full effector potential, highlighting the intimate regulatory interactions between NK cells and other components of the immune response. Thus, NK cells, like T and B cells, participate in the immunity in many different ways and undergo a process of functional maturation to fulfill these functions.

Now Vivier et al have described the rather interesting manner in which NK calls can be activated or inhibited. Simply, it is a bit of majority voting by ligands and receptors. We demonstrate this below. Activating ligands can attach to receptors as equally as inactivating.



Then below we demonstrate a somewhat simple majority voting scheme whereby the combination, subject to some putative weighting, can effect either activation or inactivation.



As Vivier et al note:

NK cells are equipped with an array of receptors that can either stimulate NK cell reactivity (activating receptors) or dampen NK cell reactivity (inhibitory receptors) . Activating receptors include receptors that interact with soluble ligands such as cytokines and receptors that interact with cell surface molecules.

Cytokine receptors that are coupled to the common gamma chain (gc), such as IL-15R, IL-2R, and IL-21R, are involved in NK cell development and effector function. In particular, IL-15 is required for the maturation and survival of NK cells, consistent with the absence of circulating NK cells in SCIDX1 patients and in mice lacking IL-15 or IL-15R components . Cytokine

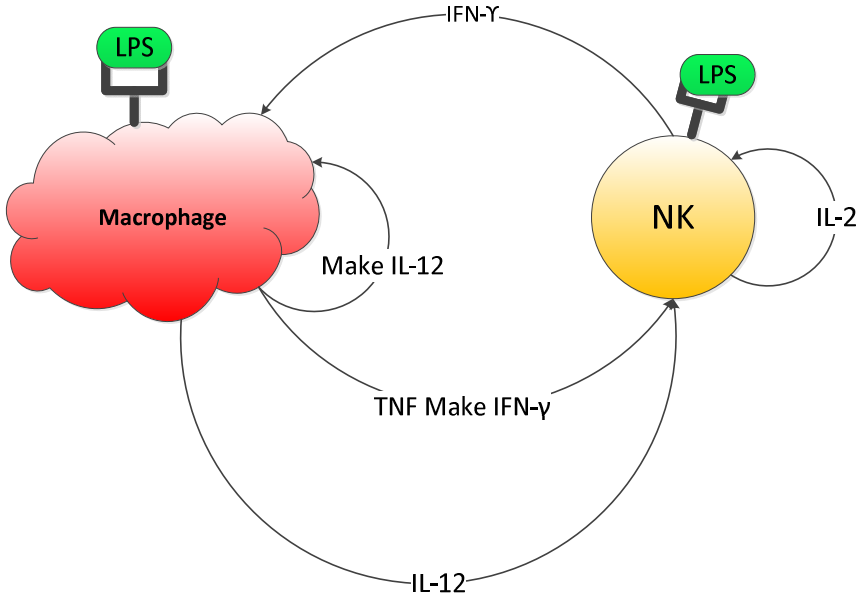
receptors that are linked to the adapter protein MyD88 are also important for NK cell maturation, namely IL-1R in humans and IL-18R in the mouse .

NK cells exert their biological functions by various means. NK cells can kill a variety of target cells, including virus-infected cells and tumors, in the absence of antibody. In the case of viruses, the mouse Ly49H activating receptor recognizes a cytomegalovirus-encoded ligand (m157) , and NKp46 has been reported to interact with hemagglutinins derived from influenza and parainfluenza viruses .

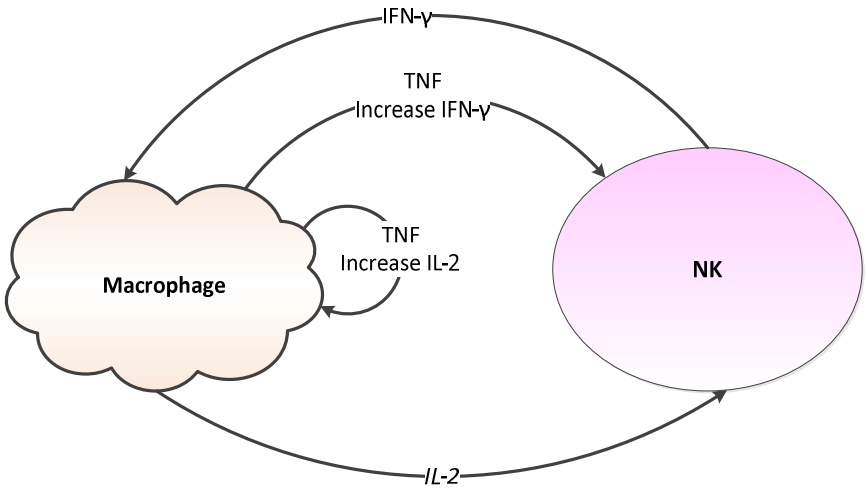
NK cells are also able to detect antibody-coated cells through the Fcg RIIIA (CD16) cell surface receptor and to exert antibody-dependent cell cytotoxicity (ADCC) and cytokine production. CD16 is coupled to the CD3z and FcRg signal transduction polypeptides bearing intracytoplasmic immunoreceptor tyrosine-based activation motifs (ITAMs).

The natural cytotoxicity receptors (NKp46/NCR1, NKp44/NCR2, and NKp30/ NCR3) are also potent activation receptors linked to the ITAM bearing CD3z, FcRg, or DAP12 molecules . In mice, the NK1.1 (Nkrp1c) molecule on CD3– cells have been a useful marker for NK cells, but its expression is confined to only certain strains of mice. NKp46 appears to be the most specific NK cell marker across mammalian species, although discrete subsets of T cells also express it

Now shown below we depict the result of this activation process. There is a flow of Interferons further activating the NK and with the macrophage introduction of a pathogen identifier, in this case a lipo-poly saccharide, LPS, we see the NK then activated and beginning its response.

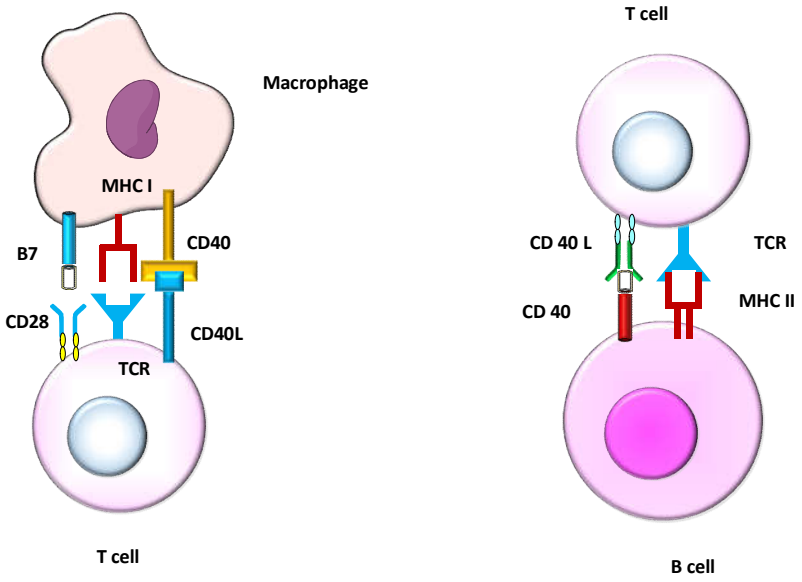


The figure below is another depiction of this process.



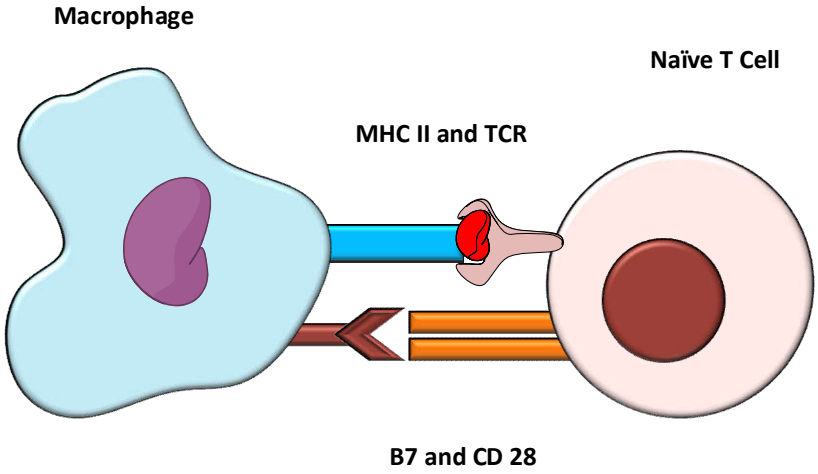
3.2.4 T Cells

T cells are the utility cells of the immune system. That function as adaptive players and from the perspective of this note become the key effect of many actions. The two step process is shown below where we have a Macrophage present to a naïve T cell an Ag via the T cell



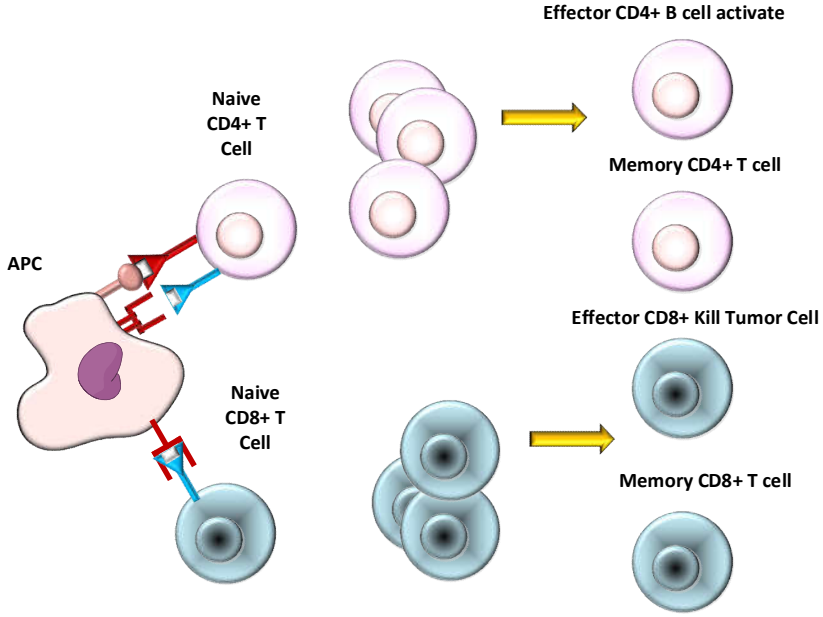
The figure below details this interface.

Signal 1 is caused by the binding of the peptide-MHC complex to the TCR.

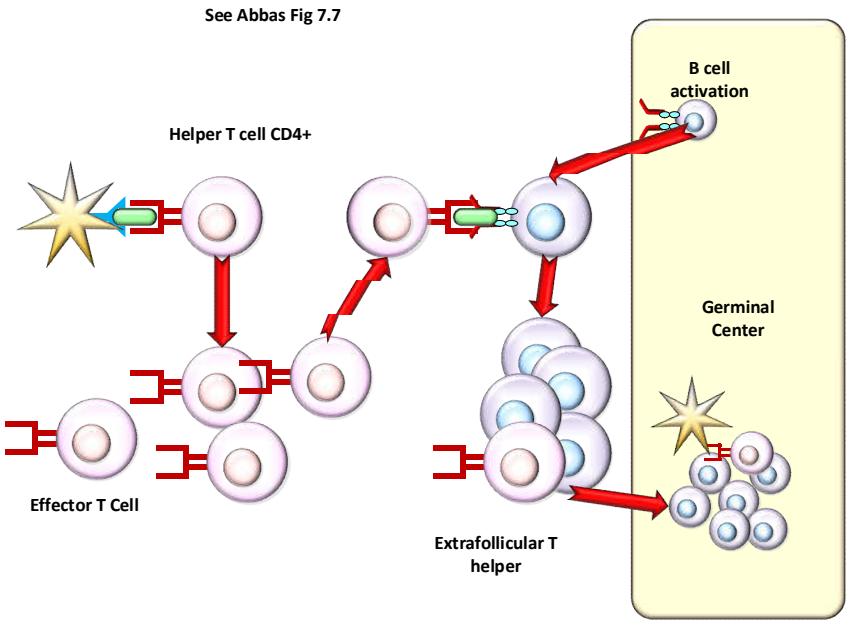


Signal 2 (or co-stimulation) is caused by the binding of B7 proteins on the dendritic cell to CD28 on the T cell. Without co-stimulation, the naive T cell will not be activated.

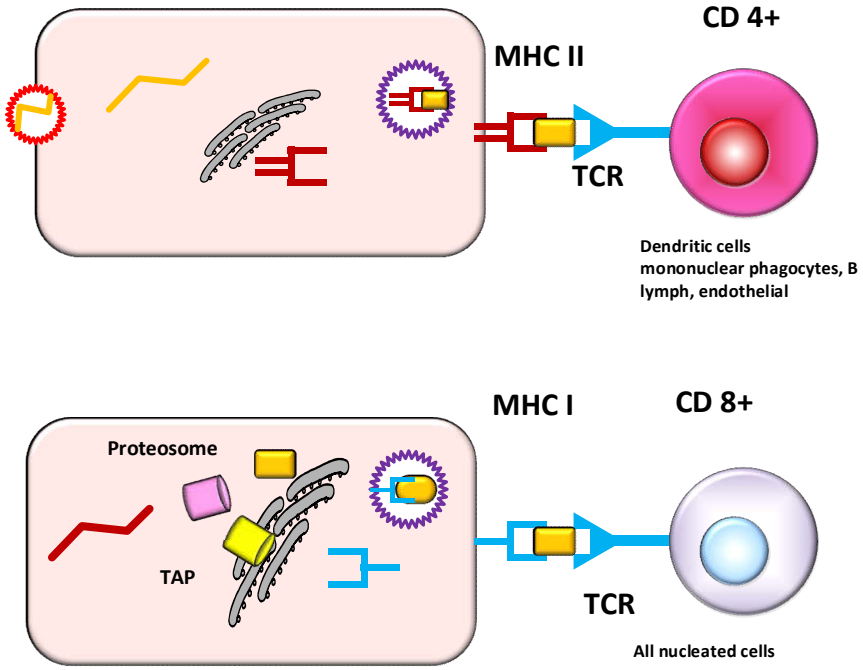
In a more complex view we have an APC dealing with both a CD4+ T cells as well as a CD8+ T cells. The resultant actions of each is then detailed.



