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Mediators of Chronic Pruritus in Atopic Dermatitis: Getting the Itch Out?

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Abstract For centuries, itch was categorized as a submodality of pain. Recent research over the last decade has led to the realization that itch is in fact a separate and distinct, albeit closely related, sensation. Chronic itch is a common complaint and has numerous etiologies. Various receptors (TRPA1, TRPV1, PAR2, gastrin-releasing peptide receptor (GRPR), Mas-related G proteins), secreted molecules (histamine, nerve growth factor (NGF), substance P (SP), proteases), and cytokines/chemokines (thymic stromal lymphopoietin (TSLP), IL-2, IL-4, IL-13, and IL-31) are implicated as mediators of chronic pruritus. While much remains unknown regarding the mechanisms of chronic itch, this much is certain: there is no singular cause of itch. Rather, itch is caused by a complex interface between skin, keratinocytes, cutaneous nerve fibers, pruritogenic molecules, and the peripheral and central nervous systems. Atopic dermatitis is one of the most itchy skin dermatoses and affects millions worldwide. The sensation of atopic itch is mediated by the interplay between epidermal barrier dysfunction, upregulated immune cascades, and the activation of structures in the central nervous system. Clinicians are in possession of an arsenal of different treatment options ranging from moisturizers, topical immunomodulators, topical anesthetic ion channel inhibitors, systemic immunomodulators, as well as oral drugs capable of reducing neural hypersensitization. Emerging targeted therapies on the horizon, such as dupilumab, promise to usher in a new era of highly specific and efficacious treatments. Alternative medicine, stress reduction techniques, and patient education are also important treatment modalities. This review will focus on the mediators of chronic pruritus mainly associated with atopic dermatitis (atopic itch), as well as numerous different therapeutic options.

Keywords Atopic dermatitis · Chronic pruritus · Barrier disruption · Nonhistaminergic itch · Neural hypersensitization · Neuropeptides · Pruritus receptor unit · Alternative itch therapies · Immunomodulators · Patient education

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Introduction

Chronic itch is defined as itch lasting more then 6 weeks. The prevalence of chronic pruritus in the general population has been reported to range from 8.4 to 13.9 % [1–3]. There are many causes of chronic pruritus; as such, it is associated with dermatologic, infectious, systemic, psychiatric, neuropathic, and psychosomatic diseases. Chronic pruritus is one of the defining features of atopic dermatitis (AD, atopic eczema, eczema). Indeed, itch is so common in AD that AD is often described as the itch that rashes, making AD an archetypal model of chronic pruritus [4]. The point prevalence of chronic pruritus in AD ranges from 87 to 100 % [5, 6]. Both quality of life and psychosocial well-being are known to negatively correlate with itch severity. The associated psychosocial morbidity of this distressing symptom includes sleep disruption, depression, agitation, anxiety, altered eating habits, reduced self-esteem, and difficulty concentrating [7]. As the prevalence of atopy continues to rise, it becomes increasingly important that clinicians understand the mechanisms responsible for itch and, in particular, atopic itch.

Pruritus in AD is orchestrated by the complex interplay of numerous different mediators. We intend to elucidate the mediators of chronic pruritus mainly in the context of AD, with particular emphasis on the neural networks involved, rather than the immune cascade.

Two Different Pathways: Histaminergic Versus Nonhistaminergic

Historically, the study of itch predominantly focused on histamine. Yet, antihistamine therapy was used often to no avail in the treatment of many itchy skin disorders. This clinical observation resulted in renewed efforts to understand the basic mechanisms responsible for itch. We now know that the transmission of pruritus can be divided into two categories: histaminergic and nonhistaminergic [8]. These two systems, while closely related, appear to exist entirely separate and independent from one another.

The separation of these two systems begins in the periphery, where each has its own respective receptors and cutaneous nerve fibers, and continues through to the central nervous system, where each has specialized tracts and neural structures [8–10]. Chronic pruritus is induced by the nonhistaminergic pathway. Nonhistaminergic itch has been replicated in studies by the insertion of spicules from the plant cowhage (*Mucuna pruriens* var. *pruriens*), which contain mucunian, a molecule known to cause strong activation of nonhistaminergic itch pathways (largely due to binding to PAR2 and PAR4 receptors). The pruritus produced by the insertion of a few cowhage spicules is robust, does not produce a wheal or flare, and is unresponsive to antihistamine treatment [11]. Nonhistaminergic itch is so well characterized by cowhage that cowhage-induced itch is synonymous with nonhistaminergic itch (Fig. 1).

Basic Schema of Neural Transmission

Autonomic and primary afferent (sensory) nerves innervate the skin to form a complex neural network. Cutaneous sensory nerve fibers originate from cell bodies in the dorsal root ganglia (DRG). These cutaneous nerve fibers terminate either around blood vessels, hair follicles, sweat glands, or in the

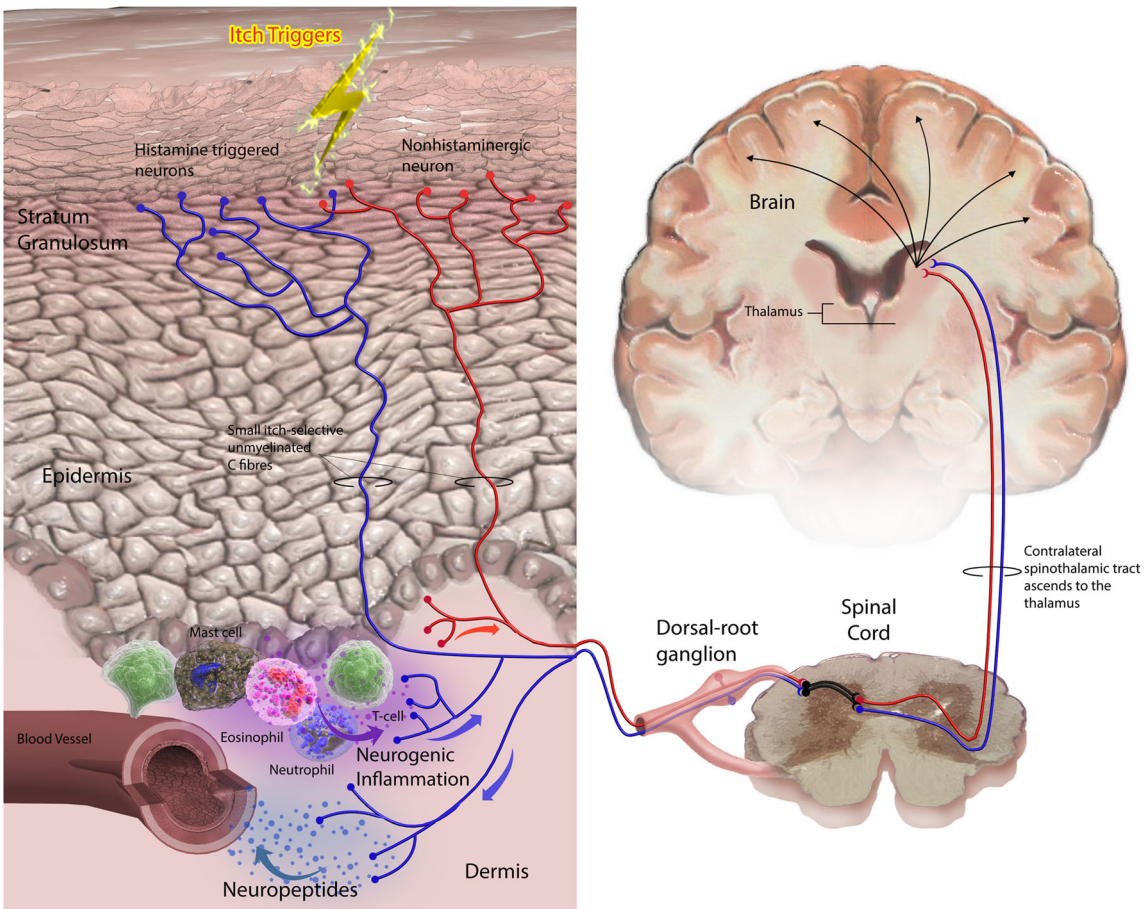

Fig. 1 Histaminergic and nonhistaminergic induced itch activate both axonal and antidromic release of pruritogenic neuromediators, resulting in vasodilation and leukocyte-mediated inflammation. Leukocyte products can amplify the inflammatory response and sensation of itch. In addition, higher level CNS itch centers can influence the perception of itch as well as axonal responses. The nerve fiber pathways for histaminergic and nonhistaminergic itch are independent and remain so as they travel from the periphery to the brain

epidermis or dermis [12, 13]. In the dermis and epidermis, the cutaneous nerve fibers terminate in close proximity to skin cells (fibroblasts, keratinocytes, mast cells, and Langerhans cells). At their terminal ends, the nerves form complex varicose-like neural webs. This complex web allows for the nonsynaptic release of neuromediators (neurotransmitters and neuropeptides) along the terminal end of the axon [14–17]. Neuromediators may directly or indirectly communicate with keratinocytes and Langerhans cells and vice versa. In addition, dysregulation of skin homeostasis may directly or indirectly stimulate sensory nerve endings and induce pruritus.

Irrespective of the inciting event, the activation signal of peripheral nerve endings of DRG neurons is transmitted to the brain via the anterolateral quadrant of the spinal thalamic tract (STT) in the spinal cord [9, 18, 19]. Lesions of this anterolateral quadrant in humans result in the contralateral loss of itch sensation below the lesion level [20–22]. Both histaminergic and nonhistaminergic itch signals are transmitted to the brain via the STT itch pathway; yet, the two disparate causes of itch do not converge on the same STT neurons [9, 10]. Indeed, a given STT neuron is capable of responding to either histamine or cowhage, but not to both (Fig. 1) [9, 10].

Brain functional imaging studies show that a common core group of brain structures are activated in response to itch signals [8]. However, different additional brain regions are selectively activated based on the type of itch induced [8]. Additionally, recent findings demonstrate that different causes of chronic pruritus (e.g., AD, psoriasis, and uremic failure) result in different activation profiles in the central nervous system (CNS) [23, 24]. This distinction is additionally noted in the distal periphery, with the finding that histamine and cowhage individually activate distinct, nonoverlapping populations of cutaneous nerve fibers in human skin [25]. The separation of histaminergic from nonhistaminergic itch is thus a consistent theme that is reiterated throughout transmission of the itch signal at every level, from the distal periphery to the cortex.