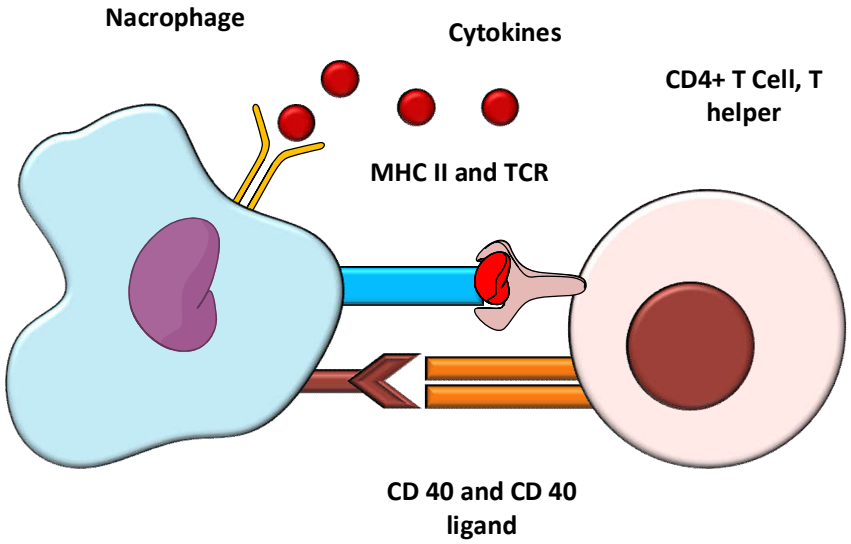
We can then also show the location of the germinal center and its impact in cell proliferation



The specifics of the different T cells is shown below.



Once activated we then get the release of the cytokines shown below.



3.3 TOLL LIKE RECEPTORS

The Toll Like Receptors, "toll" means weird or strange in German, and they play a significant role in the innate system.

As Travis notes:

At the heart of this protection are proteins, called Toll-like receptors (TLRs), on cells of the innate immune system. Over the past decade, it has become clear that TLRs are the long-sought cell-surface receptors that recognize common microbial features such as bacterial wall components or the distinctive DNA sequences of a virus. This role could date back to the earliest multicellular organisms, as humans and some of the most evolutionarily primitive animals share TLRs and the molecules involved in the TLR signaling cascade.

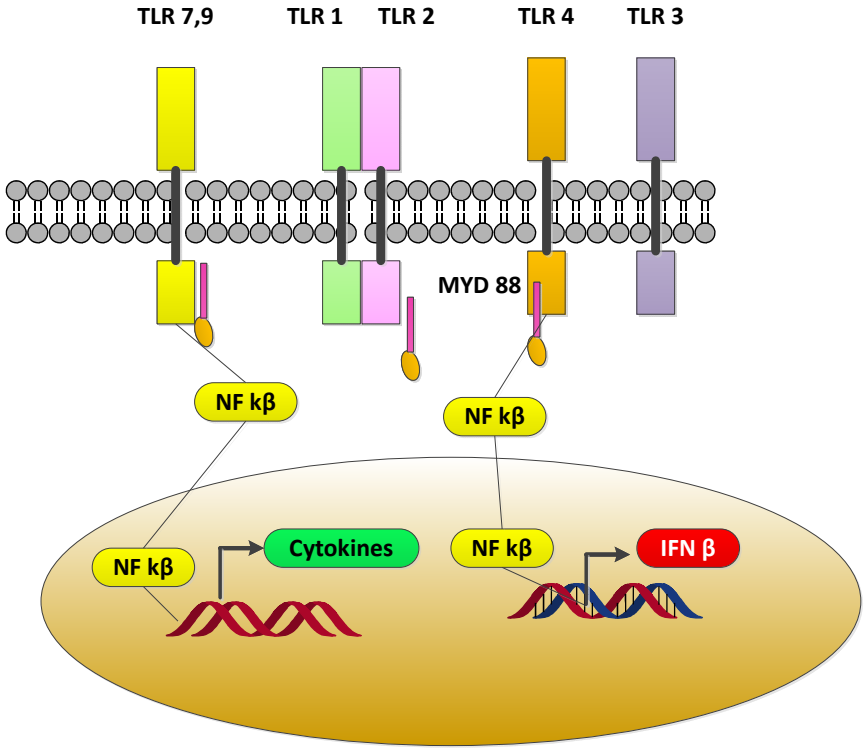
Takeda and Ashira note:

Toll receptor was originally identified in Drosophila as an essential receptor for the establishment of the dorso-ventral pattern in developing embryos . In 1996, Hoffmann and colleagues demonstrated that Toll-mutant flies were highly susceptible to fungal infection . This study made us aware that the immune system, particularly the innate immune system, has a skillful means of detecting invasion by microorganisms.

Subsequently, mammalian homologues of Toll receptor were identified one after another, and designated as Toll-like receptors (TLRs). Functional analysis of mammalian TLRs has revealed that they recognize specific patterns of microbial components that are conserved among pathogens, but are not found in mammals. In signaling pathways via TLRs, a common adaptor, MyD88, was first characterized as an essential component for the activation of innate immunity by all the TLRs.

However, accumulating evidence indicates that individual TLRs exhibit specific responses. Furthermore, they have their own signaling molecules to manifest these specific responses. In this review, we will focus on the recent advances in our understanding of the mechanism of TLR-mediated signaling pathways.

Now following their analysis, we can depict the TLR functions as shown below.

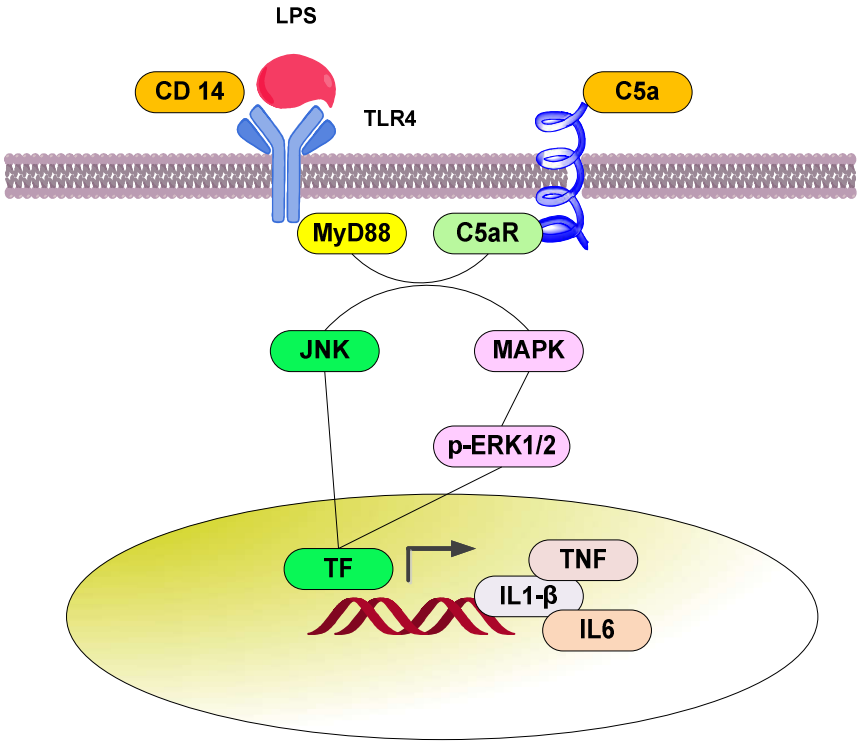


We will see more from these TLR as we proceed.

We discussed the Toll Like receptors earlier but they also play a role in Mab action and it is worth a brief discussion. As Merle et al discuss when examine the Complement system they state:

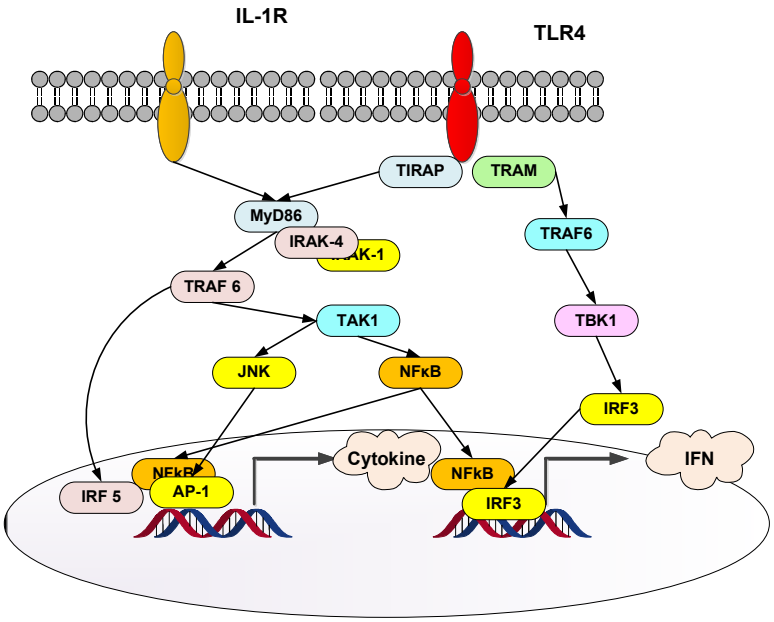
C3a and C5a are able to induce potent inflammatory pathways via their receptors C3aR and C5aR. The implication of intermediates such as NF-kB, MAPK, and c-Jun N-terminal kinase (JNK) in their transduction pathways suggests a potential crosstalk with other pathways, such as those of TLRs. Indeed, complement is involved in TLR-induced inflammation.

They show in the following Figure how this does function:



C5a/C5aR signalingpathwaycancooperatewithTLR-4activationby LPS on macrophages. Intermediate signaling pathways JNK and MAPK are activated and thus lead to proinflammatory effect by TNF-α, IL6, and IL1-β synthesis. On dendritic cells (DCs),TLR-4 and C5aR cooperate in different manner between mice and human. In vivo experiments have demonstrated an implication in Th1cells expansion, whereas in human, an anti-inflammatory role of TLR-4/C5aR collaboration has been described by an antagonized effect on IL-12 and IL-23 synthesis by DC.

Thus, when examining the effects of the complement proteins one must also examine the interactions with other receptors. Further details on this interaction are shown below.



3.4 CYTOKINES

Cytokines are produced by immune system cells to enhance other cells or attack infected cells[7]. Interferon was the first identified cytokine and we now have a significant number identified. Cytokines are small proteins generated by cells in response to certain attacks. As Duque and Descoteaux have noted:

Cytokines are mainly produced by macrophages and lymphocytes, although they can also be produced by polymorphonuclear leukocytes (PMN), endothelial and epithelial cells, adipocytes, and connective tissue. Cytokines are essential to the functions of macrophages. They mediate the unleashing of an effective immune response, link innate and adaptive immunity, and influence the macrophage's microenvironment.

Multiple subsets of macrophages have been characterized depending on the origin and microenvironment in which the macrophage is found. Contingent on activation status, macrophages have been classified as classically and alternatively activated. In turn, these different macrophage types drastically differ in the cytokines that they secrete, and consequently, their functions.

The process of cytokine secretion is masterfully regulated by a series of interorganellar exchanges that rely on vesicular trafficking and cytoskeletal remodeling. Proteins regulating neurotransmitter release, notably members of the soluble N -ethylmaleimide-sensitive factor attachment protein receptor (SNARE) family, and more recently synaptotagmins (Syt), are pivotal for the spatiotemporal regulation of cytokine secretion. In immune cells, SNAREs and

[7] See Leonard and Schreiber

Syts have been found to regulate processes ranging from cytokine trafficking to cell migration and phagocytosis. …

When macrophages are exposed to inflammatory stimuli, they secrete cytokines such as tumor necrosis factor (TNF), IL-1, IL-6, IL-8, and IL-12. Although monocytes and macrophages are the main sources of these cytokines, they are also produced by activated lymphocytes, endothelial cells, and fibroblasts.

Additionally, macrophages release chemokines, leukotrienes, prostaglandins, and complement. All of these molecules, in concert, may induce increased vascular permeability and recruitment of inflammatory cells. Aside from local effects, these mediators also produce systemic effects such as fever and the production of acute inflammatory response proteins. The inflammatory response is beneficial for the host when the aforementioned cytokines are produced in appropriate amounts, but toxic when produced in a deregulated fashion. For example, excessive production of IL-1b and TNF triggers an acute generalized inflammatory response characteristic of septic shock and multi-organ failure.

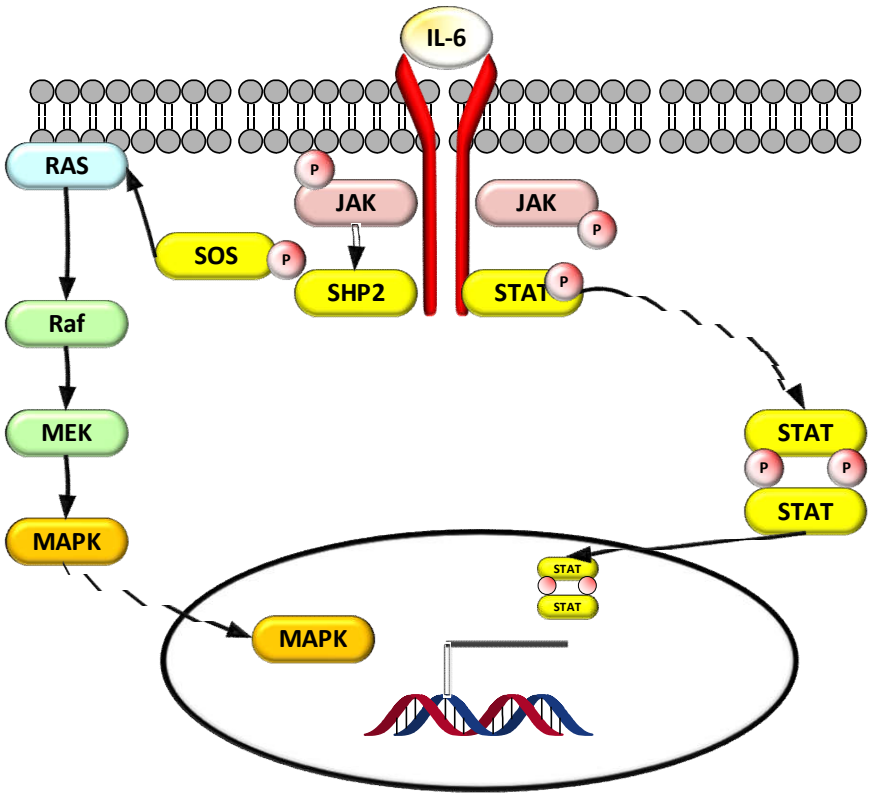
In contrast we also have chemokines and the authors note:

Chemokines are a special family of heparin-binding cytokines that are able to guide cellular migration in a process known as chemotaxis. Cells that are attracted by chemokines migrate toward the source of that chemokine. During immune surveillance, chemokines play a crucial role in guiding cells of the immune system to where they are needed. Some chemokines also play a role during development by promoting angiogenesis, or by guiding cells to tissues that provide critical signals for the cell's differentiation. In the inflammatory response, chemokines are released by a wide variety of cells involved in both innate and adaptive immunity. As already mentioned, chemokine release is often induced by proinflammatory cytokines such as TNF, IL-6, and IL-1b.

Heparin is a significant player in immune system response especially as relates to the itch syndrome. We shall examine this at length separately.

3.4.1 IL-6

IL-6 and the IL-6 family, including IL-31, is a significant set of cytokines. We have examined their impact previously in areas such as COVID infections. We show below the activation pathway of IL-6.



As Radharani et al note:

Accumulated evidences indicated that immune cells within tumor microenvironment play an important role in tumor progression.

Macrophages are one of the most common populations among inflammatory cells within breast tumor micro-environment which have been known to be involved in promoting major hallmarks of cancer. Within tumor micro-environment, cytokines released by tumor cells suppress the immune function of macrophages and polarise them into M2 phenotype which promote tumor growth, metastasis and angiogenesis and termed as tumor-associated macrophages (TAMs).

Recent studies have revealed that TAMs exhibit distinct sub populations depending upon their location in tumor micro-environment, stage, and type of tumor. Hence, polarized state of tumor promoting TAMs is still ambiguous and under discussion and depending upon the type, number and various signal from outside or within tumor micro-environment, TAMs act as double-edged sword and partially decides the development of tumor and angiogenesis. IL-6 a is a pleotropic cytokine known for its versatile role in diverse functions such as inflammation, immune response, haematopoiesis, proliferation of non-immune cells, cellular metabolism and inducing synthesis of acute phase proteins.

Studies have indicated that IL-6 plays dual role both in promoting tumor growth and inducing adaptive immunity within the tumor microenvironment. Interestingly, it has been shown that IL-6 can be secreted both by cancer and stromal cells like cancer associated fibroblasts (CAFs),

TAMs, and endothelial cells in various cancers and induces proliferation, angiogenesis and metastasis by activating STAT-3 pathway.

TAM, tumor associated macrophages, play a significant role in malignancies. M1 attack the cancer whereas M2 protect the tumor cells. The influence of IL-6 plays a key role in theis process.

Moreover, few reports have suggested that interaction of cancer cells with macrophages induces IL-6 expression, however the mechanism by which cancer cells regulate IL-6 expression in TAMs is not well defined.

Cancer stem cells (CSCs) are small population of cells within tumor which possess the ability of self-renewal and differentiation and have role in tumor initiation, progression and expansion due to intrinsic alterations in the tumor microenvironment. Various reports have demonstrated CSCs role in breast tumor growth, metastasis and resistance to therapy .

We have examined CSCs extensively for several cancers, focusing on prostate and melanoma. CSCs have a unique life cycle, generating cells to retain themselves and cells to proliferate. Thus targeting the CSC is a critical concern in dealing with cancers.

Interestingly, studies have observed co-localization of TAMs with CSCs and identified the role of TAMs in regulation of CSCs via secretion of various cytokines. However, the soluble mediators secreted by TAMs that are involved in regulation of CSCs have not been explored comprehensively yet. In the present study, we have delineated the signalling mechanism through which breast cancer cells induce IL-6 production in TAMs.

We further demonstrate the role of TAMs derived IL-6 in enrichment of CSCs and tumor progression through STAT-3 pathway in breast cancer using both in vitro and in vivo models … Interaction of cancer cells with surrounding stroma is a key phenomenon which leads to reprogramming of stromal components to create a tumor microenvironment favourable for tumor progression.

The interplay between TAMs and CSCs is a critical observation. As we will later note, IL-31 is an IL-6 family member and we suspect plays a equal role.

Previously it has been demonstrated that cancer cells induce chemokine mediated upregulation of p38-MAPK and ERK pathway in an autocrine manner which leads to tumor progression in melanoma . Recent report has shown that breast cancer cell derived osteopontin induces the resident fibroblast to myofibroblast differentiation which subsequently results in breast tumor progression .

Similarly, various other studies have established the role of cross-talk between cancer cell and stromal cells in mutual regulation and resulting tumor progression . In this study, we sought to understand the molecular mechanism of tumor-stromal interaction especially the crosstalk between macrophages and breast cancer cells in activation of macrophages into TAMs and TAM dependent enrichment of CSCs and tumor progression in breast cancer. Our work deciphers the

mechanism through which breast cancer cells induce IL-6 expression in tumor activated/educated macrophages. We further demonstrate that TAM derived IL-6 induces CSC enrichment in breast cancer via STAT3 pathway. Moreover, we establish that TAM derived IL-6 promotes metastasis, angiogenesis and tumor growth in breast cancer by in vitro and in vivo studies.

Therefore, we first activated macrophages (RAW264.7) by treatment with the CM of breast cancer cells (4T1) to convert them into tumor educated macrophages or tumor-associated macrophages (TAMs). Previously, our group have shown that tumor cell conditioned media can educate macrophages into tumor promoting type*.*

Several studies have shown that TAMs in the tumor micro-environment exhibit CD206 phenotype in different cancers . We observed that macrophages co-cultured with cancer cells exhibit higher CD206 expression indicating that cancer cells derived factor(s) modulated macrophages phenotype into TAMs. Further, to elucidate the mutual effect of crosstalk between macrophages and breast cancer cells, we emphasized on studying soluble factors secreted by these activated macrophages in response to CM of breast cancer cells by secretome analysis. The data revealed differential expression of cytokines and growth factors and remarkably IL-6 was among the top of ten upregulated cytokines in CM of activated macrophages.

Recent studies supported our observation and showed that TAMs exhibit high IL-6 expression in various cancers. TCGA analysis also demonstrated positive correlation between expression of TAM marker and IL-6. We further validated our secretomics data by ELISA, qPCR, FACS, immunofluorescence along with in vivo studies showing that TAMs demonstrate higher IL-6 expression at both transcriptional and translational levels as compared to normal macrophages. Most importantly, our data demonstrate that CM of 4T1 cells could induce IL-6 expression in mouse peritoneal macrophage suggesting that breast cancer cell can activate and enhance IL-6 expression in normal macrophages.

Overall, these data suggested that breast cancer induces IL-6 expression in TAMs.

Various reports have suggested the role of p38-MAPK pathway in regulation of IL-6 in macrophages. Wang et al. have demonstrated that Colistin, an immunostimulatory agent, can enhance IL-6 expression in macrophages by activating p38 MAPK pathway . Further, macrophages have been shown to express IL-6 in response to LPS via p38 MAPK pathway .

In light of this, we intended to study the role of breast cancer cells in regulation of p38-MAPK pathway in macrophages and the data suggested that activated macrophages have higher phosphorylation of p38 as compared to control.

The p38 pathway imparts its activity by inducing downstream molecules such as c-Jun and c-Fos and form heterodimeric complex AP-1 which can upregulate various downstream genes by binding to their promoter .

Interestingly, it has been reported that IL-6 promoter contains AP-1 binding sites suggesting the role of AP-1 in IL-6 expression in macrophages . ChIP analysis affirmed our results where pull

down of AP-1 using c-Jun antibody revealed enhanced binding of AP-1 in IL-6 promoter in CM of 4T1 treated RAW264.7 cells. In order to confirm the role of p38 signalling in regulation of IL-6 expression in TAMs, SB203580, a specific inhibitor of p38 MAPK was used.

Treatment with SB203580 resulted in abrogation of enhanced IL-6 expression in macrophages in response to CM of breast cancer cells as confirmed by in vitro studies. Thus, our results indicate that soluble factor derived from breast cancer cells can upregulate the expression of IL-6 in TAMs via p38 pathway through AP-1 mediated transcriptional regulation in TAMs. Previous literature has indicated the role of TAMs in regulation of CSCs and promotion of tumor growth.

Thus, we further examined the role of activated macrophages in breast CSC regulation and tumor progression. Our results exhibited that treatment with CM of activated macrophages induces expression of CSC specific markers (ALDH1 activity and Sca-1 expression) in breast cancer cells as compared to control. Further, an increase in expression of stem cell specific transcription factors Sox-2, Oct3/4 and Nanog in response to CM of activated macrophages validated these findings.

A plethora of studies have established that CSCs have property of mammospheres formation in suspension cultures due to their inherent anoikis resistant nature.

Our data revealed that CM of activated macrophages treated 4T1 cells form higher number of mammosphere than untreated cells hence confirming that activated macrophages induce CSC enrichment in breast cancer. Accumulated evidences have shown the role of IL-6 in progression of different types of cancers.

However, the function of IL-6 is paradoxical as it contributes in both pro and anti-tumorigenic activities. Interestingly, few reports have demonstrated the role of IL-6 in enrichment of CSC population leading to cancer progression.

Moreover, only few studies have explored the role of TAM derived IL-6 in regulation of CSCs specifically in breast cancer. We have shown here that recombinant IL-6 treatment enhanced CSC specific marker as well as transcription factor expression in breast cancer cells suggesting that IL-6 alone is able to induce CSC phenotype in breast cancer.

These results provide a clue that activated macrophage derived IL-6 may be one of the cytokines involved in CSC enrichment in breast cancer. Here, we observed enhanced expression of CSC specific markers, Sca-1 and ALDH1 which was abrogated in breast cancer cells when IL-6 was neutralized in the CM of activated RAW264.7 cells. These findings suggest that indeed TAM derive IL-6 induces CSC enrichment in breast cancer. Various reports have demonstrated that IL-6 regulates its various functions in different types of cancer primarily

3.4.2 IL-31

Now we consider IL-31 which is in the IL-6 family. As Takamori et al note:

IL-31, which is a member of the IL-6 family of cytokines, is produced mainly by activated CD4+T cells, in particular activated Th2 cells, suggesting a contribution to development of type-2 immune responses. IL-31 was reported to be increased in specimens from patients with atopic dermatitis, and IL-31-transgenic mice develop atopic dermatitis-like skin inflammation, which is involved in the pathogenesis of atopic dermatitis. However, the role of IL-31 in development of contact dermatitis/ contact hypersensitivity (CHS), which is mediated by hapten-specific T cells, including Th2 cells, is not fully understood.

Therefore, we investigated this using IL-31-deficient (Il31−/−) mice, which we newly generated. We demonstrated that the mice showed normal migration and maturation of skin dendritic cells and induction of hapten-specific T cells in the sensitization phase of FITC-induced CHS, and normal induction of local inflammation in the elicitation phase of FITC- and DNFB-induced CHS. On the other hand, those mice showed reduced scratching frequency and duration during FITC- and/or DNFBinduced CHS. Our findings suggest that IL-31 is responsible for pruritus, but not induction of local skin inflammation, during CHS induced by FITC and DNFB.

From Datsi et al,

The first major role of IL-31 was described in an induced mouse model of atopic dermatitis (AD), where it was reported to cause cutaneous inflammation*.*

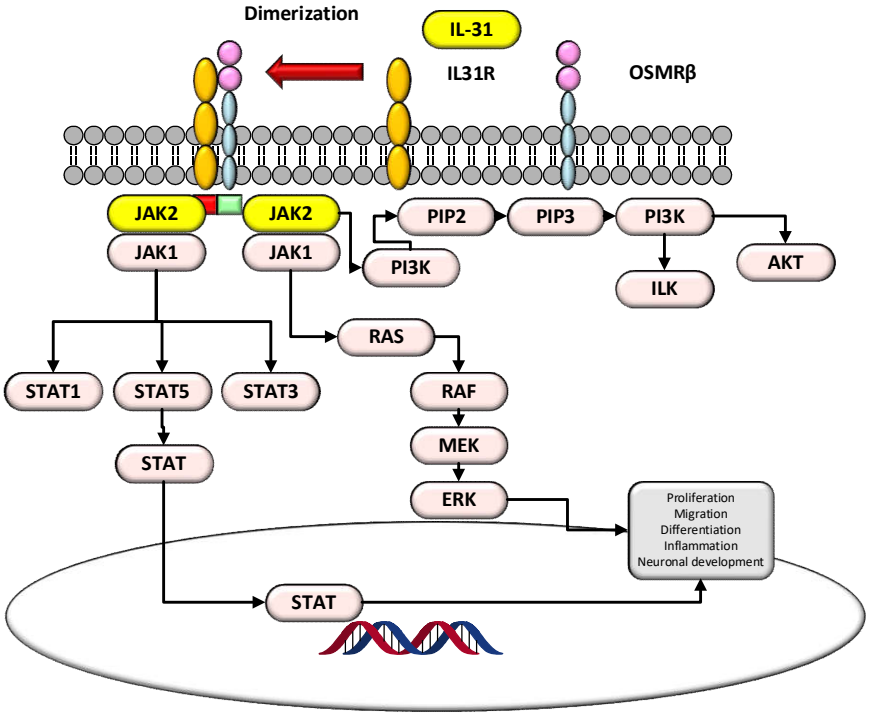
Since this initial observation, IL-31 and its respective receptor heterodimer IL-31 receptor A (IL31RA)/ Oncostatin M receptor β (OSMRβ) have been studied for their role in tissue homeostasis, inflammation, immune defense, neuroimmune circuits, and pruritus.2 IL-31 belongs to the family of IL-6-derived cytokines, a cytokine family commonly clustered based on their pro-inflammatory character and a shared signaling pathway engaging in gp130 receptor subunit activation.