Role of the Epidermis

Pruritus is a unique sensory modality, in that it is restricted to the skin, mucous membranes, and cornea—no other tissues or organs are capable of experiencing itch [7]. Reason would dictate that the sensation to itch must thus originate from a structure that is unique to those tissues capable of experiencing itch. This conjecture was validated when it was first demonstrated that removal of the epidermis abolishes the perception of pruritus, but not pain [26, 27]. The sensation of itch thus emanates from the activity of itch-specific nerve fibers located in the epidermis and dermal-epidermal junction. Itch-specific nerve (C) fibers are characterized by mechano-insensitivity, low conduction velocities, large innervation territories, and high transcutaneous electrical thresholds [28]. These itch-specific nerve fibers extend up to the stratum granulosum and dermal-epidermal junction (Fig. 1) and are in close proximity to epidermal cells, including keratinocytes.

Epidermal Barrier Dysfunction and Itch

AD is characterized by systematic epidermal barrier dysfunction, regardless of lesional versus nonlesional skin [7]. Several mutations in the gene encoding filaggrin, a filament-associated protein that binds keratin and is important to epidermal homeostasis, are highly associated with AD [29]. The mechanism linking barrier dysfunction and chronic pruritus is not clearly understood and is not limited to filaggrin mutations. In order to understand the concept of epidermal barrier dysfunction, a brief discussion regarding the general milieu of the epidermis is required.

The stratum corneum is the outermost layer of the epidermis and it is classically described by the brick wall analogy [30]. Mature keratinocytes represent the bricks in this analogy. Aside from having proteins that provide strength and elasticity, keratinocytes additionally possess a large internal class of naturally occurring molecules that are collectively referred to as natural moisturizing factor (NMF) [30]. NMF conveys the ability to retain water within keratinocytes. The mortar in the brick wall analogy is a medium that is rich in lipids that functions to hold everything in place in a structured fashion. In addition, this lipid-rich medium acts as a barrier against the loss of water [31].

Barrier dysfunction in AD results in increased transepidermal water loss. Itch intensity in AD is associated with transepidermal water loss (TEWL)—i.e., the greater the water loss, the worse the itch [32]. Additionally, TEWL is known to increase at night in patients with AD, a finding that may explain the frequent nocturnal exacerbations these patients report clinically [33]. The mechanism of this water loss occurs due to dysfunction both in the ability to retain water within the keratinocytes themselves (a function of NMF), as well as due to failure in the ability to prevent the loss of water from the epidermal environment surrounding those keratinocytes (a function of the lipid-rich medium) [31]. Furthermore, TEWL increases epidermal pH, thereby activating serine proteases such as stratum corneum chymotryptic enzyme (SCCE) [34]. Proteases are known pruritogens, the receptor for which is upregulated and sensitized in AD.

Most likely, epidermal barrier dysfunction allows for the entry of irritants and pruritogens, such as proteases and aeroallergens. Interestingly, there additionally appears to be an association between epidermal barrier dysfunction and food allergy, wherein nongastrointestinal exposure to food allergens (i.e., cutaneous or respiratory exposure) results in sensitization to food allergens (Fig. 2) [35]. A recent (2014) study reported that there is an exposure-response relationship between peanut protein levels in household dust and peanut skin prick test sensitization [36]. This new finding may

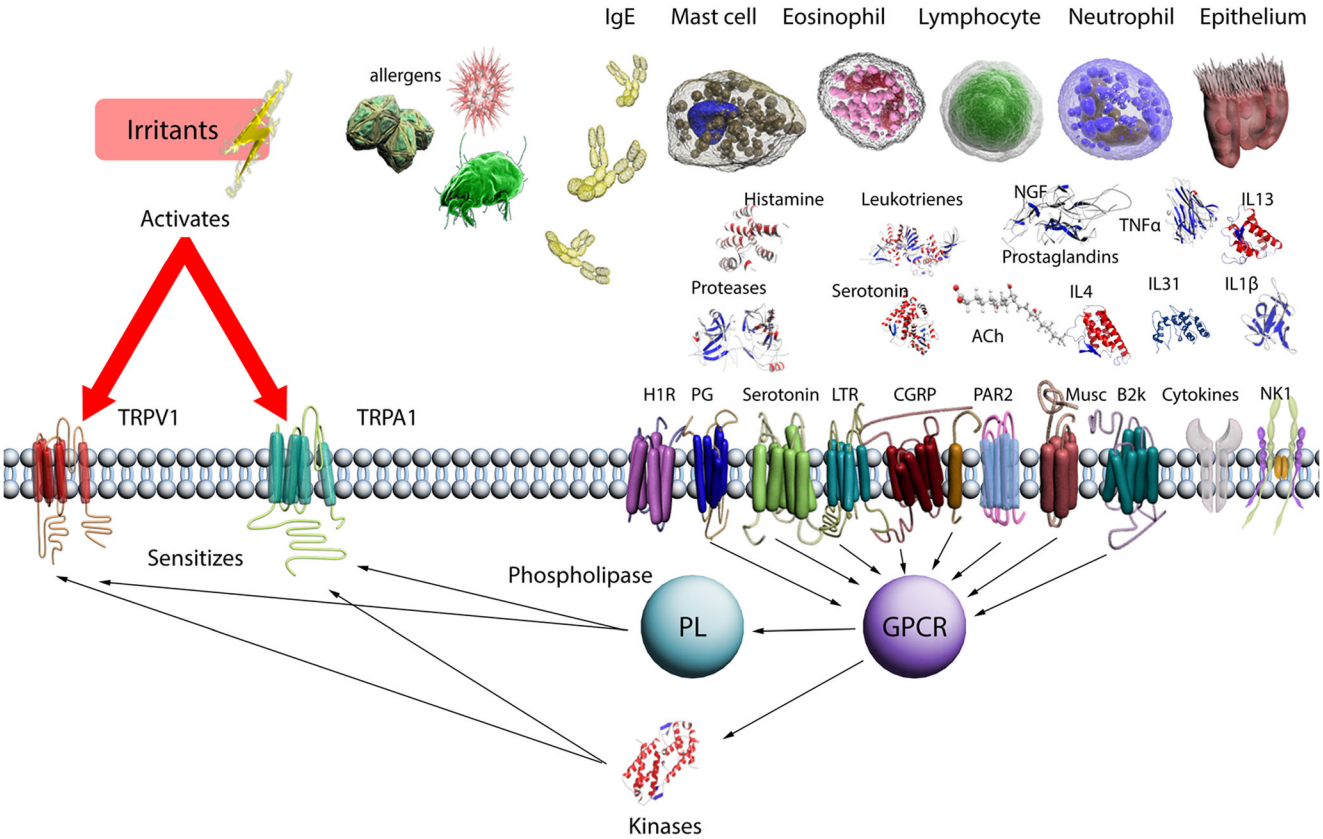

Fig. 2 There are two families of receptors involved in itch, G protein-coupled receptors (GPCRs) and transient receptor potential (TRP) channels. The cells involved include mast cells, eosinophils, lymphocytes, neutrophils, and epithelial cells (keratinocytes). There are numerous molecules capable of activating these various itch-specific receptors, including histamine, proteases, serotonin, leukotrienes, nerve growth factor (NGF), prostaglandins, acetylcholine (Ach), and cytokines (IL-4, IL-31, and IL-13). The itch sensation can be induced by direct activation of either GPCR or TRP channels. In addition, GPCRs can indirectly activate TRP channels, via linked kinases and/or phospholipase systems, resulting in their sensitization. Sensitization results in a reduced threshold for activation of TRPA1 and TRPV1 by physical, mechanical endogenous, and exogenous chemical irritants

explain why history and severity of AD are known risk factors for peanut allergy [36]. While much remains unknown regarding the specific mechanisms, the thymic stromal lymphopoietin (TSLP)-basophil axis appears to be involved [37].

Of note, in the absence of atopic eczema, icthyosis vulgaris, which is caused by a loss-of-function mutation in the filaggrin gene, is not associated with chronic pruritus. Therefore, not all barrier dysfunction disorders result in itching. This finding strongly suggests that filaggrin itself is not a cause of pruritus.

Pruritus Receptor Unit

Keratinocytes are the predominant cell type in the epidermis and their primary purpose is to aid in the barrier formation process. To that end, keratinocytes represent a highly active class of cells that engage in a host of complex interactions with structural proteins (e.g., filaggrin, keratin), enzymes (e.g., proteases), lipids, and antimicrobial peptides (e.g., defensins). In order to accomplish these various tasks, keratinocytes express myriad different receptors and produce numerous molecules for secretion.

With regard to pruritus, keratinocytes release pruritogenic molecules (e.g., opioids, proteases, substance P, nerve growth factor, neurotrophin 4, endocannabinoids) and express various receptors involved in the sensation of itch, including but not limited to PAR2, vanilloid, TRPV ion channels, TrkA, TrkB, cannabinoid receptor 1, IL-31 receptor, and μ and κ opioid receptors (Fig. 2). Additionally, keratinocytes possess voltage-gated ATP channels and adenosine receptors. Keratinocytes also excrete the neurotransmitter acetylcholine (Ach), which is an ancient "danger" response molecule. The secretion of Ach can both directly activate sensory nerves, as well as indirectly, via lowering their threshold of activation to other stimuli. In many ways, keratinocytes are thus remarkably similar in composition and expression profile to the itch-specific nerve fibers, as they share the same receptors and also emanate from the same embryonic structure.

In summation (Fig. 2), keratinocytes can activate pruriceptors by secreting factors that mediate itch, can themselves be activated by binding pruriceptive molecules to surface receptors, and can communicate the itch sensation downstream in a similar fashion to axonal transport [38]. This multiplicity of

interactions implicates the keratinocyte as the sentinel itch receptor, wherein keratinocytes act as the initiators of the itch sensation and are additionally responsible for the communication of the itch signal to cutaneous sensory nerves.

Receptors and Nerve Fibers

Receptors

The primary function of the peripheral nervous system (PNS) is to receive inputs from the environment and to transduce that signal to the CNS [39]. As such, nerve fibers of the PNS must express specialized receptors that are able to detect changes in external cues (e.g., heat and pressure) [39]. Myriad different receptors exist and respond to as many or more specific ligands. The one thing shared in common between said receptors, is that collectively, the majority are members of the G protein-coupled receptor (GPCR) superfamily.

Mas-Related G Protein-Coupled Receptors

Mas-related G protein-coupled receptors (Mrgpr, Fig. 3) represent a diverse family of receptors that exist within the GPCR superfamily [40]. Unlike other GPCRs, Mrgprs do not have one common ligand. For reasons that as of yet remain unknown, mice appear to have undergone significant gene expansion, as they are known to have in excess of 50 different members in the family [41]. Conversely, humans have a relatively limited selection with only 10 members noted [40, 42].