The IL-6 cytokine family is often referred to as the gp130/IL-6 family of cytokines, which includes IL-6, IL-11, IL-21, IL-27, neuropoietin, ciliary inhibitory factor, cardiotropin-1, leukemia inhibitory factor, oncostatin M (OSM), and IL-31.

Besides IL-31, IL-6 family cytokines signal through a heterodimeric receptor composed of two subunits of which one typically is gp130.3 IL-31 interacts with a heterodimer complex that is composed of the gp130-like subunit IL31RA and OSMRβ.1 The OSMRβ subunit is widely expressed throughout the mammalian body, whereas IL31RA expression is predominantly observed in epithelial and neuronal cell types.

In humans, IL31RA forms either a long or a short isoform, with the short isoform resuming a non-signaling inhibitory function. In rodents, only the long isoform has been detected.4 Engagement of OSM or IL-31 with the IL31RA/OSMRβ heterodimer initiates activation of canonical JAK/STAT, Akt/PI3K, and MAPK-JNK/p38 pathways. The physiological function of IL-31 is still not fully understood. However, a role for IL-31 has been proposed in various inflammatory

They then present a set of cell dynamics as shown below:



As O'Hehir et al note:

Pruritus is a hallmark of AD, and the underlying processes involved are complex. Mice that overexpress the T cell–derived cytokine IL-31 develop intense pruritus and dermatitis, and patients with AD have CLA+ T cells that produce higher levels of IL-31.

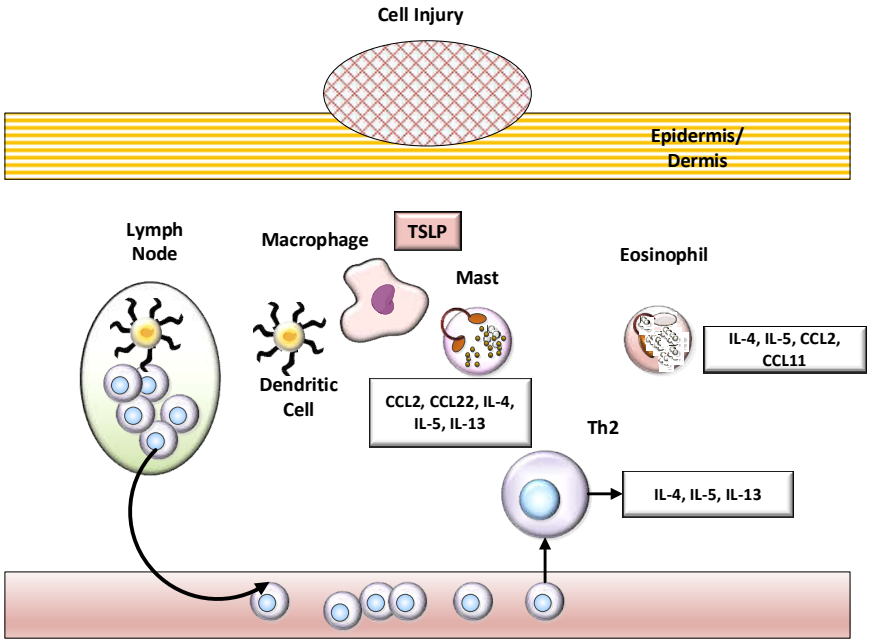
In patients with AD as well as allergic contact dermatitis (ACD, another pruritic dermatosis), expression of IL-31 is associated with expression of IL-4 and IL-13, which are Th2 cytokines that characterize the atopic phenotype. In addition, S. aureus superantigen rapidly induces IL-31 expression in atopic individuals, and because patients with AD are heavily colonized with toxin-producing S. aureus, this can further contribute to their pruritus.

Calcineurin inhibitors and other agents that target T cells are effective at reducing pruritus in AD patients, and new insights into the role of IL-31 in AD may reveal new targets for anti-pruritic therapy. Increasingly, as previously discussed, the keratinocyte-derived cytokine TSLP has been recognized as the 'master switch' for allergic inflammation. In AD the TSLP-induced Th2 cytokine milieu can participate in a vicious cycle impacting the skin barrier and microbial colonization. Genetic variants in TSLP have been shown to be associated with AD and eczema herpeticum.

The authors continue:

Chemokines and atopic dermatitis. Atopic dermatitis begins with intense pruritus, chronic scratching, and mechanical injury to the skin. Mechanical trauma leads to mast cell release of Th2 cytokines and CC chemokines and upregulates local TSLP production, whilst loss of normal

barrier function increases exposure to allergens and SEB. TSLP-activated dendritic cells travel to the draining lymph nodes and promote Th2 cell differentiation. Th2 cells enter the skin and release Th2 cytokines, thus amplifying the allergic response in the skin.



3.4.3 Cytokines in NK cells

NK cells are potent cytokine generators. As Lacy and Stow have noted:

The production and release of cytokines from innate immune cells are critical responses to inflammation and infection in the body. Innate immune cells comprise populations of white blood cells such as circulating dendritic cells (DCs), neutrophils, natural killer (NK) cells, monocytes, eosinophils, and basophils, along with tissue-resident mast cells and macrophages.1

Residing at the frontline of defense in immunity, these cells control opportunistic invasion by a wide range of viral, fungal, bacterial, and parasitic pathogens, in part by releasing a plethora of cytokines and chemokines to communicate with other cells and thereby to orchestrate immune responses.

This array of soluble mediators secreted by different innate immune cells includes TNF, IFN, interleukins IL-1, IL-4, IL-6, IL-10, IL-12, IL-18, CCL4/RANTES, and TGF. Cytokine release can be directly evoked by immunoglobulin- or complement receptor-mediated signaling or by pathogens through a diverse array of cellular receptors, including pattern recognition receptors such as TLRs.1,2 The Gram-negative bacterial coat component lipopolysaccharide (LPS), the main culprit behind toxic shock syndrome and sepsis, is a highly potent trigger of cytokine secretion through TLR4. For the immune system to function appropriately, the synthesis and

release of cytokines must be highly regulated and sequentially and temporally orchestrated. Thus, cascades of cytokines released by innate immune cells initially mount inflammatory or allergic responses and then later ensure that the responses subside in a timely fashion.3 Proinflammatory cytokines also serve to recruit and active T lymphocytes and other cells to mount adaptive immune responses.

However, even with the overwhelming and detailed literature on cytokine actions, just how cytokines are released or secreted by innate immune cells remains a significant "black box" in immunology. Most diagrams in textbooks and reviews show a simple arrow indicating cytokine release from a given cell type after activation of a signaling cascade in response to receptor stimulation. Perhaps surprisingly, the precise mechanisms of cytokine trafficking and release remain obscure in most cell types.

3.5 HYPERSENSITIVITY: IMMUNE RELATED PRURITUS SYNDROMES

Hypersensitivity reactions may provide some paradigms for dealing with the itch issue. Hypersensitivity is generally understood to be the bodies self-attack as a result of a repetitive attack by an antigen. As Abbas et al have noted:

The immune system serves the important function of host defense against microbial infections, but immune responses are also capable of causing tissue injury and disease. Disorders caused by immune responses are called hypersensitivity diseases. This term arose from the clinical definition of immunity as sensitivity, which is based on the observation that an individual who has been exposed to an antigen exhibits a detectable reaction, or is sensitive, to subsequent encounters with that antigen.

Pathologic, or injurious and excessive, reactions were then called hypersensitivity. Normally, immune responses eradicate infectious pathogens without serious injury to host tissues. However, these responses are sometimes inadequately controlled, inappropriately targeted to host tissues, or triggered by commensal microorganisms or environmental antigens that are usually harmless. In these situations, the normally beneficial immune response is the cause of disease.

Perhaps then, the recurrent intractable itch we see in cancer patients is the immune system being attacked again and again by the antigens generated by the cancer cells. We also know that there are four general classes of hypersensitivity reactions. They are:

1. Immediate or Type 1: These are the hypersensitivity reactions involving Th1 cells and IgE antibodies with the interaction of mast cells and the resulting emission of massive amounts of cytokines.
2. Antibody Mediated or Type 2: In this case we have involvement of IgM and IgG resulting in opsonization of cells. The attack here is against self cells. This included pemphigus vulgaris, thrombocytopenic purpura, hemolytic anemia, myasthenia gravis, Grave's disease, Goodpasture syndrome.

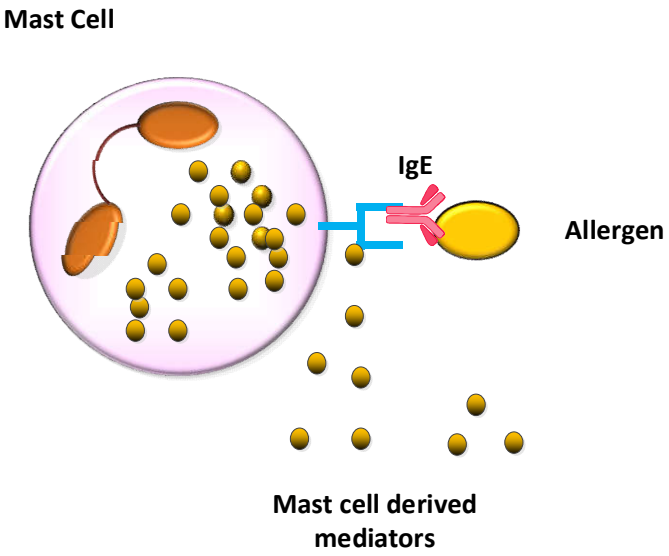
3. Immune Complex or Type 3: In this case the immune complexes of IgM and IgG in the blood stream result in the recruitment and activation of leukocytes. The diseases seen here are lupus, polyarteritis nodosa, serum sickness and glomerulonephritis.
4. T cell mediated or Type 4: This is an attack by CD4+ and/or CD8+ T cells with the release of cytokines. It is a delayed action. Here we have organ types such as RA, MS, T1 diabetes, psoriasis. Psoriasis is a possible proto-example for the intractable itch syndrome.

From Abbas et al (Table 19.1) we have the following Table depicting the four major categories:

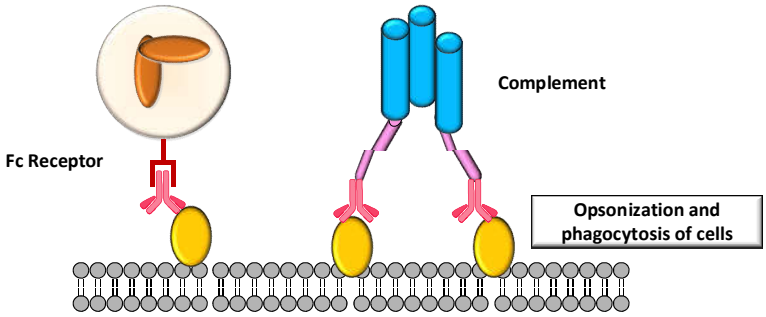
Type of Hypersensitivity	Pathologic Immune Mechanisms	Mechanisms of Tissue Injury and Disease
Immediate: Type I	IgE antibody, Th2 cells	Mast cells, eosinophils, and their mediators (vasoactive amines, lipid mediators, proteolytic enzymes, cytokines)
Antibody-mediated: Type II	IgM, IgG antibodies against cell surface or extracellular matrix antigens	Opsonization and phagocytosis of cells Complement- and Fc receptor–mediated recruitment and activation of leukocytes (neutrophils, macrophages) Abnormalities in cellular functions, for example, hormone receptor signaling, neurotransmitter receptor blockade
Immune complex–mediated: Type III	Immune complexes of circulating antigens and IgM or IgG antibodies	Deposition in blood vessel walls and tissues Complement-mediated and Fc receptor–mediated recruitment and activation of leukocytes
T cell–mediated: Type IV	$CD4^+$ T cells (Th1 and Th17 cells) $CD8^+$ CTLs	Cytokine-mediated inflammation and macrophage activation Direct target cell killing, cytokine-mediated inflammation

We depict the four types graphically below:

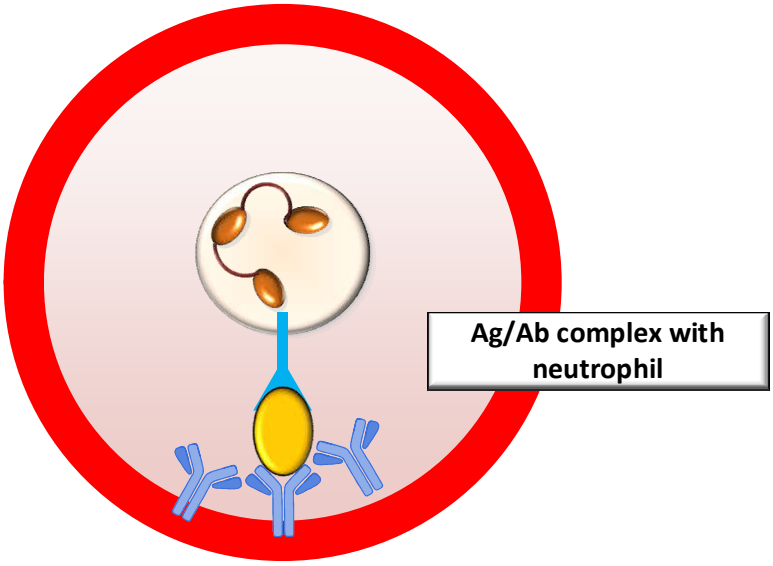
Type 1: This is dominated by the mast cell release of cytokines. The mast cells are activated by antigens and an almost instantaneous release occurs.