Many members of the Mrgprs are expressed exclusively by neurons in the DRG and the trigeminal ganglia, which possess axons that project to and terminate in the skin [39]. These receptors are responsible for detection of various peripheral sensations, such as noxious mechanical stimuli and temperature [41]. In 2009, itch induced by the antimalarial drug chloroquine (CQ) was found to involve a specific Mrgpr, thereby implicating the family as a mediator of pruritus [43]. That seminal study noted that in Mrgpr knockout mice, neither nociception nor histaminergic itch was reduced, while CQ-induced itch was reduced by over 65 % [43]. Furthermore, the authors noted that CQ-induced itch resulted in an increase in intracellular calcium and action potential generation in wild-type DRG neurons, findings that were abolished in Mrgpr knockouts [43].

Further investigation leads to the identification of a specific Mrgpr (MrgprA3AA[1]) involved in CQ-induced itch and its human ortholog, MrgprX1. In humans, the most specific ligand for MrgprX1 is a fragment of bovine adrenal medulla peptide (BAM8-22) [44]. Full-length BAM is a ligand for both opioid receptors, as well as for MrgprX1 [39]. The BAM8-22 fragment is selective for MrgprX1 alone. Subcutaneous injection of BAM8-22 induces scratching in mouse models [43]. In humans, topical application of BAM8-22 results in a pronounced itch sensation that is not relieved by topical antihistamine cream [45]. Application of a truncated BAM8-22 that lacks the Mrgpr-interacting motif does not induce itching [45].

In a mouse model where investigators genetically modified MrgprA3+ neurons to express a specific pain receptor, injection of nociceptive ligand resulted in activation of MrgprA3 neurons and induced itching, but noticeably not pain [46]. Thus, despite activation by a known pain-causing ligand (algogen), the neuronal circuit activated transmitted itch signals to the brain, as opposed to pain [11]. These findings are firmly in line with one of the principles of neuroscience, which states that sensation does not depend on the type of stimulus, but rather on the specific neuronal pathway that is activated [11, 47].

Proteases and Protease-Activated Receptors

Protease-activated receptors (PAR) belong to the GPCR family and are unique from most other GPCRs (Fig. 3), in that they are activated by the proteolytic cleavage of their own extracellular N terminus [11]. Activation of PAR2 and PAR4, by endogenous or exogenous proteases, results in the induction of nonhistaminergic itch [48, 49]. PAR2-mediated nonhistaminergic pruritus can be activated by various endogenous and exogenous proteases, including but not limited to mucunain (cowhage), cathepsin S, tryptase, dust mites, and *Staphylococcus aureus* [49–52]. Tryptase is an endogenous agonist of PAR2. Expression profiles for both tryptase and PAR2 were significantly increased in lesional skin of AD patients [53]. Interestingly, histamine levels did not differ in lesional skin from patients with AD when compared to healthy controls, further supporting the notion that AD-related itch is not mediated by histaminergic activity [53]. Both PAR2 and PAR4 are expressed on a multitude of different cell types, including keratinocytes and pruriceptive neurons in the DRG [11]. Expression of PAR2 on keratinocytes was upregulated in both lesional and nonlesional skin of patients with AD, with the highest level of expression occurring in lesional skin [54]. Application of intralesional PAR2 agonist induced prolonged itch sensation in AD patients [53].

Transient Receptor Potential

The transient receptor potential (TRP) superfamily consists of membrane proteins that transmit positively charged ions

[1] While MrgprA3 mediates CQ-induced itch in mice, a separate receptor, MrgprC11, is activated by BAM8-22. This is in direct contrast to that in humans, wherein MrgprX1 activation is responsible for both mechanisms.

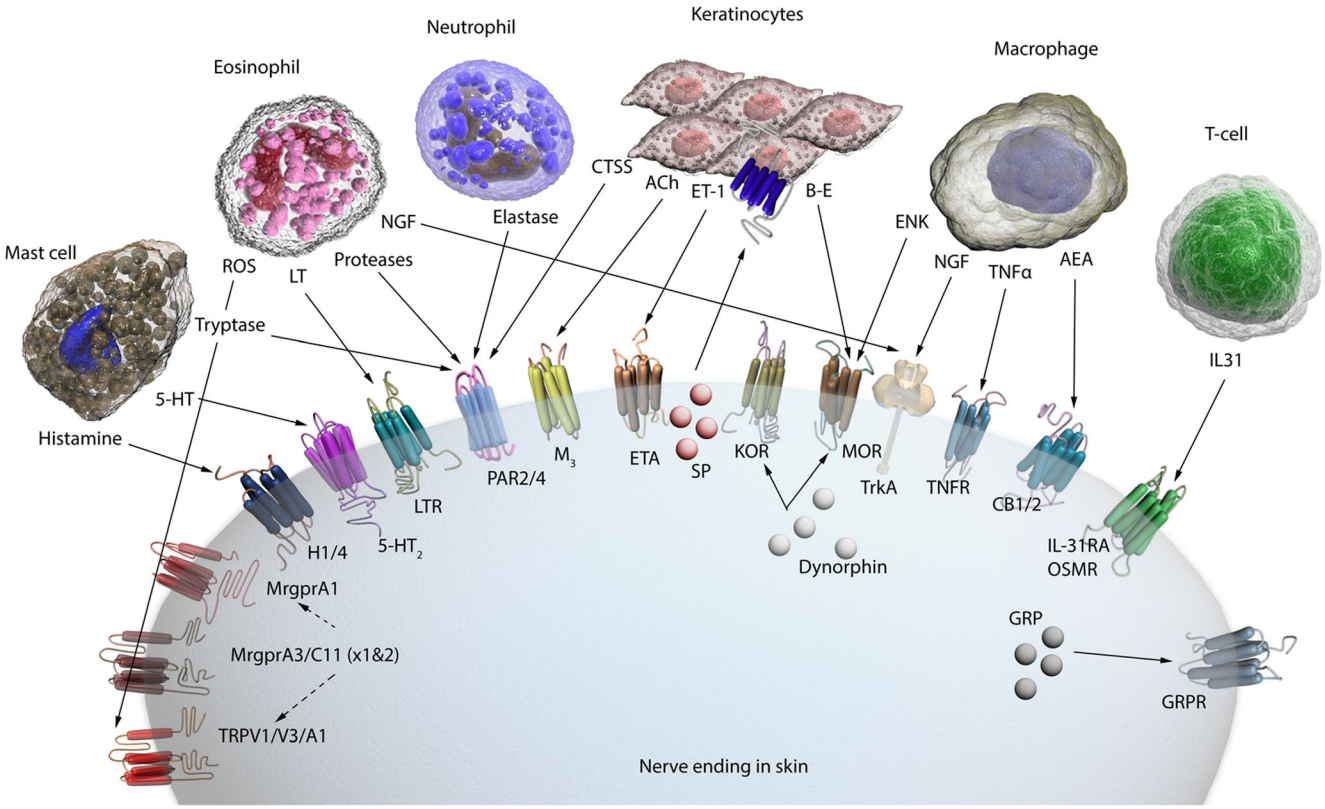

Fig. 3 Effector cells in the skin release various pruritogenic mediators that in turn act on receptors expressed on the terminal ends of sensory nerve fibers in the skin. Two families of receptors are implicated in the itch sensation: G protein-coupled receptors (GPCRs) and transient receptor potential (TRP) channels. The GPCR superfamily includes protease-activated receptors (PAR), Mas-related G protein-coupled receptors (Mrgpr), muscarinic-3 acetylcholine receptors (M3), cannabinoid receptors (CB1/2), and histamine receptors (H1/H4). Ligands are secreted from numerous effector cells, including lymphocytes (T-cells), mast cells, eosinophils, neutrophils, and keratinocytes. The multitude of mediators and receptors whose activations are implicated in the itch sensation illustrates that there is no singular cause of itch

across the cell membrane. As a class, this superfamily is a major component of sensory perception, including itch, as well as other various sensory modalities (e.g., chemical and thermal) [55–57]. Several subfamilies of the TRP superfamily are expressed in normal human skin and have been implicated in itch: TRPV1, TRPA1, and TRPM8 (Fig. 3).

TRPV1

TRPV1 is expressed in cutaneous sensory nerves, keratinocytes, and mast cells [58] Activation of TRPV1 has been implicated in mediating histaminergic itch [46, 59, 60]. Originally, TRPV1 was described as being activated by capsaicin. We now know that TRPV1 is activated by a litany of molecules including histamine and cannabinoids (anadamide) [61], temperatures above 42 °C [62], pH below 5.9 [62], ATP, products of lipoxygenase, prostaglandins, and changes in chemical and inflammatory conditions [58, 62, 63]. Histamine causes activation of the TRPV1 signaling pathway, resulting in the sensation of itch [64]. The hallmark axonal reflexive flare that accompanies histaminergic itch is thought to occur via TRPV1-controlled release of neuropeptides such as substance P and calcitonin gene-related peptide [65].

Activation of the thermoheat receptor TRPV1 explains the hot-burning quality of histamine-induced itch. The role of TRPV1 in histaminergic itch is largely due to its expression in histamine sensitive C nerve fibers [58]. Interestingly, TRPV1 expression is upregulated in AD skin lesions, and its activation results in the release of molecules that promote both inflammation and pruritus [53, 66]. These findings resulted in increased interest in the TRPV1 as a potential therapeutic target for the treatment of AD. A recent randomized clinical trial examining the effects of a novel topical TRPV1 inhibitor (SB705498) failed to demonstrate a clinically significant effect on pruritus induced by cowhage or histamine, when compared to placebo [67].

TRPA1

The TRPA1 receptor is expressed by keratinocytes, melanocytes, fibroblasts, and sensory C fibers [68, 69]. TRPA1 is involved in the transmission of several different sensory modalities (cold, pain, and pruritus) and also is implicated as a

mediator of neurogenic inflammation [70]. With regard to pruritus, TRPA1 is a known transducer of histamine-*independent* itch to the CNS [57, 60]. Expression of TRPA1 in dermal sensory nerves, mast cells, and the epidermis was markedly elevated in lesional skin biopsies from patients with AD, when compared to healthy controls [71]. TRPA1 is thought to mediate itch as a downstream transduction channel, since activation of TRPV1+ neurons by pruritogens appears to require a downstream intracellular signal-transducing mechanism [59, 72]. In addition to transducing chronic itch signals from the periphery to the CNS, TRPA1 is implicated in the dramatic skin changes that arise as a consequence of the itch-scratch cycle evoked by dry skin [73]. The recent revelation that TRPA1 is involved in dry skin-related skin changes is consistent with previous findings that TRPA1 is a major sensor of skin barrier insult [57, 73].