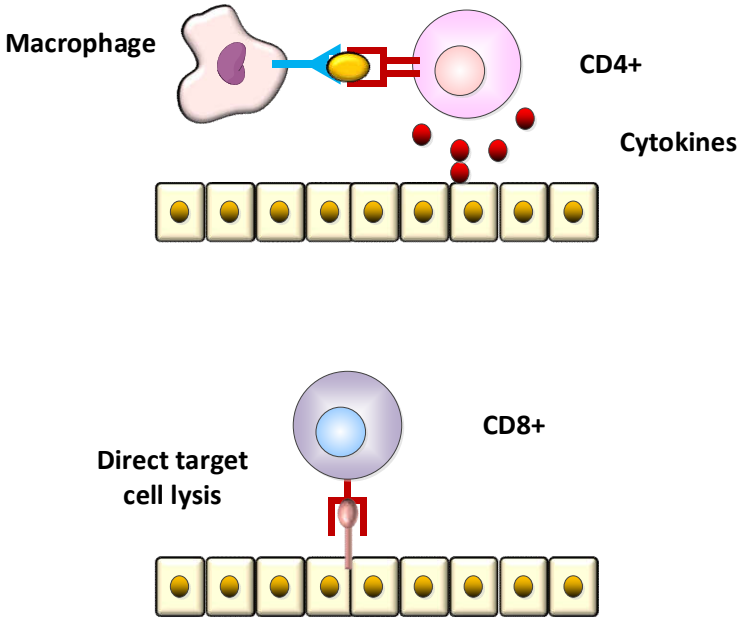
Type 2: Opsonization is the attack of the antibodies on the surface of a cell carrying an Ag. Unlike neutralization, this attacks the cell whereby damage from hypersensitivity occurs.



Type 3: This class occurs primarily in the blood stream where Ab are attached to the wall and the reaction results in damage there.



Type 4: This is a delayed release. One need just think of the poison ivy effect, first exposure, and then a delayed but intense hypersensitivity reaction.



3.6 ATOPIC DERMATITIS

We often try to use analogs to understand an existing disease. This does not always work but in this case it may be worth the effort. Atopic dermatitis, AD, is a disease that commences almost always in childhood and reflects itself with both skin lesions and often intractable itch syndrome. As Stander notes:

Atopic dermatitis is one of the most prevalent inflammatory skin diseases. It usually develops in childhood and may persist into adult hood; less frequently, it starts in midlife or late life. The disorder is characterized by recurrent, pruritic, localized eczema, often with seasonal fluctuations. Many patients also have allergic asthma, allergic rhino-conjunctivitis, food allergies, and other immediate hypersensitivity (type 1) allergies.

The disease was described and termed atopic dermatitis in the 1930s, with "atopic" reflecting the Greek word atopos ("without place") to indicate the frequent, concomitant occurrence of IgE-mediated hypersensitivity reactions such as asthma. Atopic dermatitis remains the preferred term for the disorder, but several other labels have been used, including atopic eczema, neurodermatitis, atopiform dermatitis, and most commonly, eczema.

As Leung at al note:

Atopic dermatitis (AD) is a chronic inflammatory skin disease associated with cutaneous hyperreactivity to environmental triggers that are innocuous to normal nonatopic individuals. Although written descriptions of AD date back to the early 1800s, an objective laboratory test does not exist for AD.

The diagnosis of AD is based on the following constellation of clinical findings: pruritus, facial and extensor eczema in infants and children, flexural eczema in adults, and chronicity of the dermatitis. AD usually presents during early infancy and childhood, but it can persist into or start in adulthood. The lifetime prevalence of AD is 10–20% in children and 1–3% in adults. Its prevalence has increased two- to threefold during the past three decades in industrialized countries but remains much lower in countries with predominantly rural or agricultural areas. Wide variations in prevalence have been observed within countries inhabited by groups with similar genetic backgrounds, suggesting that environmental factors play a critical role in determining expression of AD.

A precise understanding of the mechanisms underlying AD is critical for development of more effective management strategies. Various studies indicate that AD has a complex etiology, with activation of multiple immunologic and inflammatory pathways. The clinical phenotype that characterizes AD is the product of complex interactions among susceptibility genes, the host's environment, defects in skin barrier function, and systemic and local immunologic responses.

An understanding of the relative role of these factors in the pathogenesis of AD has been made possible by a variety of approaches, including the analysis of cellular and cytokine gene expression in AD skin lesions in humans as well as gene knockout and transgenic mouse models of candidate genes in AD. The current review will summarize progress in our understanding of the pathophysiology of AD and implications for therapy. Atopy as a systemic disease Several observations suggest that AD is the cutaneous manifestation of a systemic disorder that also gives rise to asthma, food allergy, and allergic rhinitis.

These conditions are all characterized by elevated serum IgE levels and peripheral eosinophilia. AD is often the initial step in the so-called "atopic march," which leads to asthma and allergic rhinitis in the majority of afflicted patients. In experimental models of AD, the induction of

allergic skin inflammation by epicutaneous application of allergens has been found to augment the systemic allergic response and airway hyperreactivity characteristic of asthma. At least two forms of AD have been delineated: an "extrinsic" form associated with IgE-mediated sensitization involving 70–80% of the patients, and an "intrinsic" form without IgE-mediated sensitization involving 20–30% of the patients.

Both forms of AD have associated eosinophilia. In extrinsic AD, memory T cells expressing the skin homing receptor, cutaneous lymphocyte-associated antigen (CLA), produce increased levels of Th2 cytokines. These include IL-4 and IL-13, which are known to induce isotype switching to IgE synthesis, as well as IL-5, which plays an important role in eosinophil development and survival. These CLA+ T cells also produce abnormally low levels of IFN-γ, a Th1 cytokine known to inhibit Th2 cell function. Intrinsic AD is associated with less IL-4 and IL-13 production than extrinsic AD.

As Stander has recently noted:

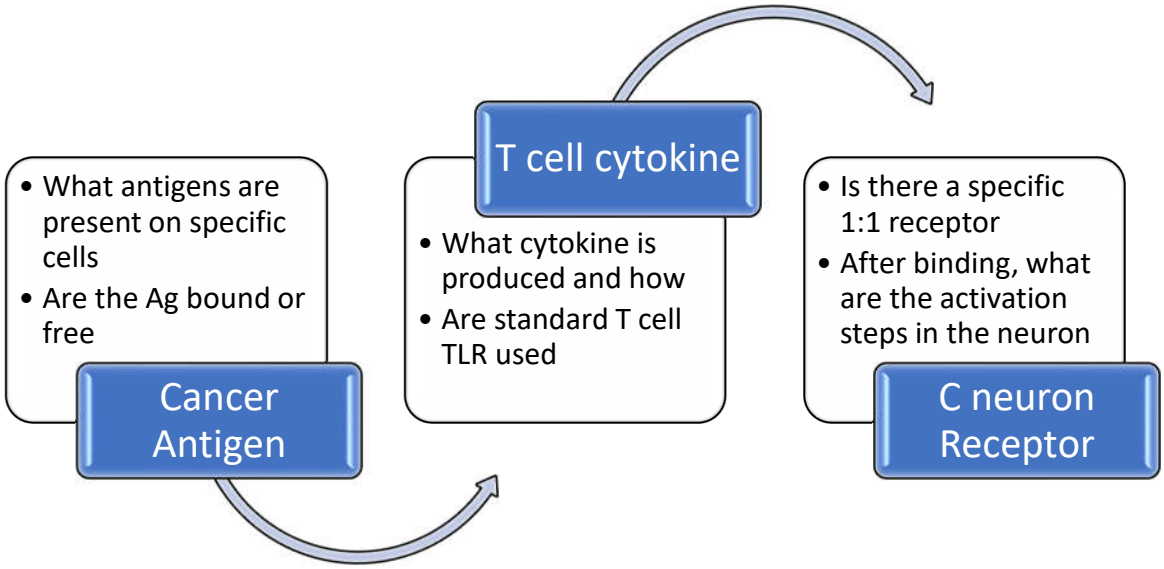
Pruritus is a hallmark of atopic dermatitis, and the intensity of the itching broadly corresponds to the severity of the disease. Pruritus is aggravated by stress, sweating from physical activity or environmental heat, and humidity, as well as from contact with woolen clothes. Pruritus-related scratching induces excoriations, bleeding, or the formation of hemorrhagic crusts. Persistent scratching leads to lichenification as well as prurigo nodularis, which is characterized by generalized, severely itchy nodules

Thus, it does beg the question as to some underlying cause and commonality.

4 CANCER RELATED

Cancer cells often have antigen compounds on their surface which then activate T cells as we discussed previously. The T cell activation result in cytokines which in turn activate the itch response on the C neurons in the skin. This simplistic view however lacks a great deal of specificity. Understanding of cancer cell antigens is evolving rapidly and success in cases such as melanoma and breast cancer has allowed for Mab approaches to therapeutics. However this has not led to an understanding of what specific Ag drive the itch process. Thus at best we can accomplish is establishing an awareness of what is known and suggest lines of research to see what the connection is.

Simply stated, the problem is as below:



This section of our paradigm is now discussed. It must be noted that many of the underlying elements are yet to be fully understood. As a result we have some conjecture mixed with experimental fact.

4.1 CANCER CELL ANTIGENS

Cancer cells generate Ags as a result of the genetic mutations and changes that result in a malignant presentation. As Olsen et al noted there is a substantial body of data on tumor T cell Ag. They note:

Tumor T cell antigens are both diagnostically and therapeutically valuable molecules. A large number of new peptides are examined as potential tumor epitopes each year, yet there is no infrastructure for storing and accessing the results of these experiments. We have retroactively

cataloged more than 1000 tumor peptides from 368 different proteins, and implemented a web-accessible infrastructure for storing and accessing these experimental results.

All peptides in TANTIGEN are labeled as one of the four categories:

(1) peptides measured in vitro to bind the HLA, but not reported to elicit either in vivo or in vitro T cell response,

(2) peptides found to bind the HLA and to elicit an in vitro T cell response,

(3) peptides shown to elicit in vivo tumor rejection, and

(4) peptides processed and naturally presented as defined by physical detection.

In addition to T cell response, we also annotate peptides that are naturally processed HLA binders, e.g., peptides eluted from HLA in mass spectrometry studies.

4.2 SPECIFIC MALIGNANCIES

We now consider several specific malignancies. As Coulie et al had noted:

Overexpression of proteins in tumours may provide an opportunity for a specific T cell response. This is because a threshold level of antigen is required for recognition by T cells. If tumour cells present an amount of peptide–HLA complexes that is above the threshold and if normal cells do not, a specific antitumoural T cell response could occur. However, such tumoural overexpression is difficult to rigorously show.

Quantitative reverse transcription PCR of tumoural and normal tissues can provide a useful indication of appropriate overexpression. However, this approach provides average values for expression within tissues, and it is therefore difficult to rule out that a high expression occurs in a small subset of cells from normal tissues. Immunohistochemical analysis can offer complementary information but is not easily amenable to quantification.

The oncogene and growth factor receptor ERBB2 (also known as HER2 and NEU) is overexpressed in many epithelial tumours, including ovarian and breast carcinomas, owing to increased transcription and to gene amplification. Several antigenic peptides have been defined.

Vaccination with these peptides in a therapeutic and adjuvant setting does not seem to produce harmful side effects in patients with breast cancer.

Treatment of patients with breast cancer with trastuzumab (Herceptin; Genentech), which is an antibody that blocks ERBB2, might also trigger immune responses that target the receptor.

The gene that encodes the transcription factor Wilms' tumour protein (WT1) is expressed at a 10-fold to 1,000-fold higher level in leukaemic cells than in normal cells. After birth, it is mainly

expressed in kidney podocytes and CD34+ haematopoietic stem cells. Patients with leukaemia received an allogenic haematopoietic cell transplant, followed by an infusion of donorderived CTL clones that recognized peptide WT1 on HLA-A2. A decrease in the number of leukaemic cells was observed, without evidence of autoimmune toxicity. An interesting case of protein overexpression on most adenocarcinomas is mucin 1 (MUC1), which also presents tumourspecific glycoforms that bear novel T cell and B cell epitopes

4.2.1 Breast Cancer

Breast cancer is the greatest cancer amongst women and in fact almost 1 in 8 women will be diagnosed with this. As Morisaki et al have noted:

Neoantigens are tumour-specific antigens that arise from non-synonymous mutations in tumour cells. However, their effect on immune responses in the tumour microenvironment remains unclear in breast cancer.

We performed whole exome and RNA sequencing of 31 fresh breast cancer tissues and neoantigen prediction from non-synonymous single nucleotide variants (nsSNVs) among exonic mutations. Neoantigen profiles were determined by predictive HLA binding affinity (IC50 < 500 nM) and mRNA expression with a read count of ≥ 1. We evaluated the association between neoantigen load and expression levels of immune-related genes.

Moreover, using primary tumour cells established from pleural fluid of a breast cancer patient with carcinomatous pleurisy, we induced cytotoxic T lymphocytes (CTLs) by coculturing neoantigen peptide-pulsed dendritic cells (DCs) with autologous peripheral lymphocytes. The functions of CTLs were examined by cytotoxicity and IFN-γ ELISpot assays.

Neoantigen load ranged from 6 to 440 (mean, 95) and was positively correlated to the total number of nsSNVs. Although no associations between neoantigen load and mRNA expression of T cell markers were observed, the coculture of neoantigen-pulsed DCs and lymphocytes successfully induced CTLs ex vivo.

***These results suggest that neoantigen analysis may have utility in developing strategies to elicit T cell responses**.*

4.2.2 Hematological

From DiSalvo et al:

***Pruritus is one of the most common symptoms experienced by neoplastic patients**.*

The pathogenesis of neoplastic itch is complex and multifactorial and could be due to an unbalanced production of humoral mediators by altered immune effector cells.

IL-31 is a pro-inflammatory cytokine produced by CD4+T helper cells.

The aim of this review was to evaluate the role of this Th2 cytokine and its receptor IL-31RA, in the onset of neoplastic pruritus. We analysed scientific literature looking for the most relevant original articles linking IL-31to itch in oncologic diseases. Interleukin-31 seems to be a main itch mediator in several hematologic disease such as Cutaneous T cells lymphomas.

In these patients IL-31 was positively linked to itch level, and IL-31 matched with disease stage. IL-31 seems to play an important role in the signalling pathway involved in pruritus, but it is also suggested to play a proinflammatory and immunomodulatory role which could play a part in the progression of the neoplastic disease.

Further studies will be fundamental in facing pruritus in oncologic patients, since this problem compromise their quality of life worsening an already critic picture *...*

Cutaneous T cells lymphoma (CTCL) have been associated to augmented levels of pro-inflammatory cytokines and among these, a Th2 cytokine called interleukin 31 (IL-31) appeared particularly involved. Interleukin (IL)-31, a cytokine cloned by Dillon et al. in 2004, is primarily secreted by activated T cells, especially T helper Th2 cells (CD4+CXCR3- CCR4+CCR6-cells) .

Recently, it was reported that the IL-31 receptor is expressed in the peripheral nerves of mice and humans , suggesting that IL-31 secreted by Th2 cells may influence right peripheral nerves, triggering the pruritus linked to atopic dermatitis (AD).

This cytokine, in fact, belong to the IL-6 family, and have been frequently associated to pruritic skin diseases *.*

CD45RO+cutaneous T lymphocytes are responsible for IL-31 production. Its receptor is IL-31R, which is heterodimeric and ubiquitously represented. It has 2 subunits, the IL-31 receptor alpha (IL-31RA) and the oncostatin-M receptor beta (OSMR). These two subunits are expressed by IL-31-activated monocytes.

Firstly IL-31 was thought to be secreted only by Th2 and Th1 lymphocytes; recently also mast cells were reported being capable of producing IL-31, as well as monocytes, macrophages, and monocyte-derived dendritic cells and human mast cells. According to these data, innate and adaptive immunity appear to be linked to this interleukin role, in particularly when skin is involved. More specifically, intracellular signaling involving the IL-31receptor by IL-31 is facilitated by the Janus kinase (JAK)-signal transducer and activator of transcription (STAT), phosphatidylinositol-3 kinase (PI3K)/AKT, and mitogen-activated protein kinase (MAPK) pathways .

The lone phosphorylation of extracellular signal-regulated kinase 1/2 (ERK1/2) is not sufficient to stimulate JAK1/JAK2 and STAT3 . Additionally, it was observed that missense mutations in the OSMR β gene were isolated in patients of familial primary localized cutaneous amyloidosis (FPLCA), hereditary skin disease associated with severe pruritus and deposition of amyloid material in the dermis . OSMRβ is a component of IL-31R and OSM type II receptor. FPLCA keratinocytes were stimulated with OSM and IL-31, the expression levels of phosphorylated STATs, ERK1/2, and AKT were diminished. JAK/STAT, ERK1/2 and PI3K/ AKT signaling

pathway have anti-apoptotic effect in several tumor cell lines; so apoptosis and accumulation of degenerate keratinous material deposition in the dermis are a possibility in the OSMRβ mutated FPLCA patients.

These data indicated that OSM and IL-31 signaling are involved in keratinocyte cell proliferation, differentiation, apoptosis and inflammation

4.2.3 Melanoma and Other Skin Cancers.

It is well known that moles that itch have a propensity to be malignant melanomas[8]. In a similar manner squamous cell cancers are also demonstrative of itch syndromes[9].

4.3 CHEMOTHERAPEUTIC/TARGETED THERAPY/IMMUNOTHERAPY

In addition to the cancers themselves, we also note treatment related itch phenomenon. This has been well observed and the exact cause of such effects is not fully understood. For example in the taxanes the cause may be from the chemotherapy per se or it may be driven by the breakdown of the tumors and the Ag created therein.

We have observed the itch phenomenon in breast cancer patients where the itch was established just before diagnosis, and became intractable after the full course of paclitaxel.

As Sibaud et al have noted:

Taxanes (docetaxel and paclitaxel) are among the most commonly prescribed anticancer drugs approved for the treatment of metastatic or locally advanced breast, non-small cell lung, prostate, gastric, head and neck, and ovarian cancers, as well as in the adjuvant setting for operable nodepositive breast cancers.

Although the true incidence of dermatological ***adverse events (AEs)*** *in patients receiving taxanes is not known, and has never been prospectively analysed, they clearly represent one of the major AEs associated with these agents.*

With an increase in the occurrence of cutaneous AEs during treatment with novel targeted and immunological therapies when used in combination with taxanes, a thorough understanding of reactions attributable to this class is imperative.

Moreover, identification and management of dermatological AEs is critical for maintaining the quality of life in cancer patients and for minimizing dose modifications of their antineoplastic regimen. This analysis represents a systematic review of the dermatological conditions reported with the use of these drugs, complemented by experience at comprehensive cancer centres. The conditions reported herein include skin, hair, and nail toxicities.

[8] See Abbasi et al.

[9] See Alam and Rattner

Lastly, we describe the dermatological data available for the new, recently FDA-and EMA-approved, solvent-free nab-paclitaxel

Similar results also come with radiation treatment.

5 THERAPEUTICS

There are frankly few therapeutics for intractable itching in many cancer patients. Part of the problem is a lack of understanding the scientific basics as well as there being no focus on the problem. For example, atopic dermatitis (AD), has received attention albeit of still limited extent. Yet for cancer patients the itch syndrome may be worse than the sequellae from the underlying cancer itself. Oncologists are no prepared to deal with the issue, they treat the cancer per protocol, dermatologists are not generally able to deal with non-demagogical issues and the internists are all too often focusing on other issues.

The therapeutic approaches fall within three general categories.

Symptomatic: Many of these try to emulate the symptomatic approaches for the more common varieties of itching. Namely emoluments, steroidal, and the like.

Secondary: These are directed at attacking secondary organs such as the use of anti-depressants and substances like gabapentin.

Targeted: These target the specific sources of the itch syndrome such as IL-31. Typically we see Mabs as therapeutic vehicles.

5.1 SYMPTOMATIC

As Tivoli and Rubenstein had noted some of the classes of symptomatic mediators are:

Topical therapies.

***Capsaicin cream**. Capsaicin cream can be effective for itching because it desensitizes neurons in the skin by activating the release of substance P from type C nociceptive fibers. However, the major side effect of capsaicin cream is the transient burning sensation secondary to the release of substance P at the application site. This burning sensation has been the cause of nonadherence in 30 percent of patients.*

Use of the topical anesthetic, lidocaine, prior to applying capsaicin cream may counteract this side effect, but should be limited to only a few days so as to avoid contact dermatitis and systemic absorption resulting in cardiac arrhythmias.

Alternatively, more frequent application of capsaicin cream during initial treatment of pruritus can help bring about desensitization in a shorter period of time.

Capsaicin has been shown to be effective for localized itching as in nostalgia paresthetica,2 brachioradial pruritus, and uremia.

Menthol and phenol. *Menthol and phenol are agents that have been added to aqueous cream to form a 1 to 2% compound cream that will activate nerve fibers to transmit a cool sensation. This cooling sensation can reduce the perception of itching.*

Topical corticosteroids. *Topical corticosteroids alleviate pruritus that is secondary to inflammatory disorders. However, their usefulness is limited to short-term treatment given that they can cause adverse effects, such as telangiectasia, atrophy, and striae if used long term.*

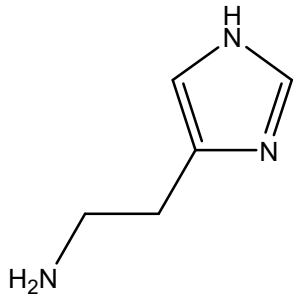
Aspirin. *A study of the use of topical 3% aspirin solution conducted on patients with chronic localized itch demonstrated significant reduction in pruritus. Salicylic acid. Topical salicylic acid in combination with topical immunomodulators, such as tacrolimus and pimecrolimus, may be effective in reducing itch. New possibilities in the reduction of itch for patients with atopic dermatitis include topical agents that inhibit serine proteases and those that inhibit nerve growth factor and neurotrophin.*

5.2 SECONDARY

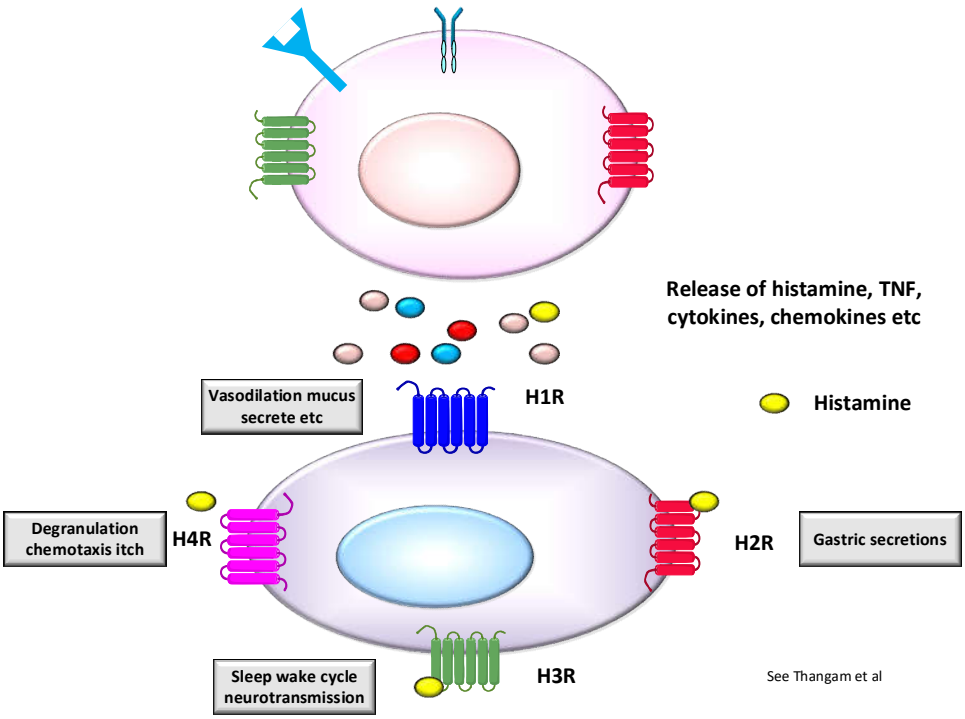
As Tivoli and Rubenstein had noted some of the classes of secondary mediators are:

5.2.1 Histamine.

Histamine is released by cells and then can aggravate other cells especially nerve endings. Histamine is shown below:



In turn the graphic below demonstrates the various H receptors on cells. H1 through H4 depict the receptors for each of the histamine actions.



Tivoli and Rubenstein state:

The most notable itch-mediating substance is histamine. It is stored in mast cells and keratinocytes.

In the 1920s, Sir Thomas Lewis demonstrated that intradermal injection of histamine elicited itch and a vascular response with erythema, wheal, and flare. These are the symptoms exhibited in urticaria. Antihistamines usually treat the symptoms of urticaria, but some cases respond poorly, indicating there are other mediators, such as cytokines and chemokines.

Though efficacious, the actual role of antihistamines in reducing itch may be due more to the sedative effect. It seems nonsedating antihistamines do not have any effect on itching dermatoses absent of erythema and wheal formation. Histamine can also be released via immunoglobulin E receptors, complement, C5a, and tachykinins, including the neuropeptide substance P (SP).4 Histamine displays tachyphylaxis upon repeated injection of histamine, and thus it generally will not mediate chronic persistent itch. Serotonin (5-HT). Serotonin (5-HT) is another amine compound stored in human platelets.

It is released when platelets aggregate. This substance may regulate itch by acting on 5-HT3 receptors. A placebo-controlled study of a 5-HT3 antagonist, ondansetron, demonstrated significant reduction in itch 30 to 60 minutes after the drug was administered and lasted up to six hours.4 Acetylcholine. Acetylcholine, a neurotransmitter, stimulates histamine-sensitive and insensitive C-fibers. The flare response with intradermal injection of acetylcholine is smaller than that of histamine injection. Studies have demonstrated that patients with atopic dermatitis

have increased sensitivity to acetylcholine versus normal subjects. Normal patients experienced pain upon administration of acetylcholine injection, but the atopic subjects experienced itching.

Receptor	Function	Antagonists
H1	ileum contraction modulate circadian cycle itching systemic vasodilatation bronchoconstriction (allergy-induced asthma)	H1-receptor antagonists Diphenhydramine Loratadine Cetirizine Fexofenadine Clemastine Rupatadine
H2	speed up sinus rhythm Stimulation of gastric acid secretion Smooth muscle relaxation Inhibit antibody synthesis, T-cell proliferation and cytokine production	H2-receptor antagonists Ranitidine Cimetidine Famotidine Nizatidine
H3	Decrease Acetylcholine, Serotonin and Norepinephrine Neurotransmitter release in CNS Presynaptic autoreceptors	H3-receptor antagonists ABT-239 Ciproxifan Clobenpropit Thioperamide
H4	mediate mast cell chemotaxis.	H4-receptor antagonists Thioperamide JNJ 7777120

The Table below provides further detail regarding each of the receptors.

Receptor	Location	Function
H1	• **CNS:** Expressed on the dendrites of the output neurons of the histaminergic tuberomammillary nucleus, which projects to the dorsal raphe, locus coeruleus, and additional structures. • **Periphery:** Smooth muscle, endothelium, sensory nerves	• **CNS:** Sleep-wake cycle (promotes wakefulness), body temperature, nociception, endocrine homeostasis, regulates appetite, involved in cognition • **Periphery:** Causes bronchoconstriction, bronchial smooth muscle contraction, urinary bladder contractions, vasodilation, promotes hypernociception (visceral hypersensitivity), involved in itch perception and urticaria.
H2	• **CNS:** Dorsal striatum (caudate nucleus and putamen), cerebral cortex (external layers), hippocampal formation, dentate nucleus of the cerebellum • **Periphery:** Located on parietal cells, vascular smooth muscle cells, neutrophils, mast cells, as well as on cells in the heart and uterus	• **CNS:** Not established (note: most known H_2 receptor ligands are unable to cross the blood-brain barrier in sufficient concentrations to allow for neuropsychological and behavioral testing) • **Periphery:** Primarily involved in vasodilation and stimulation of gastric acid secretion. Urinary bladder relaxation. Modulates gastrointestinal function.
H3	Located in the central nervous system and to a lesser extent peripheral nervous system tissue	Autoreceptor and hetero receptor functions: decreased neurotransmitter release of histamine, acetylcholine, norepinephrine, serotonin. Modulates nociception, gastric acid secretion, and food intake.
H4	Located primarily on basophils and in the bone marrow. It is also expressed in the thymus, small intestine, spleen, and colon.	Plays a role in mast cell chemotaxis, itch perception, cytokine production and secretion, and visceral hypersensitivity. Other putative functions (e g., inflammation, allergy, cognition, etc.) have not been fully characterized.