The role of TRPA1 in the pathophysiology of AD is complicated by the fact that its activation triggers barrier recovery and the maintenance of epidermal permeability homeostasis [57]. Further complicating matters, the application of a topical TRPA1 agonist hastened barrier recovery in animals, while TRPA1 antagonism blocked recovery [74]. Treatment with icillin, a potent TRPA1 and TRPM8 agonist, increased expression of epidermal adhesion molecules and of extracellular matrix proteins in cultured keratinocytes [68].

The role of TRPA1 in AD is thus not completely one sided. Indeed, its effects seem to be multifactorial and, at times, contradictory. TRPA1 activation most likely plays a part in transmitting itch signals. Yet, agonism of TRPA1 provides the benefit of barrier repair. Thus, any treatment that antagonizes TRPA1, while having the benefit of relieving itch, would additionally have the negative effect of acting as an impediment to barrier repair. As such, investigators should consider the balance of agonism and antagonism in pursuit of developing future molecules for the therapeutic treatment of chronic atopic-related pruritus.

TRPM8

TRPM8 is a temperature-sensitive calcium-conducting channel that is expressed by cutaneous sensory nerves, mast cells, and epidermal keratinocytes [75, 76]. TRPM8 is activated by menthol, eucalyptol, and icillin [57]. Activation of the TRPM8 results in an influx of intracellular calcium and the experience of a cooling sensation [77–79]. The subsequent cooling sensation may explain the finding that the use of TRPM8 agonists, such as menthol and icillin, relieves chronic itch [57]. Interestingly, TRPM8 may also be involved in epidermal barrier maintenance and homeostasis, since application of topical menthol to mice with mechanical skin barrier injures significantly accelerated barrier repair, an effect that was blocked by TRPM8 antagonism [80]. Moreover, TRPM8 is expressed on myelinated cutaneous nerves (A-delta fibers) [81]. A-delta fiber activation is implicated in the transmission of itch signals in a subset of subjects, which may explain the diversity of chronic pruritus patient experiences [82, 83].

Neuronal Hypersensitivity

There is a growing degree of evidence implicating hypersensitivity as a leading cause of chronic pruritus, whether due to increased innervation, decreased activational threshold, or some combination of the two. The origins of this theory were predicated on the observation that the perception of itch in response to a previously nonitchy stimulus (alloknesis) is commonly seen in the setting of chronic pruritus [84]. Similarly, patients with AD report increased sensitivity to itch stimuli, as well as alloknesis. These changes are due to peripheral sensitization of the itch neural pathway, which results in increased excitability of the primary itch-sensing neurons [11]. Increased excitability of sensory nerves can occur either by hyperinnervation or by decreasing the threshold for activation. Numerous animal and human studies have documented increased epidermal innervation by itch-sensitive nerve fibers and expressional changes resulting in the hyperexcitability of said sensory nerves [84–88]. This phenomenon is also noted in the central nervous system. Brain imaging studies in AD patients demonstrated increased activation in the anterior cingulate cortex and dorsolateral prefrontal cortex, areas that are also known to be involved in hypersensitization phenomena of chronic pain [89].

Irritants, such as wool clothing, can cause intense itching in patients with AD, which supports the theory of surrounding cutaneous nerve hyperreactivity [90]. In lesional skin of patients with AD, the distribution density of cutaneous nerve fibers was much higher than in normal controls [91]. Furthermore, the diameters of cutaneous nerve fibers were much larger, secondary to an increase in the number of axons in each fiber bundle [91]. The quantity of peripheral nerves in lesional AD skin is significantly increased when compared to unaffected AD skin [92]. Under electron microscopy, peripheral nerves from lesional skin revealed bulging axons and numerous mitochondria—both of which are characteristics of increased neuronal activity and suggestive of hyperactivity [92, 93].

Increased expression profiles of various molecules are additionally implicated in sensitization of the peripheral itch pathway [11]. In animal models of AD, MrgprA3 and TLR3 (a receptor implicated in pruritus) expression levels are significantly increased in sensory neurons [73, 94]. Additionally, a human study showed that PAR2 expression is upregulated in AD [48]. Peripheral itch sensory neurons can additionally be sensitized via the actions of endogenous mediators. The neurotropin nerve growth factor (NGF) is a classic example of the endogenous sensitization of peripheral itch nerve fibers. Expression of NGF and its receptor (TrkA) is upregulated in

AD [95]. NGF sensitizes primary itch-sensing neurons by promoting nerve sprouting, elongation, and survival [96, 97]. NGF-mediated sensitization of cutaneous nerve endings appears to involve increased expression of gated ion channels (TRPV1), which leads to enhanced membrane current (Fig. 2). Fittingly, pretreatment of the skin of human subjects with NGF results in a dramatic enhancement of cowhage-induced itch [98].

Cytokines, Neuropeptides, and Endogenous Secreted Factors

Cytokines

Cytokines play a critical role in the pathogenesis of atopic eczema and are of significant importance in the mechanisms underlining atopic itch. Our discussion below will focus on the cytokines and chemokines implicated in mediating chronic pruritus in the setting of atopic eczema. More comprehensive discussions of all the cytokines involved in AD and their associated actions exist elsewhere, and we highly encourage readers with interest in the subject matter to refer to the cited documents [99, 100].

Thymic Stromal Lymphopoietin

TSLP is a cytokine long implicated as an important mediator of T-lymphocyte maturation and activation. Signaling between epithelial cells and immune cells through TSLP is thought to be a major driver of AD [101]. Numerous studies have reported that TSLP acts as a master switch, triggering both the initiation and maintenance of AD [102, 103]. In addition, TSLP is thought to mediate the atopic march phenomenon [104–106]. Expression of TSLP is upregulated in keratinocytes in AD [107]. Overexpression of TSLP in keratinocytes results in the development of AD-like skin phenotype in mice [102, 108, 109]. Interestingly, PAR2 appears to drive keratinocyte production of TSLP [101]. Several studies have reported a correlation between PAR2 activity and TSLP expression in the skin of AD patients [110–112]. Indeed, PAR2 activation triggers robust TSLP expression in keratinocytes [103, 113]. More recently (2013), TSLP was found to promote itch directly via activation of cutaneous sensory neurons [101]. The authors additionally reported that TSLP-induced itch required TRPA1 and that the expression and release of keratinocyte-derived TSLP depended on the ORAI1/NFAT calcium signaling pathway [101]. These findings firmly establish TSLP as a pruritogenic molecule. The additional associations with PAR2 and TRPA1 suggest TSLP as a major mediator in atopic itch. Furthermore, these recent developments further validate the role keratinocytes play as the gatekeeper of the itch sensation. Agents targeting TSLP or its receptor represent a novel category of potential antipruritic therapeutics.

IL-2

Intravenous IL-2 is used in the treatment of metastatic cancer, and severe pruritus is a known side effect of treatment [114–116]. When IL-2 was injected intradermally in either healthy subjects or in patients with AD, it induced itching and erythema that lasted 48–72 h [117]. Calcineurin, via the actions of protein phosphatase and transcription factor NFATc, activates IL-2 synthesis and secretion [116]. Cyclosporine A, a known calcineurin inhibitor, downregulates IL-2 synthesis and results in decreased pruritus in patients with treatment-resistant Sezary syndrome, as well as in patients with AD [118, 119].

IL-31

IL-31 is a cytokine that is produced primarily by Th2 cells and signals via binding to its receptor (a complex composed of IL-31 receptor A and oncostatin M receptor), which is expressed on keratinocytes, epithelial cells, and by DRG pruriceptors (Fig. 2) [116, 120–122]. Activation of the IL-31 receptor (IL-31R) complex results in activation of the JAK family of tyrosine kinases, which in turn leads to activation of transcription factors (STAT-1/5 and ERK-1/2) and induction of the MAP kinase signaling cascade [123, 124]. IL-31 levels are highly elevated in numerous pruritic disorders, including AD, prurigo nodularis, allergic contact dermatitis, and cutaneous T-cell lymphoma (CTCL) [120, 125–128]. IL-31 expression is significantly elevated in pruritic lesional skin of patients with AD compared to nonpruritic lesional skin of patients with psoriasis [120]. The colonization of lesional skin by superantigen producing staphylococcal species is a known exacerbant of AD. In vivo and in vitro exposure to staphylococcal superantigen rapidly induces IL-31 expression in individuals with AD [120]. Activated leukocytes in patients with AD expressed higher levels of IL-31 transcripts compared with healthy, nonatopic individuals [120]. Serum IL-31 levels are elevated in patients with chronic urticaria and AD [129]. In addition, IL-31 levels positively correlate with disease severity in AD and with itch severity in CTCL [125, 126].

Interestingly, mouse and human DRG neurons that additionally coexpress TRPV1 express IL-31R [130]. IL-31-induced itching appears to require TRPV1 and TRPA1, a finding that demonstrates the complex interplay between the mediators of pruritus [130]. In a recent study (2014), IL-31 was shown not to induce an immediate itch response in humans [131]. Rather, IL-31 induced a late onset (mean delay of 143 min) pruritus [131]. The delayed itch induction suggests that IL-31 exerts its pruritic action via indirect mechanisms, rather than through cutaneous receptor activation

[131]. Such an indirect mechanism of action may involve keratinocytes. The keratinocyte is further implicated by the recent (2014) discovery of IL-31 receptor expression on keratinocytes in the lesional skin of patients with severe AD [132].

The culmination of all these findings has resulted in interest in IL-31 and its receptor as a novel target for treatment of pruritus. Currently, a phase 1 study (NCT01614756) of an anti-IL-31 monoclonal antibody is underway—at the time of authorship, no data have been published [133].

IL-4 and IL-13

Moderate to severe atopic dermatitis is driven by the activation and expression of type 2 helper T-cells (Th2 cells). The cytokines IL-4 and IL-13 are necessary for the development, initiation, and maintenance of the Th2 subset of cells. IL-4 and IL-13 are thus described as Th2 cytokines. Expression of IL-4 and IL-13 is associated with eosinophilic infiltration and increased production of NGF, as well as increased expression of the NGF receptor, TrkA [134–136]. Both IL-4 and IL-13 are implicated in the pathophysiology of AD (Fig. 2). Transgenic mice overexpressing IL-4 and IL-13 in the epidermis develop all the hallmark features of AD, including pruritus [137, 138]. The levels of IL-4 and IL-13 are both elevated in human lesional skin samples of patients with AD [139]. IL-13 messenger RNA (mRNA) is expressed in both acute and chronic lesions of AD [140, 141]. Serum levels of IL-13 are elevated in AD patients and correlate with disease severity [142]. In a more recent (2013) mouse model investigation, IL-13 was reported to be a potent stimulator of pruritus in AD and appears to involve, at least in part, TRPA1 [71]. A novel monoclonal antibody targeting the actions of IL-4 and IL-13 (dupilumab) demonstrated a 55.7 % reduction in pruritus severity (a more detailed discussion can be found in the therapeutic section of this review) thereby further implicating both cytokines as mediators in pruritus [143].