As Thangam et al have noted:

Mast cells are the major producer of histamine and express a vast array of receptors on their surface such as FcεR1, FcγRI, and receptors for complement components (C3aR and C5aR), nerve growth factor (NGF) (Trk A), substance P, vasoactive intestinal peptide (MrgX2), adenosine phosphate, etc..

Activation through these receptors by their respective stimulants, such as allergens, complement peptides C3a, C5a , NGF , neuropeptides, adenosine mono-phosphate activate human cord blood-derived mast cells to release various inflammatory mediators including histamine.

Histamine can also be produced by basophils and other immune cells but much higher concentrations of histamine may be found in intestinal mucosa, skin, and bronchial tissues.

Histamine regulates a plethora of pathophysiological and physiological processes, such as secretion of gastric acid, inflammation, and the regulation of vasodilatation and bronchoconstriction . In addition, it can also serve as a neurotransmitter ….

The H1R is ubiquitously expressed and is involved in allergy and inflammation. H1R is expressed in many tissues and cells, including nerves, respiratory epithelium, endothelial cells, hepatic cells, vascular smooth muscle cells, dendritic cells, and lymphocytes.

Histamine activates H1R through Gαq/11, which then activates phospholipase C and increases intracellular Ca++ levels. As a consequence, histamine elicits the contraction of smooth muscle of the respiratory tract, increases vascular permeability, and induces the production of prostacyclin and platelet activating factor by activating H1R…

The Gαs-coupled H2R is highly expressed in various cells and tissues, such as B cells, T cells, dendritic cells, gastricparietal cells, smooth muscle cells, and the brain and cardiac tissues. Activation of the receptor can induce airway mucus production, vascular permeability, and secretion of gastric acid. The role of the H2R is well studied in histidine decarboxylase knockout mice (HDC−/−) models which suggest that the lack of histamine can enhance downregulation of H2R expression in a tissue-specific manner . Furthermore, the H2R is importantly accountable for the relaxation of the airways, uterus, and smooth muscle cells in the blood vessels. Moreover, the H2R is involved in the activation of the immune system, such as Th1 cytokine production, reduction of basophil degranulation, T-cell proliferation, and antibody synthesis…

The H3R is coupled to Gαi/o and exclusively expressed in neurones. It is important for homeostatic regulation of energy levels, sleep-wake cycle, cognition, and inflammation (Figure 1). H3R-deficient mice exhibit altered behavior and locomotion and display a metabolic syndrome characterized by obesity, hyperphagia, and increased leptin and insulin levels . Similarly, several studies suggest that H3R knockout can also lead to an increase in severity of neuro-inflammatory diseases and can enhance the expression of IFN-inducible protein 10, MIP 2, and CXCR3 in T cells . These investigators also showed that H3R can be involved in blood–brain barrier function. The H3R has also been associated with rhinitis .

This is likely because it is expressed on presynaptic nerves in the peripheral sympathetic adrenergic system and also on nasal sub-mucosal glands. Stimulation of H3R suppressed norepinephrine release at presynaptic nerve endings and stimulated nasal sub-mucosal gland secretion…

The histamine H4R is coupled to Gα/io proteins and is expressed on a variety of immune cells as well as on other cells such as spleen, intestinal epithelia, lung, synovial tissue, central nervous system, sensory neurons, and cancer cells. Stimulation of H4R reduces forskolin-induced cyclic AMP formation, which leads to the activation of MAPK and enhanced Ca++ release. H4R mediates the pro-inflammatory responses of histamine in both autocrine and paracrine manners. Histamine enhances adhesion molecule expression, cell shape change, and cytoskeletal rearrangement via H4R, leading to the increased migration of eosinophils

5.2.2 Prostaglandins.

Prostaglandins, arachidonic acid metabolites, are not themselves pruritogenic, but rather they potentiate itching caused by histamine and other mediators. Studies have shown that when abraded skin was pretreated with prostaglandin E, the itch threshold was lowered.2,4 There has

been some evidence that leukotrienes may have some relevance with respect to itching. An article by Miyoshi et al9 found a correlation between elevated urinary leukotriene B4 levels in patients with atopic dermatitis with associated nocturnal itch.

5.2.3 Other mediators.

Other mediators of the itch response have been appreciated historically. Mucuna pruriens, a tropical plant with pods that are covered by cowhage spicules, is known to cause ferocious itching. Although this plant was first described by an English physician who accompanied the Duke of Albermarle on a trip to Jamaica in 1688, the natives knew about it for some time. The natives would eat this inhospitable bean in times of scarcity only. They would heat the spicules to prevent the itching, for it was felt for some time that the spicules themselves caused the itching. In fact, the term cowhage is from the Hindu kiwach, or bad rubbing. In the late 18th century, William Chamberlain sprinkled cowhage on intestinal roundworms and noted their hyperactivity (which may have been caused by itching), causing them to release their hold on the intestinal mucosa. He noted that prior boiling of the spicules eliminated this effect and the worms stayed happily attached to the intestine.

From Bassari and Koes we have the following list:

Rifampicin

Rifampicin is an antibiotic and has been used in the treatment of pruritis. Rifampicin induces phase I,II and III biotransformation enzymes and transporters such as CYP3A4, UGT1A1, SULTA1, and MRP2

Ursodeoxycholic acid

Ursodeoxycholic acid has been used in the treatment of primary biliary cirrhosis at a dose of 750 mg/d and improved a number of biochemical parameters but did not improve pruritis

Antidepressants

Antidepressants have been used in the treatment of pruritis. Both paroxetine and setraline are selective serotonin reuptake inhibitors. Mirtazapine and doxepin (both tricyclic antidepressants) have antihistaminic effects and serotonergic effects and have been used to treat pruritis

Anticonvulsant agents

Anticonvulsants are effective in the treatment of pruritis and probably act at a spinal level by inhibiting transmission. They often do not reach full effectiveness until after 5-6 wk of treatment. Gabapentin (900-2700 mg/d) is currently under investigation although initial analysis of a double blind trial suggested that there was no therapeutic advantage seen over placebo

Antihistamines

Antihistamines have two potential modes of action in treating pruritis. Firstly they prevent binding of histamine to the H1 receptor and have a second sedating and anticholinergic effect although clinically they are rarely effective. The newer H4 receptor antagonists may have a potential role although this is yet to be formally assessed

Immunosuppressants

Cyclosporin (3-5 mg/kg) has a significant anti-pruritic effect within several days of beginning therapy although no trials specifically looking at it use in the treatment of pruritis have been described

Dronabinol

Dronabinol is a psychoactive compound extracted from Cannabis sative and 5 mg administered to patients with intractable cholestasis associated pruritis decreased itch and improved sleep. Dronabinol may act by increasing the threshold to noxious stimuli

As Cohen et al have noted regarding the following approaches:

Corticosteroids

Although corticosteroids are not directly antipruritic, they are believed to produce their therapeutic effects by alleviating the inflammation associated with some skin conditions, such as atopic dermatitis and psoriasis. Corticosteroids should be used sparingly. Higher-potency steroid creams and ointments may provide an improved anti-inflammatory response, but they also put the patient at increased risk for adverse effects, including skin atrophy, telangiectasia, and suppression of the hypothalamus–pituitary axis.

Topical corticosteroids should be used with caution in the elderly; these individuals may be particularly susceptible to the skin-thinning effects of these drugs.

This latter effect is critical. If a patient has undergone chemotherapy with a taxane and as such has microtubule block, the keratinocytes are already reduced. The added steroid further reduces the keratinocyte layer and exposes the C neurons for an intractable itch syndrome.

Topical Immunomodulators

The topical calcineurin inhibitors tacrolimus (Protopic, Astellas) and pimecrolimus (Elidel, Novartis) are commonly used in the treatment of atopic dermatitis. These agents are nonsteroidal selective inhibitors of the production and release of inflammatory cytokines in T cells and of other pro-inflammatory mediators in mast cells. In a randomized trial comparing pimecrolimus cream 1% with placebo in patients with atopic dermatitis, 56% of the pimecrolimus group experienced a significant reduction in the severity of pruritus compared with 34% of the placebo group within 48 hours after treatment.

In another study, Ständer et al. evaluated the efficacy of tacrolimus 0.1% and pimecrolimus 1% in patients with prurigo nodularis (pruritic nodules of an unknown etiology) and in patients with localized or generalized pruritus. Of the 20 patients who received these medications, eight (40%) achieved a complete cessation of itching (a reduction of 70% to 90%). Adverse drug effects included stinging and burning at the application site. If tolerated, topical immunomodulators might be a good option for elderly patients with pruritus, because thinning and atrophy of the skin are not a concern.

Local Anesthetics

Agents that contain local anesthetics, such as lidocaine (Lidoderm, Endo) and lidocaine/prilocaine (Emla, AstraZeneca), may relieve itching, especially when they are applied with occlusive dressings of cloth or nylon. A local anesthetic made by Abbott, pramoxine HCl (also known as pramocaine) has antipruritic properties and has been used in hemodialysis patients with uremic pruritus. Prax Lotion (Ferndale) is another product that contains pramoxine. Polidocanol is a non-ionic surfactant with moisturizing and local anesthetic properties, both of which help to ameliorate pruritic symptoms. In an open-label study, polidocanol lotion 3%, when combined with urea 5%, significantly reduced pruritus in patients with xerotic disorders, including atopic dermatitis, contact dermatitis, and psoriasis.

Topical Cannabinoids

Cannabinoids act at peripheral sites and produce analgesia through their actions on CB1 and CB2 receptors. The local analgesic actions of agonists for CB2 receptors, such as N-palmitoyl-ethanolamine (PEA), include the inhibition of mast-cell function and inflammatory pain. PEA has been incorporated into topical analgesic preparations and has been shown to reduce pruritus in patients with atopic dermatitis, lichen simplex, and prurigo nodularis; it has also decreased itching associated with chronic kidney disease.

Topical Antihistamines

Topical antihistamines, such as diphenhydramine and pyrilamine, are used primarily to treat urticaria and insect bites. These products are not usually used for other pruritic conditions, such as idiopathic local and generalized pruritus, because of the side effects of erythema and skin irritation. Doxepin (Sinequan, Pfizer), a tricyclic antidepressant, exhibits potent histamine receptor (H1 and H2) antagonism. In a double-blind study, Drake and Milikan compared the antipruritic efficacy and safety of doxepin HCl cream 5% (e.g., Prudoxin, Healthpoint) with a placebo vehicle in patients with lichen simplex chronicus, nummular eczema, or contact dermatitis.

Twenty-four hours after initiation of treatment and for the remainder of the 7-day study, almost all of the doxepin patients experienced significantly greater relief of pruritus compared with those receiving placebo ($P < 0.002$). The most common side effects included a transient stinging sensation after application (20.7%) and drowsiness (15.5%) resulting from systemic absorption. Although the drowsiness subsided over time, this undesirable side effect may limit the use of doxepin cream in elderly patients.

They then list some systemic approaches:

Antihistamines

Traditionally, the treatment of pruritus associated with various skin disorders has focused on medications that antagonize histamine receptors. It has been proposed, however, that the relief of itching achieved with these medications might be a result of their sedating properties and not necessarily the antagonism of histamine, especially in pruritic conditions such as eczema, psoriasis, and lichen planus.84 Pruritus that results from the stimulation of histamine receptors (as in urticaria) may be effectively treated with antihistamines, such as diphenhydramine because of their ability to antagonize histamine H1 receptors.

The use of systemic antihistamines should be avoided in elderly patients because of the anticholinergic effects of these drugs. Pruritus that is caused by the release of histamine is mediated by H1 receptors. Therefore, the nonsedating H2 receptor antagonists, such as loratadine and fexofenadine are generally not effective in the treatment of histamine-related pruritus. These agents, however, have favorable side-effect profiles, are relatively safe in older persons, and may be an option for elderly patients with pruritic dermatoses accompanied by erythema and wheals.

Serotonin Receptor Antagonists

The antidepressant mirtazapine (Remeron, Organon), a serotonin (5-HT2/5-HT3) receptor antagonist, is an effective therapy for pruritus, particularly in patients with advanced cancer, cholestasis, or hepatic or renal failure.

The drug's potential for causing drowsiness may be beneficial in patients with nocturnal pruritus.86 In an open-label study, patients with chronic pruritus received long-term treatment with the selective serotonin reuptake inhibitors (SSRIs) paroxetine (e.g., Paxil, GlaxoSmithKline) and fluvoxamine (Luvox, Abbott).87 An antipruritic effect was observed in 68% of the patients. Paroxetine and fluvoxamine did not differ significantly in their efficacy.

The best responses occurred in patients with atopic dermatitis, systemic lymphoma, or solid carcinoma. Patients with cholestatic pruritus showed an antipruritic response after they were treated with the antiemetic agent ondansetron, a 5-HT3 receptor antagonist. The use of serotonin receptor antagonists in elderly patients may be limited by the occurrence of adverse effects, including excessive CNS stimulation, sleep disturbances, and increased agitation. It is important to consider the risk–benefit ratio of these agents in the elderly; they should be administered only as second-line or third-line therapy.

Opioid Antagonists and Agonists

Opioid-induced pruritus occurs after activation of the muopioid receptors in the CNS. It is through this central process that mu-opioid receptor antagonists, such as the generic drugs naltrexone, nalmefene, and naloxone, are believed to have an effect in treatment-resistant

pruritus. These agents have been used successfully to treat uremic and cholestatic pruritus, chronic urticaria, atopic dermatitis, prurigo nodularis, and opioid-induced pruritus.

The activation of kappa-opioid receptors is known to reduce pruritus. The kappa-opioid receptor agonists butorphanol and have been beneficial in patients with intractable itching and uremic itching, respectively. Both opioid-receptor antagonists and agonists should be used sparingly with supervision and caution in elderly patients. These medications can put patients at risk for sedation and insomnia, and they have a potential for abuse.

Neuroleptic Agents

The antiepileptic drugs gabapentin and pregabalin decrease neuronal transmission. Gabapentin is effective in the treatment of neurological pruritus (including brachioradial pruritus and notalgia paresthetica) when used as a localized patch worn on the infrascapular area of the back.