IL-33

IL-33 is a promoter of Th2-mediated inflammation implicated in the pathogenesis of AD [144–147]. IL-33 expression is increased in lesional skin cells in patients with AD [144, 145]. Serum levels of IL-33 are significantly higher in patients with AD, correlate with disease severity, and decline with lesion improvement [148]. Interestingly, serum levels of IL-33 correlated with disease severity in AD [148]. Despite all of these recent discoveries and associations, little is known about the role of IL-33 in the generation of pruritus (Fig. 2). The involvement of IL-33 in chronic pruritus thus represents a topic of promising research.

Notch Signaling

Notch proteins comprise a family of transmembrane receptors that mediate the differentiation of the epidermis, hair follicles, and sebaceous glands [149–151]. Recently, an expansive amount of evidence has emerged linking deficient Notch signaling to some of the key pathological features of AD, including epidermal barrier dysfunction and induction of the Th2-driven inflammatory cascade [152, 153]. In the skin of lesional AD patients, Notch receptors are significantly downregulated, compared to healthy control patients [154]. Deficiency of Notch results in upregulation of TSLP, inducing a Th2-driven inflammatory response and subsequent production of IL-4 and IL-31 [130, 152, 155–158]. Both IL-31 and TSLP are known to stimulate cutaneous sensory nerve fibers involved in the induction of itch [130].

Histamine

Histamine is released from immune cells in response to tissue inflammation or stimulation by allergens [59, 159, 160]. Direct application of histamine to human skin induces itching and a subsequent axonal reflexive (antidromic) vasodilation or flare [84]. There are a total of four histamine receptors, all of which are GPCRs. Of the four receptors, two (H1R and H4R) have been identified as potential mediators of pruriproception (Fig. 3) [160]. Prior studies showed that the H1-receptor (H1R) is expressed in the DRG and that inhibitors of H1R can completely suppress histamine-induced itch in human skin [160, 161]. Thus, the H1 receptor is implicated as an important mediator of histamine-induced itch reactions. The role of H1R in atopic itch is limited, however.

More recent studies demonstrate that inhibitors of a different histamine receptor, H4R, can block itching in a contact dermatitis mouse model, thereby suggesting that it too is a mediator of itch [162]. Perhaps of even greater clinical import, in a subsequent study, Cowden et al. showed that inhibitors of H4R have dual effects on pruritus and Th2-mediated inflammation, resulting in significant reductions in both [162, 163]. Furthermore, concomitant blockade of H1R and H4R was more effective at reducing itch and inflammation than either alone [163]. A novel H4R antagonist (JNJ 39758979) reduced histamine-induced pruritus in a randomized control trial of healthy subjects, while histamine-induced wheal and flare were unaffected [164]. The latter finding definitively demonstrated the selectivity of this novel compound to target H4R. Importantly, these findings were in the context of histamine-induced pruritus, which plays little role in the nonhistaminergic pathways that drive atopic itch.

Neuropeptides

Substance P

Substance P (SP) is a neuropeptide involved in afferent neuronal signal transduction [165]. Activation of sensory neurons in the skin causes release of SP [116, 166]. Once released, SP binds to neurokinin receptors (NK1) found on mast cells, keratinocytes, and cutaneous nerve ending, resulting in the release of additional itch mediators [27, 166]. Thus, SP appears to act to induce itch, albeit indirectly. This potential to induce itch is further confirmed by the finding that intradermal injection of SP in humans results in mast cell activation and release of histamine and is associated with a wheal and flare reaction [167–170]. The wheal and flare reaction, though not the pruritus, is inhibited by pretreatment with antihistamines or use of histamine liberating compounds (48/80), which act to deplete local histamine stores [167–169]. The persistence of pruritus, even in the absence of functioning histamine, indicates that SP-induced itch is not dependent on histamine, but rather on mast cells. Unsurprisingly, SP activates mast cell (MC) release of inflammatory mediators such as leukotriene B4, prostaglandin D2, and TNF-alpha [171–174]. In addition to its actions on MC, SP triggers the release of pruritogenic compounds from keratinocytes, endothelial cells, and immune cells [175, 176]. Serum levels of SP have been reported to be increased in patients with AD and correlate with itch intensity [177]. Lesional skin from patients with AD and prurigo nodularis is characterized by increased SP-positive sensory neurons [178, 179]. In an uncontrolled case series study, aprepitant, an antiemetic with NK1-receptor antagonist properties, effectively reduced pruritus due to various cutaneous and systemic causes [180–183].

Nerve Growth Factor

NGF is a neurotrophin that modulates the development of the peripheral nervous system, including cutaneous innervation, and is implicated as a major culprit in the pathophysiology of pruritus. More specifically, NGF has effects on neuronal growth, differentiation, and regeneration. Serum levels of NGF directly correlate with scratching behavior in mice—wherein the higher the level, the greater the degree of scratching [184]. In humans, NGF levels did not correlate to itch in AD [185]. These contradictory findings from animal and human experiments question the role of NGF in atopic itch. More research is needed in order to definitively establish its role in atopic itch.

NGF is thought to precipitate the neurohyperplasia that seems to define the lesional skin of patients with AD [95, 186]. The increased nerve density in lesion skin is mediated, in part, by the release of keratinocyte-derived NGF. In animal models, NGF upregulates neuropeptides, such as SP and calcitonin gene-related peptide (CGRP) [187]. SP and CGRP are involved in neurogenic inflammation and in the hypersensitization of itch pruriceptors [172]. Histamine release from mast cells increases levels of NGF [188]. Intradermal injection of NGF sensitizes receptors for nonhistaminergic itch in human skin [98]. Thus, the role of NGF as a mediator of chronic itch in AD is most likely multifactorial, wherein NGF stimulates increased cutaneous innervation and release of puritogenic substances (CGRP and SP) and primes existing nerves by lowering the threshold for itch sensation. Eosinophils are the main source of NGF and release of NGF is associated with TRK1 activation. TRK1 activation increases PI3 kinases, which increases TRPV1 expression and intracellular calcium, which in turn releases SP and CGRP via SNARE/synaptogoin/synaptobrevin mechanisms. SP and CGRP both increase eosinophil chemotaxis, activation, and survival, thus propagating a vicious itch cycle.

Gastrin Releasing Peptide and Gastrin Releasing Peptide Receptor

Gastrin-releasing peptide (GRP) is a neuropeptide that is thought to be involved in the sensation of itch, since intradermal injections of GRP elicit scratching in mice [189]. GRP is released by neurons in the dorsal root ganglion [190–193]. Once released, GRP activates dorsal spinal cord neurons expressing the GRP receptor (GRPR), which in turn transmits the itch signal to higher order neurons [194]. Ablation of GRPR expressing spinal cord neurons results in substantial deficits in scratching behavior in response to all itch stimuli [191]. In macaques suffering from chronic idiopathic pruritus, GRPR and the GRP ligand were highly expressed in both the spinal cord and skin; this was the first report of such findings in a primate model [195]. Most of our current understanding of GRP and GRPR as mediators of pruritus come from animal studies that do not focus on their role in the specific setting of atopic itch. Thus, the role of GRP and GRPR in AD is untenable, at best. To that end, a recent (2013) study of severe pruritus in AD patients (n=88) demonstrated a positive correlation between serum GRP levels and pruritus [196]. More research is needed in order that the role of GRP and GRPR in the context of AD may be better understood.

B-Type Natriuretic Peptide

B-type natriuretic peptide (BNP) was recently (2013) found to activate neurons responsible for the release of GRP, thereby implicating it as a mediator in the transmission of itch signals from the periphery to the brain [193]. More specifically, BNP mRNA was expressed in select TRPV1 spinal neurons [193]. In a knockout model of BNP, mice were found to selectively lose almost all behavioral responses to itch-inducing agents [193]. Intrathecal injection of BNP in both wild-type and

knockout mice triggered potent scratching behavior [193]. A more recent (2014) next-gen RNA-Seq study reported that GRP is not transcribed in sensory ganglia, while BNP is [197]. However, those findings could not be replicated in a subsequent study [190].

Endogenous Secreted Factors

Acetylcholine

All of the myriad different components of the cholinergic system exist in human nonneuronal cell populations, including the skin [198]. Said components have been detected in several skin structures, including keratinocytes, eccrine glands, and sebaceous glands [198]. Ach plays an intermediary role in the interactions of nonneuronal cells with hormones, growth factors, cytokines, and the neural systems. The role of Ach in the setting of atopic itch is not completely understood, but there is evidence to suggest its involvement and thus implicate it as a novel mediator.

Expression of choline-acetyltransferase (ChAT), the enzyme responsible for the synthesis of Ach, is increased in the lesional skin of patients with AD [199]. Ach is known to stimulate both histaminergic and nonhistaminergic cutaneous sensory nerve C fibers [27, 200]. Intradermal injection of Ach results in induction of axonal reflexive flare response similar to that noted in histaminergic itch, though the flare is comparatively smaller in size [201]. AD patients are more sensitive to intradermal injections of Ach than to histamine [202]. In healthy subjects, intradermal injections of Ach causes pain, while in patients with atopy, it causes itching [203].

Keratinocytes express different Ach receptor profiles depending on their state of maturation and differentiation [204]. The use of corticosteroids modifies this Ach receptor expression profile of keratinocytes [205, 206]. Nonneuronal Ach is released by human skin cells and is known to bind to the Ach receptors of its source and neighboring cells, thereby establishing autocrine and paracrine regulatory loops [207]. Binding of Ach to nicotinic or muscarinic (M1 and M3) receptors expressed on the surface of epithelial keratinocytes results in increased influx of calcium into the inner cellular space and leads to the activation of numerous signal transduction cascades [204, 208]. Long-term blockade of nicotinic and muscarinic receptors induces cell-cell detachment and changes the expression profile of specific structural proteins (E-cadherin and catenin) in keratinocytes [204]. Thus, Ach is implicated as a potential mediator in the epidermal barrier dysfunction that invariably plays a role in atopic itch (Fig. 3).

Ach additionally plays a part in modulating inflammatory responses. Ach activity is involved in the induction process of CD4 and CD8 T-cell maturation [209, 210]. On lymphocytes, Ach activation results in increased potassium channel activity. The proliferation and differentiation of lymphocytes is strongly associated with potassium channel activation. Thus, the regulatory effects of Ach on lymphocyte differentiation may be linked to Ach activity. Ach is additionally implicated in modulation of immune responses, since activation of a subset of nicotinic receptors (alpha-7) is involved in the generation of immunomodulating antibodies [209, 211]. Stimulation of the same nicotinic receptor subtype, by either neuronal or nonneuronal Ach, inhibits the release of proinflammatory mediators (TNF-a, IL-1B, IL-6, and IL-18); this phenomenon is classically described as the cholinergic anti-inflammatory reflex pathway [212, 213]. These dual roles on the immune system evidence the autocrine and paracrine loops mediated by Ach that regulate immune cell activity. Dysfunction of these complex and interrelated loops may potentially mediate atopic itch.

The role Ach may play in chronic pruritus in patients with AD is not completely understood. In addition to the findings discussed above, we now know that enhanced levels of Ach are associated with pruritus, thickening of the stratum spinosum, enhanced blood flow, and impaired barrier function [199]. These findings suggest that a complex interface between keratinocytes, inflammatory cells, cutaneous nerve endings, and Ach may be one of the drivers of atopic itch. Ach is thus a novel potential mediator of itch.

Cannabinoids

The endogenous cannabinoid system aids and actively participates in regulating immune response [214–216]. Cannabinoid-based drugs are known to inhibit the production of proinflammatory cytokines and chemokines [216]. Two variants of the cannabinoid receptor, CB1 and CB2, are expressed on cutaneous sensory nerve fibers, mast cells, and keratinocytes [216]. In mouse models of allergic contact dermatitis, mice lacking the CB1 and CB2 receptors developed increased allergic immune responses when exposed to contact allergens [217]. Topical application of CB2 agonist (HU-308) causes an increased contact allergic response, while blockade of CB2 alone suppresses the allergic immune response [217, 218]. Thus, CB2 activation in the skin appears to be proinflammatory (Fig. 3). CB1 receptors are expressed on keratinocytes and participate in the regulation of allergic skin inflammation by modulating the secretion of proinflammatory cytokines [216, 219]. A recent (2014) investigation using a mouse model for an allergic dermatitis that shares many features with AD (fluorescein isothiocyanate) found that CB1 receptor-deficient mice exhibit delayed epidermal barrier repair and an enhanced epidermal immune response, characterized by increased expression of proinflammatory mediators, such as TSLP, IL-4, and TNF [216]. In direct contrast to CB2, CB1 receptors appear to attenuate allergic skin inflammation. CB1 receptor agonists thus represent a new and interesting therapeutic agent for the treatment of AD. Interestingly,

topical tetrahydrocannabinol (THC) appears to attenuate allergic skin responses independently of the CB1 and CB2 receptors [219].

Psychological Stress

Psychological stress is associated with myriad dermatologic disorders, including atopic eczema and pruritus [220, 221]. In the setting of AD, the role of stress is quite complex: chronic pruritus in AD is known to cause significant patient distress, yet stress in its own right can induce, trigger, or aggravate disease [222–224]. The hypothalamic-pituitary axis (HPA), as well as the sympathetic and serotonergic nervous systems, is activated in response to psychological stress, resulting in increased expression and secretion of catecholamines, glucocorticoids, and a host of other molecules [225–227].

Glucocorticoid secretion inhibits Th1-secreted factors and stimulates the upregulation of cytokines that mediate Th2 responses, such as IL-4, IL-10, and IL-13 [228]. The secretion of glucocorticoids in response to stress thus triggers a skew toward Th2-mediated cytokines. As discussed earlier in this review, IL-4 and IL-13 are Th2 cytokines implicated in the pathogenesis of atopic itch. Glucocorticoid secretion in response to psychological stress is thereby implicated as a mediator of atopic itch, since its release triggers a skew toward Th2-mediated cytokines that are known mediators of atopic itch.

Mast cells express various neuropeptide and neurohormonal receptors that can be activated by hormones released in response to psychological stress [229–231]. Once activated, mast cells produce and secrete numerous additional molecules, including cytokines, SP, and proteases [232–235]. These mast cell-derived secreted factors drive neurogenic inflammation, leading to the stimulation of the surrounding cutaneous nerve fibers, which invariably evokes pruritus [236].

Treatments: Getting the Itch Out

Topical Therapies

Emollients/Moisturizers

The terms emollient and moisturizer are often used interchangeably. The world emollient originates from Latin for "a material designed to soften the skin." Emollients accomplish this task of softening the skin predominantly via three mechanisms: occluding, rebuilding, and rehydrating [237–239].

Epidermal barrier dysfunction is one of the underlining mechanisms driving atopic itch, since it facilitates the entry of irritants, allergens, and infectious pathogens—all of which are known to precipitate itch [240]. Emollients are known to reduce atopic itch [241]. Furthermore, emollients are known to be steroid-sparing agents, since their use results in the decreased need for topical corticosteroids [242–244]. The use of emollients in combination with topical corticosteroids leads to increased treatment efficacy and improvement in pruritus, when compared to topical corticosteroid use alone [245].

By coating the skin with nonphysiologic lipids, emollients create an effective barrier that prevents the movement of water out of the skin. Emollients, thus, have the immediate benefit of preventing further water loss by restoring epidermal barrier dysfunction. Emollients also facilitate active processes for epidermal rehydration via the actions of the hydrating class of molecules known as humectants (NMF). Humectants, such as urea and glycerin, are able to penetrate the epidermis and diffuse into keratinocytes, thereby restoring some of the ability of keratinocytes to retain water [246, 247]. Aside from allowing for epidermal rehydration, emollients also drive efforts to rebuild new, healthy skin. The rebuilding efforts of emollients are largely due to the presence of physiologic lipids, which replenish the constituents of the lipid-rich medium surrounding keratinocytes.

Patients often find ointments to be messy, difficult to use consistently, and generally report dissatisfaction with the delivery vehicle. The past decade has witnessed the development of numerous novel skin delivery formulations, including nonalcohol-based hydrating gels.

Colloidal Oatmeal

Oatmeal has been used for centuries in the treatment of various xerotic dermatoses due to its soothing properties and its ability to relieve itching [248]. A host of studies have reported on the anti-inflammatory, barrier repair, and moisturizing properties of oatmeal extract [249]. The various clinical benefits of colloidal oatmeal seem to arise from the breath of molecules that make up the colloidal suspension.

Numerous studies have documented the intrinsic anti-inflammatory and antipruritic effects of avenanthramides, which represent a group of phenolic alkaloids that are present in oats [250–252]. Avenanthramides are implicated as the agents driving the antipruritic effects of oatmeal-based therapies. Oatmeal extract decreased arachidonic acid, cytosolic phospholipase A2, and tumor necrosis factor-alpha (TNF-alpha), all of which are known inflammatory mediators [250]. In keratinocytes, oatmeal extract inhibited the activity of nuclear factor kappa B (NF-kappa B), a transcription factor responsible for both innate and adaptive immune responses [251]. In addition, colloidal oatmeal inhibited keratinocyte release of proinflammatory cytokines (such as IL-8) and histamine [251]. In a recent (2012) review of the use of colloidal oatmeal as an adjunct treatment in AD, daily use of moisturizers and/or cleansers containing colloidal oatmeal significantly improved

the clinical outcomes of AD from baseline, including itch severity [249].

Ceramides

Ceramides represent a family of waxy lipid molecules that are a component of sphingomyelin, the predominant lipid found in the lipid bilayer membrane of numerous cells. In addition, ceramides are present in the lipid-rich matrix surrounding mature keratinocytes of the stratum corneum, which influences skin barrier function [253].

Nearly half of the intercellular lipids in the stratum corneum are ceramides [254, 255]. The lipid-rich matrix of the stratum corneum prevents epidermal water loss and impedes the entry of chemicals, infectious agents, and allergens [256, 257]. Levels of ceramide in the skin of patients with AD are decreased [258, 259]. Dysfunctional ceramide synthesis is thought to play a role in the skin barrier dysfunction of AD [260, 261]. In a recent (2014) cohort study, a ceramide-containing cleanser and moisturizer regimen substantially improved SCORAD scores, QoL measures, and overall disease severity in patients with AD, including itch severity [262]. Ceramide-containing skin products have been shown to protect, hydrate, and moisturize the epidermis, as well as aid in the epidermal rebuilding process [30, 263, 264]. It is highly unlikely that these externally applied ceramides are incorporated into the extracellular lipid matrix. More likely, ceramides aid in the creation of an environment that supports barrier repair [262]. Both the creation of an environment that is conducive to epidermal repair, as well as the prevention of further transepidermal water loss, together most likely account for the antipruritic properties of these agents. An equimolar ratio of cholesterol, ceramides, essential free fatty acids, and nonessential free fatty acids allows for normal barrier recovery [265]. Interestingly, a 3:1:1:1 ratio of the respective aforementioned agents allows for accelerated barrier recovery [265].

Nonsoap-Based Cleansers

Human skin is naturally coated with a very fine slightly acidic film, known as the acid mantle, which acts as barrier to bacteria, allergens, and other environmental threats that might seek to penetrate the skin [266, 267]. Production of the acid mantle is largely accomplished via sebaceous gland secretions. The natural pH of the skin is thus acidic, ranging from between 4.5 and 6.2 [266]. Nonsoap-based cleansers are recommended for patients with AD because they support and maintain optimal epidermal surface pH [268, 269]. In order to maintain the integrity of the acid mantle, current guidelines recommend the use of mild synthetic detergents (syndets) with a pH ranging from 5.5 to 6.0 in the treatment of AD [268]. The use of syndet as a cleansing product in place of normal, more alkaline, detergents (e.g., regular soap) in patients with AD resulted in reduced lesion severity, improved overall skin condition, and decreased epidermal water loss [270].

Low pH (Acidic) Cleansers and Moisturizers

Skin surface pH in healthy subjects is 5.2, while in patients with AD, skin pH in nonlesional skin is 5.5 [267]. The elevation in AD patients compared to healthy subjects may partly explain the increased perception of itch. Alkaline cleansers are known to increase the secretion of serine proteases, which results in the endogenous activation of PAR2, an itch-mediating receptor [271, 272]. Thus, alkaline-based soaps and moisturizers themselves are implicated in initiating itch. For this reason, patients with AD should be advised to use low pH (acidic) cleansers and moisturizers. Interestingly, a recent (2014) study reported that the itch intensity did not differ between healthy subjects and AD subjects, in response to the application of artificial alkaline sweat to their forearms after cowhage-induced itch [273].

Topical Corticosteroids

Topical steroids have been the first-line treatment for the acute management of AD since their introduction nearly 50 years ago and their usefulness continues to be well-documented in the literature [274–278]. While numerous studies have validated the efficacy of these agents in AD, few present data are directly related to pruritus [279]. Of 83 randomized controlled trials (RCTs) discussed in a systematic review, only 39 evaluated pruritus, and only 7 of said studies presented data specific to pruritus [279, 280]. In two of the RCTs that reported itch-specific data, patients treated with topical corticosteroids demonstrated significant improvement in itch symptoms when compared to vehicle control, with one study showing statistically significant improvement by day 4 of treatment [281, 282]. With over 30 different topical steroid options on the market, it becomes increasingly relevant to discuss the efficacy of different agents. In that vein, the literature suggests that low potency topical steroids are less effective at reducing pruritus than moderate or high potency options [283, 284]. Furthermore, moderate and high potency topical steroids appear to have similar efficacies [279]. Therefore, we recommend clinicians start treatment with moderate potency topical corticosteroids.