Gabapentin is also effective in the treatment of uremic pruritus. Because it is chemically similar to gabapentin, pregabalin has been proposed as a therapy for chronic pruritus. Both gabapentin and pregabalin are eliminated by the kidneys; therefore, they must be administered appropriately in elderly patients and in patients with impaired renal function to avoid an overdose and adverse side effects.

5.3 TARGETED

From Wang and Kim we have the following for targeted therapeutics:

Target	Medication	Mode	Disease
H4R	JNJ-39758979 ZPL-3893787	antagonist	AD
KOR	difelikefalin	agonist	uremic pruritus
IL-31 RA	nemolizumab	mAb	AD, PN
IL-33	etokimab	mAb	AD
TSLP	tezepelumab	mAb	AD
IL-4Ra	dupilumab	mAb	AD, PN, chronic pruritus
JAK	baricitinib, tofacitinib ruxolitinib delgocitinib	inhibitor	AD, CPUO
NK1-R	serlopitant, tradipitant	antagonist	AD, PN, CPUO, psoriasis

5.3.1 JAK2 Pathway

As Al-Mashdali et have noted:

Polycythemia vera (PV) is a Philadelphia-negative myeloproliferative neoplasm (MPN) characterized by the overproduction of red blood cells. The presence of JAK2 mutation is detected in up to 99% of patients with PV. Pruritis is commonly encountered in patients with PV and is considered the most troublesome symptom. Multiple treatment modalities are used for treatment; however, their efficacy is variable. Sometimes, pruritis will not improve even by the use of combined therapies.

Recently, Ruxolitinib (a JAK2 inhibitor) has been shown to be very effective, especially in patients with refractory pruritis in the setting of other treatment modalities failure….

Recently, Ruxolitinib, a JAK2 inhibitor, has been shown to be very effective in the treatment of PV-related pruritis, especially treatment-resistant cases.

In this case, we describe a PV patient who presented with severe itching, especially after showering. We tried multiple treatment options for pruritis control but without any considerable benefit. After starting a low dose of Ruxolitinib, we appreciated a dramatic and complete relief of itching without any significant adverse effect

5.3.2 Antidepressants

As Tivoli et al note:

Psychotropic agent. Doxepin, a tricyclic compound, typically used to treat depression and anxiety, has been found to exhibit potent H1 and H2 antihistamine and anticholinergic properties. In one study, doxepin was found to be more effective than hydroxyzine or diphenhydramine in relieving pruritus in patients with idiopathic urticaria. Doxepin can be applied topically or given systemically. Its utility is occasionally limited because it causes drowsiness in approximately 25 percent of patients.

5.3.3 GABA Pathway

Gabapentin has become a significant therapeutic. Although its actual action is still poorly understood it does target neural pathways in the brain. As Yusiaian et al note:

Recently, gabapentin, an antiepileptic agent, has been reported to be an effective antipruritic agent in brachioradial pruritus. It has been suggested that gabapentin may be useful in chronic itching that is unresponsive to other treatments.

In our patients, we started gabapentin therapy at a dose of 300 mg/d on day 1, increasing it to 600 mg/d and 900 mg/d on days 2 and 3, respectively.

Thereafter, the dosage was increased to 1800 mg/d during the next 3 to 4 weeks, titrating the dose to symptom control.

Both patients had an excellent response, with complete control of the itching within the first month. They have continued with a maintenance dosage (based on symptom control) of

gabapentin and have remained symptom free for longer than 9 months, with no adverse effects due to the medication.

One must be careful on titrating gabapentin both up and down. Taking a patient off of gabapentin demands significant monitoring and patient compliance. They continue:

Gabapentin is an antiepileptic drug that has been used in different conditions associated with chronic pain19 and, recently, in pruritic disorders. It has a novel molecular structure, and although its precise mechanism of action is unknown, various hypotheses have been proposed to explain it. Its primary effect is inhibition of voltage-dependent calcium ion channels located in the spinal cord (with particular high density in the superficial laminae of the dorsal horn), inhibiting the release of excitatory neurotransmitters.

Gabapentin neither acts directly on the -aminobutyric acid receptor nor affects the reuptake of -aminobutyric acid. It increases the synthesis of -aminobutyric acid from glutamate by altering the activity of glutamic acid decarboxylase in neurological tissue.20 Its effect on pruritus may be central and peripheral.

Gabapentin is known to secondarily inhibit calcitonin gene–related peptide (a mediator of itching) release from primary afferent neurons through a primary increase of -aminobutyric acid in the spinal cord.

Furthermore, it has been hypothesized that opioid receptors are involved in the mechanism of action of gabapentin. Although not directly agonistic or antagonistic to the opioid receptors, modulation of the μ-opioid receptors may affect the central perception of itching. Opioid peptides also have a peripheral action, potentiating itching due to other agents.

5.4 SUMMARY

In a recent treatment in NEJM by Yosipovitch and Bernhard, the authors noted the following current list of treatments for intractable itch syndromes:

Medication	*Side Effects*	*Medical Condition*
Topical therapy		
Emollients	None	Atopic eczema itch, dry-skin itch, skin-barrier damage
Glucocorticoids	Skin atrophy, telangiectasia, folliculitis	Atopic dermatitis, psoriasis, skin inflammation
Anesthetic agents		
Capsaicin	Burning sensation for the first 2 wk	Neuropathic itch, itch caused by chronic kidney disease
Pramoxine	Skin irritation and dryness at the affected area	Facial eczema, genital itch, itch caused by chronic kidney disease, neuropathic itch
Lidocaine and prilocaine mixture	Methemoglobinemia	Neuropathic itch, postburn itch

Medication	*Side Effects*	*Medical Condition*
Menthol	Skin irritation (including hypersensitivity and burning sensation) with higher concentrations	Itch that responds well to the application of an ice cube or to cold showers
Calcineurin inhibitors	Transient stinging or burning sensation	Atopic dermatitis, contact dermatitis, and particularly for facial or anogenital itch
Systemic therapy		
Oral antihistamines		
Hydroxyzine	Drowsiness, dry mouth; abrupt withdrawal may cause confusion	Chronic urticaria, nocturnal itch, drug-related itch; pruritic conditions in which drowsiness is desired effect
Doxepin	Same as for hydroxyzine; can prolong QT interval, so should be used with caution in patients with electrocardiographic abnormalities	Same as for hydroxyzine
Diphenhydramine	Same as for hydroxyzine	Same as for hydroxyzine
Glucocorticoids	Skin atrophy, telangiectasia, folliculitis	Atopic dermatitis, psoriasis, skin inflammation
Anticonvulsants		
Gabapentin	Drowsiness, constipation, leg swelling	Neuropathic itch (high dose, up to 3600 mg daily); pruritus from chronic kidney disease (low dose, 100 to 300 mg three times a week after dialysis)
Pregabalin	Drowsiness, leg swelling	
Antidepressants		
Paroxetine	Insomnia, dry mouth, sexual dys-function	Generalized pruritus, paraneoplastic itch, psychogenic pruritus
Mirtazapine	Drowsiness, dry mouth, increase in appetite, weight gain	Generalized pruritus, nocturnal itch
Amitriptyline	Drowsiness, dizziness, constipation, dry mouth, blurred vision	Neuropathic itch
Opioids		
Mu antagonist	Nausea and vomiting, abdominal cramps, diarrhea, hepatotoxicity	Intractable itch, cholestatic pruritus, possibly pruritus from chronic kidney disease
Kappa agonist and mu antagonist	Drowsiness, dizziness, nausea, vomiting	Intractable itch
Ultraviolet B radiation (broad and narrow band)	Burning sensation, initial pruritus; long-term risk of skin cancer	Atopic dermatitis, psoriasis, pruritus from chronic kidney disease

In our experience the targeting of one or more of the above therapeutics is still currently a clinical exercise. Typically one starts with an antihistamine, then a steroidal, then an antidepressant, then possibly gabapentin. Dose titration is also a key in the process and monitoring the response is critical.

There is also the challenge of balancing the neurogenic factor with a psychogenic especially with cancer patients. We generally have seen that it requires a broadly based physician willing to take the time with the patient. Generally, the oncologist is just following the “cookbook” and may not have the time or expertise to deal with this complex issue.

Ultimately identifying the cause of the itching may currently be a futile task. Typically the approach is start with minimal therapeutics such as antihistamines, then steroids, and then progress. Timing, dosage, and patient interaction is a complex issue.

6 OBSERVATIONS

Based upon the diverse elements discussed above we and make the following observations.

6.1 THE SOURCE AND THE NETWORK OF ACTIONS RESULTING IN NEUROGENIC ITCH ARE NOT FULLY UNDERSTOOD

As we have demonstrated, we have a paradigmatic view of the process going from antigen source through full neural networking. This is to some degree a logical assumption based upon available data. However there are a multiplicity of links missing and these may change the model or just suggest alternative therapeutics. However, obtaining an understanding of each of these issue could dramatically enlighten our understanding of multiple malignancies.

6.2 THERE ARE A MULTIPLICITY OF TARGETS FOR THERAPEUTICS BUT NONE ARE DISPOSITIVE

As noted above we have suggested targets for therapeutics but none dispositive. The work done on AD with IL-31 does represent something worth examining in general since IL-31 seems to have a broader impact.

6.3 THE IMMUNE SYSTEM CLEARLY INTERACTS WITH THE MALIGNANT CELLS BUT THE DETAILS ARE UNCLEAR

Malignant cells are known to emit a variety of detectable antigens. Moreover there impact of the tumor micro environment including macrophages and fibroblasts[10] and add additional confusion as well as protecting of the tumor cells themselves[11].

6.4 ITCHING, ESPECIALLY IN CANCER PATIENTS, CAN ADD DRAMATICALLY TO THE DISEASE BURDEN

The burden on a cancer patient of the itching can result in a dramatically increased psychological burden. It is thus possible if not probable that psychogenic itch may arise and confound the overall diagnosis as well as treatment.

6.5 DEALING WITH ITCHING IN CANCER PATIENTS DEMANDS A MULTIDISCIPLINARY TEAM OF COMPETENT AND OPEN PHYSICIANS

It is clear that treatment of a cancer patient with itch syndrome may not be handled in the best interests of the patient. Oncologists, surgeons, radiation oncologists are all highly focused and

[10] https://www.researchgate.net/publication/341788660_Fibroblasts_and_Cancer_The_Wound_That_Would_Not_Heal

[11] https://www.researchgate.net/publication/321319216_Microbiome_Immune_System_and_Cancer

dermatologists will not have the expertise of neurogenic or psychogenic effects. Thus the inclusion of a well-rounded Internist willing to work with the [patient is in our opinion a sine qua non.

6.6 POLYCLONAL ANTIBODIES PRESENT AN INTERESTING TARGETING OF MULTIPLE RECEPTORS

We have discussed polyclonal antibodies previously. We believe that they can become a strong therapeutic as we try to address both antigens and target tumor cells[12].

6.7 THERE ARE MANY YET TO BE ANSWERED QUESTIONS ON EACH OF THE STEPS PROPOSED.

We proposed a paradigm at the beginning of this note. However, the paradigm was based upon a paucity of facts and an attempt to use what facts were available with logical interconnections to propose a therapeutic approach. Let us examine each of the steps and see what needs to be accomplished.

6.7.1 Cancer cell emits an antigen: We know that many cancer cells emit antigen like substances which are collected by the immune system. The collection is usually done by M1 macrophages which then present the result to the immune system cells.

An itch has frequently been a prodrome to the diagnosis of cancers. More than likely the cancer cells are emitting antigens which in turn create immune responses including the itch. We have limited evidence at this stage but it would be helpful to better understand the antigen producing and presenting dynamics of a wide variety of malignancies. We know that there are exosomes that can be used to detect cancers in the bloodstream. Prostate cancers can now be detected in such a manner and many other cancers. However these may not be true antigens. The antigens may be protein segments produced by the malignant cells or possibly by remnants of the malignant cells still being attacked by Nk cells or CTLs. Clearly this is a large area of research investigation with scant data at this time.

6.7.2 Dendritic cells take up antigen: Not only do we have macrophages but we can see dendritic cells collecting the antigens as well.

DCs will often take up the Ags as will DCs. They are Ag presenting cells, APC, and this starts the process of initiating an full immune response. Examining the APCs in the case of a malignancy to see what the Ag could be and tracking it back to a source would be essential.

6.7.3 Naive T cells are activated: The immune system then kicks in with the naïve T cells getting activated. We demonstrate that process later.

If the above steps are effected then the normal process of the immune system should be effected.

[12] https://www.researchgate.net/publication/346245151_Poly-specific_Antibodies

6.7.4 T cells emit cytokines: T cells generally react via cytokines. There are a multiplicity of such cytokines and in many itch scenarios we see IL-31 being one of the most significant. We also have others.

Cytokines of various types are released by the T cells and other cells having been activated. Just what cytokines, such as IL-31, are released, we do not have a dispositive list. However this can be a readily addressable set of targets.

6.7.5 Cytokines bind to neurons: The cytokines often then bind to receptors on the neurons in the skin. These are C neurons.

We now "assume" that the cytokines bind to receptors on the neurons. We need a cytokine/receptor match for this to work. Furthermore, we need to understand what the impact of the binding is. Namely the binding should activate the C neurons and commence the itch process. The details of this process are missing and do not appear to be readily available.

6.7.6 Neurons are excited: The cytokines than cause the neurons to be excited sending a message to the dorsal root ganglion.

The progression of neural signals is well understood. They move to the dorsal root ganglion which may be a target.

6.7.7 Message sent to dorsal root: The DRG receives the message and it then proceeds up the spinal cord.

The next step is also generally well understood.

6.7.8 Message sent to cerebellum: The itch message arrives at the cerebellum and then to the cerebrum where it is processed.

The movement up the spinal cord to the cerebrum is generally well understood but there may also be a cerebellum path. The assumptions here are based on well know neural pathways. One should always revalidate these paths.

6.7.9 Impact on limbic system: There is a putative impact on elements of the limbic system creating a putative limbic valence.

Neurogenic and psychogenic itch may very well have a locus in the limbic system. Known circuits do involve parts of the system but we also know that the system is complex network of intercommunicating elements. These elements can evoke strong responses both physiologically and psychologically. Thus, we believe that a better understanding the limbic system and its networking effects is essential.

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