Topical Calcineurin Inhibitors

Topical calcineurin inhibitors (TCIs) tacrolimus and pimecrolimus are known to reduce erythema, pruritus, and excoriations [285, 286]. In a systematic review of 22 randomized controlled trials from 2012, TCIs were shown to reduce pruritus by 36 % when compared to placebo [287]. In a more recent study, tacrolimus reduced AD-associated cytokines and

chemokines in monocytes, some of which are implicated in pruritus [288]. Randomized trials demonstrated that TCIs improve pruritus within 48 h of the first application and maintain their antipruritic effects with continued use, thereby proving treatment efficacy [289].

The mechanism of action of these agents is not entirely clear and may prove multifactorial. TCIs are known to regulate T-cell activation and inhibit the release of inflammatory cytokines [290, 291]. In addition, TCIs may orchestrate a direct antipruritic effect by overstimulation of TRPV1 ion channels on cutaneous nerve fibers, resulting in desensitization of itch transmitting nerve fibers [292]. Clinically, TCIs are particularly effective in the treatment of children with AD and are an effective alternative for AD on the face, eyelids, and skin folds that is unresponsive to low potency topical corticosteroids [257]. Moreover, twice weekly proactive application of TCIs is an effective prophylactic treatment for AD [293].

TCIs may cause an initial burning sensation when applied. The noted burning sensation may be due to the activation of TRPV1 on cutaneous nerve fibers. This sensation often subsides after repeated use over several days. A benefit of TCI use is that they do not cause skin atrophy with prolonged use, in contrast to topical steroids. Topical application of calcineurin inhibitors does not achieve significant systemic levels and does not cause systemic immunosuppression [294–297].

Clinicians and patients often express reservations about using TCIs due to the 2005 FDA decision to assign a boxed warning concerning the theoretical risk of increased malignancy with the use of TCIs. The FDA's decision was primarily based on a 39-week toxicity study conducted in monkeys [298]. In that study, investigators fed animals oral pimercrolimus at a dose that produced systemic immune suppression and was 30-fold greater than the maximal exposure achieved in humans via topical application [298]. To date, no causal relationship between malignancy and TCI use has been definitively proven. Long-term safety studies demonstrate similar safety profiles between TCIs and low potency topical steroids [299–302]. In fact, the observed number of malignancies, from postmarketing surveillance and data reported to the FDA via its adverse events reporting system, is much lower among TCI-exposed patients than the expected number for the general population [303–305].

Capsaicin

Capsaicin is a naturally occurring alkaloid and one of the active components of chili peppers. Topical application of capsaicin is used in the treatment of pruritus due to numerous different etiologies [306–309]. Mechanistically, capsaicin binds to and activates the TRPV1 ion channel [310, 311]. The TRPV1 ion channel is expressed on cutaneous nerve fibers and its activation results in the release of pruritogenic neuropeptides (e.g., SP and CGRP) [310]. The ability of topical capsaicin to alleviate itch is thought to involve desensitization of TRPV1 expressing cutaneous nerve fibers [312]. In a small study (n=33) of patients with prurigo nodularis, application of topical capsaicin for 12 days resulted in complete alleviation of itch in all patients [309]. In addition to alleviating pruritus, topical capsaicin additionally induces neurogenic inflammation [306]. Application of capsaicin is characterized by an initial period of burning and erythema. This initial discomfort complicates patient compliance and treatment efficacy [313]. Instructing patients to apply a topical anesthetic (such as lidocaine and EMLA) before capsaicin during the first 2 weeks of treatment may reduce patient discomfort and increase compliance [314, 315]. Clinically, capsaicin works best in the setting of localized atopic itch.

Local Anesthetics

Topical anesthetics such as pramoxine 1 % and lidocaine 5 % have known antipruritic effects [316–318]. A pramoxine-based topical therapy was found to be more effective than control lotion in the treatment of uremic pruritus [319]. Polidocanol represents a topical agent with both local anesthetic properties and moisturizing effects [320]. An open-label study of 5 % urea and 3 % polidocanol demonstrated a significant reduction of pruritus in patients with AD, contact dermatitis, and psoriasis [321].

Wet Wrap Treatment

Wet wrap treatment (WWT), also known more colloquially as the wet pajama method, is used to reduce severe AD [322, 323]. WWT can be used with either emollients or corticosteroids alone, or in combination. Numerous observational case series have documented the benefits of utilizing diluted corticosteroids and emollients in WWT [322–325]. One RCT using topical corticosteroids first without wraps and second with wet wraps found that corticosteroids performed better in the setting of WWT [326]. A separate RCT comparing corticosteroids to vehicle found that WWT with corticosteroids produced significant improvements compared to WWT with vehicle alone [327]. More recently (2014), in a randomized double-blind placebo-controlled study of children with severe AD, WWT with diluted corticosteroids acted faster and was more efficacious than WWT with emollients alone [328].

WWT produces a cooling sensation on the skin due to evaporation; in addition, it softens the skin, thereby increasing the penetration of topical medications. The predominant mechanism driving the WWT, however, appears to be that it provides a mechanical barrier against scratching. AD is driven by the itch-scratch cycle, which is best understood by the interplay between internal hypersensitivity and external stimuli. Occlusion of lesional skin in AD is thus beneficial and improves barrier function.

Sodium Hypochlorite (Bleach) Baths

Sodium hypochlorite, more commonly known as bleach, has been used for more than 70 years for its bactericidal, antiviral, and sporicidal properties [329]. Bleach is an exceptionally useful product, as its use does not lead to the development of antimicrobial resistance [329]. Furthermore, dilute solutions are known to be nontoxic to both tissues and mucosal surfaces [329]. Numerous studies have reported the safety and efficacy of twice weekly dilute bleach baths in patients with moderate to severe AD [330]. One randomized, placebo-controlled, investigator-blinded 3-month study found significant reductions in disease severity in the bleach bath group compared to control [331]. In a 2-month prospective, randomized, double-blinded, placebo-controlled study in Malaysia, there was a significant reduction in disease severity and bacterial (*S. aureus*) density [332]. With regard to itch, the investigators found that there was a significant reduction in itch severity after 2 months of treatment [332]. How bleach baths work from a pathophysiological viewpoint is not entirely clear. Colonization with *s. Aureus* is a common finding in AD and there appears to be a connection, whether through bacterial toxins, superantigens, or proteases, with pruritus.

Hypochlorous Acid

Hypochlorous acid (HOCl) is an endogenous product in humans recently implicated in the modulation of itch mediators [333]. HOCl decreases protease activity and cytokine expression, which may explain its antipruritic effects [333]. In an open-label pilot study (n=20) evaluating the use of an HOCl and NaOCl combination hydrogel in patients with mild to moderate AD, daily application resulted in 23, 44, and 71 % reductions in itch severity on days 1, 3, and 7, respectively [334]. Aurstat is a second-generation hypochlorous acid-derived hydrogel that contains only HOCl. Eliminating NaOCl reduces the formulary pH, thereby making it more comparable to the pH of normal healthy skin.

Topical Strontium Chloride (TriCalm™)

Topical strontium chloride can be formulated in water-soluble salts and is available in a 4 % hydrogel solution over the counter as TriCalm. Topical strontium is well known to inhibit sensory irritation and to reduce histamine-induced itch [335–337]. More recently (2013), in a double-blinded, vehicle-controlled study, topical strontium was reported to reduce cowhage-induced itch [338]. Additionally, strontium significantly reduced peak intensity and duration of itch [338]. The authors concluded that topical strontium was superior to topical diphenhydramine and hydrocortisone, as well as control vehicle [338]. Itch induced by cowhage is mediated by PAR2, which is thought to be involved in the pathophysiology of AD [339].

Topical Cannabinoids

Palmitoylethanolamide (PEA) is an endogenous fatty acid amide with endocannabinoid-like properties. PEA has little affinity for cannabinoid receptors [340, 341]. PEA is thought to exert its cannabinoid activity by inhibiting the breakdown of anandamide, a potent endocannabinoid, thereby increasing the concentration and activity of anandamide [320]. More recently, the incorporation of PEA into topical creams has decreased the severity of atopic itch [342–344]. New therapies targeting the cannabinoid receptors represent an interesting area of development for the treatment of chronic pruritus.

UV Therapy

Phototherapy is an efficacious and safe therapeutic option for the treatment of AD and associated pruritus [345]. There are numerous wavelengths that can be used, but the most effective seems to be narrow band UVB [313]. How phototherapy works mechanistically on AD is not fully understood. The use of phototherapy appears to result in a reduction of cutaneous sensory nerve fibers, which may explain its ability to reduce itching [346]. UVB, narrow band UVB (NB-UVB), UVA/B combination, and UVA have all been shown to improve both AD and associated atopic itch [347–350]. Patients receiving UVA report reduced itch intensity on the half of their body receiving phototherapy [347]. In patients receiving NB-UVB therapy, 90 % report decreased itch severity, whereas 63 % of patients receiving UVA reported a similar reduction [351]. Within the first 2 weeks of treatment with systemic PUVA, nearly all subjects reported relief of their pruritus [352]. The use of excimer laser is a new phototherapy treatment option for AD offering promising results. After 1 month of treatment with excimer, subjects report an average 81 % reduction in baseline itching [353, 354].

Systemic Agents

From immunomodulators to antidepressants, there are numerous systemic agents that can be used in the treatment of AD. The past 20 years has born witness to countless studies, from observational to randomized control trials that document the efficacy of these systemic therapies.

Oral Immunosuppressants

Patients with moderate to severe AD may require systemic immunosuppression for adequate disease control. Ambulatory care data suggests that in excess of 10 % of all patients with

AD receive systemic anti-inflammatories [355]. Myriad different immunomodulators are used in the clinical setting: cyclosporin A (CsA), methotrexate (MTX), azathioprine (AZA), glucocorticoids, and mycophenolate mofetil. While RCTs for many of these agents exists, these studies mostly encompass small cohorts with limited data regarding important secondary end points, such as pruritus. We present a focused discussion of the most efficacious agents below.

Cyclosporin A

CsA is a potent immunosuppressant originally used in the prevention of transplant rejection. A recent (2014) systematic review of 34 RCTs testing 12 different systemic treatments (n=1653) recommended CsA as the first-line treatment for short-term use in moderate to severe AD [356]. Importantly, CsA is not FDA approved for AD, though it is the only immunosuppressant approved for the treatment of AD in Europe and the UK [279].

In a systematic review from 2007, all 15 of the included studies reported a decrease in the mean severity of AD after treatment with CsA [357]. After just 6–8 weeks of continuous treatment, most reported a 50 % reduction in severity [279, 357]. In the context of atopic itch, CsA remains an exceptional treatment option. In three separate RCTs, continuous treatment with CsA resulted in a decline in itch severity by 71–78 % [279, 358, 359]. Based on years of clinical practice, CsA is the most potent and rapid treatment for the short-term treatment of severe atopic itch. Interestingly, a recent (2013) RCT comparing low-dose treatment of severe AD with either MTX or CsA reported that both were equally effective in decreasing overall disease severity [360]. The side effects of CsA include hypertension, elevated creatinine, elevated blood urea nitrogen, opportunistic infection, immunosuppression, and renal toxicity. In addition, there is risk of patients suffering from a rebound flare after discontinuation. Nevertheless, CsA is currently the most rapidly acting oral immunosuppressants used in the treatment of AD.

Mycophenolate Mofetil

Mycophenolate mofetil (MMF), also known as Cellcept, is a potent immunosuppressant that acts as a selective inhibitor of lymphocyte proliferation and antibody production. More specifically, MMF works as a reversible inhibitor of inosine monophosphate dehydrogenase, which results in the inhibition of T- and B-cell growth and proliferation. Treatment of severe AD in adults with oral MMF is safe, well tolerated, and effective [361]. A 2011 randomized, unblinded trial comparing MMF to CsA found that MMF is as effective as CsA for maintenance therapy in patients with severe AD [362]. Despite these findings, MMF requires a longer period of time to have an effect on disease severity. For this reason, we recommend that patients be started on MMF in conjunction with CsA. After 2–3 months of combo therapy, CsA can be tapered down and MMF can be used as a mono maintenance therapy. The side effect profile for MMF is minimal in comparison to CsA; thus, prolonged therapy with MFF is preferred.

Azathioprine

AZA is a purine analog that has been used for its immunosuppressant activities for more than 50 years. A recent (2014) systematic review of systemic immunomodulators in the treatment of moderate to severe AD recommended AZA as a second-line treatment option [356]. AZA is superior to placebo and has previously been shown to be as efficacious as MTX in improving disease severity and quality of life, as well as in decreasing itch severity [363, 364]. A systematic review failed to find any *serious* adverse events (SAEs) up to 24 weeks after treatment with AZA [356, 363–365]. The weekly rate of *any* adverse event during treatment with AZA varied between 5.6 and 22.9 %, with the most common AE being abnormal lymphocyte counts [364, 365]. In a recent (2015) study of the adverse effect profile of AZA in pediatric AD patients, AZA treatment was associated with frequent mild adverse effects and infrequent serious adverse effects in blood indices [366]. The majority of pediatric patients required little to no treatment alteration. Approximately 11 % of the population has reduced levels of the enzyme thiopurine methyl transferase (TMPT), and this is particularly common in African Americans. In these patients, toxic levels of the drug can cause bone marrow myelosuppression; therefore, lower doses of AZA and careful monitoring are required [367].

Methotrexate

The use of MTX has evolved, some might say serendipitously, from its original use as a chemotherapeutic to become one of the most commonly used and affordable immunosuppressants. Today, MTX is used in the treatment of various inflammatory skin diseases, psoriasis, and atopic dermatitis [279]. In a recent (2014) systematic review, MTX was recommended as a third-line treatment option for moderate-severe AD [356]. When compared to AZA, MTX is equally efficacious at improving disease severity and quality of life measures [365]. A systematic review failed to find any SAEs after both 4 and 24 weeks of continuous therapy [356, 365].

Systemic Corticosteroids

While systemic corticosteroids are excellent immunosuppressants, they are not antipruritics and are not recommended for prolonged use in the treatment of AD, due to their safety profile. One double-blinded, placebo-controlled trial comparing prednisolone to CsA for severe AD was terminated early

due to rebound withdrawal [357, 368]. Nearly every patient in the systemic corticosteroids group experienced a serious rebound flare after cessation. The authors reported that systemic prednisolone was less efficacious than CsA and induced stable remission in 1 of 21 patients [357, 368].

Nonimmune Modulating Systemic Therapies

Antihistamines

The itch in AD, from its origins in the periphery to its processing and activation profile in the brain, is a separate and distinct entity from histaminergic itch. Thus, the role for antihistamine therapy in the treatment of atopic itch is limited. Antihistamine therapy is often prescribed to patients with chronic pruritus, to little avail. What little benefit is provided from treatment with these agents is largely due to their known soporific effects. Unsurprisingly, conventional use of antihistamines in the treatment of atopic itch often fails to be of benefit. Based on the findings of numerous placebo-controlled experiments, there is little evidence for the use of antihistamines in the treatment of atopic itch [93, 369]. Anecdotal evidence of the efficacy of antihistamines in AD is most likely secondary to the sedating effects of traditional antihistamine therapy. That said, there is some limited evidence in support of cetirizine to relieve pruritus in AD [370]. A multicenter randomized, double-blinded, placebo-controlled trial of cetirizine in 817 children found that treatment reduced both the use of moderate to strong topical corticosteroids, as well as the development of urticaria [371].

Mirtazapine

Mirtazapine (Remeron) is a selective serotonin–norepinephrine reuptake inhibitor (SNRI) known to reduce pruritus in patients with AD, among a host of other disease entities [320, 372–374]. Centrally, mirtazapine interferes with neuronal reuptake of serotonin and norepinephrine, thereby increasing serotonergic and noradrenergic neurotransmission [320, 375]. In addition, mirtazapine has sedating properties due to its H1-mediated antihistaminergic properties. Which of the aforementioned mechanisms of actions explains the antipruritic properties of mirtazapine is unclear. Interference with the neuronal reuptake of norepinephrine and serotonin may reduce the cortical perception of pruritus [376].

Butorphanol

Butorphanol is a synthetic dual acting opiate that activates the mu (μ) opioid receptor (MOR) and antagonizes the kappa (κ) opioid receptor (KOR) [377]. Activation of the MOR causes generalized pruritus, while activation of the KOR suppresses itch [378–380]. An imbalance between the mu and kappa opioid systems is implicated in generalized pruritus [377]. Thus, the activity profile of butorphanol represents a novel therapeutic treatment option. In a small case study (n=5) of patients with severe, intractable pruritus, intranasal butorphanol produced rapid and marked improvement of pruritus [377]. Importantly, the relief provided by butorphanol does not treat the underlying cause of pruritus. Rather, butorphanol acts mainly to mask the perception of itch via blocking its neuronal transmission [377]. A recent (2014) functional neuroimaging study assessing the actions of butorphanol in the treatment of cowhage-induced itch found that butorphanol produced bilateral deactivation of neural structures activated during the itching process (claustrum, insula, and putamen) [23]. In addition, reduction of cowhage-induced itch with butorphanol correlated with altered cerebral perfusion activity in the midbrain, thalamus, S1, insula, and cerebellum [23].

Phosphodiesterase 4 Inhibitors

Phosphodiesterase 4 (PDE4) is vital to the pathogenesis of inflammation, as it catalyzes the conversion of cAMP to AMP [381–384]. Inhibition of PDE4 thus promotes an anti-inflammatory state. In a 2012 investigator-initiated, open-label pilot study of apremilast (an oral PDE4 inhibitor) in adults with moderate to severe AD (n=16), there was a significant reduction in baseline pruritus in both treatment cohorts [385].

Author Commentary on Systemic Therapies

As discussed above, there are numerous systemic therapies with various mechanisms of action in the clinician's arsenal that can be used to treat AD. Not all of these agents have FDA approval for use in AD; yet, preliminary publications in the literature nevertheless suggest their efficacy. A recent (2014) systematic review on the efficacy of systemic treatments for AD in racial and ethnic minorities in the USA demonstrated that there are virtually no data on the effectiveness or safety of systemic agents in these minority populations [386]. The prevalence of AD in African American children appears to be much higher than other racial groups and presents with unique characteristics [367]. For these reasons, future RCTs should endeavor to recruit cohorts that adequately represent the epidemiologic disease manifestation characteristics, with particular attention to said ethnic minorities.

Alternative Medical Therapies

Acupuncture

Acupuncture is a practice of traditional Chinese medicine, wherein practitioners stimulate specific points of the body,

most often via the insertion of thin needles through the skin. Acupuncture reduced histaminergic itch in healthy volunteers [387–390]. In addition, acupuncture reduced allergen-induced itch in patients with AD [391]. In a patient- and examiner-blinded, randomized, placebo-controlled crossover trial comparing acupuncture to oral antihistamine in adults with AD, abortive verum acupuncture significantly reduced allergen-induced itch, when compared to both placebo and no-intervention controls [392]. In a more recent (2014) functional magnetic resonance imaging (fMRI) study evaluating the underlying brain circuitry supporting allergen-induced itch reduction in AD patients receiving acupuncture, oral antihistamine, or placebo treatments, the greatest itch reduction was noted following acupuncture therapy [393]. In addition, acupuncture was associated with a greater reduction in putamen activity, which is an area implicated in the urge to scratch [393]. Acupuncture thus appears to be an effective adjunct antipruritic treatment strategy in the setting of atopic itch. The specific neurochemical processes underlining this activity remain unknown.

Stress Reduction

Psychological interventions, such as habit reversal training, arousal reduction, and cognitive behavioral therapy, result in reductions in the frequency and severity of itch in different dermatoses [394, 395]. In a recent (2012) meta-analysis, the use of psychological interventions had the largest net positive effect in the treatment of itching and scratching [395]. We will focus our discussion of psychological intervention on the role of habit reversal training.

The goal of habit reversal training (HRT) is to alter dysfunctional behavior by teaching patients how to replace negative thoughts/behaviors with neutral ones. HRT was developed in 1973 [396]. Early in its nascency, HRT was shown to have positive effects in the treatment of some compulsive, anxiety-related disorders (e.g., onychophagia, trichotillomania, and head jerking), with treatment resulting in a reduction of about 99 % of the nervous habits after 3 weeks of training [396]. Soon thereafter, HRT was successfully used to decrease the frequency of scratching in patients with itch-related dermatoses [397, 398]. Subsequent studies demonstrated that, when compared to patients who received medical treatment alone, those who received medical treatment in addition to HRT had a greater improvement in their skin status and a greater reduction of overall scratching behavior [399, 400].

Despite the relative ease and effectiveness of HRT, there are surprisingly a limited number of studies that utilized HRT, in combination with more conventional therapies, as a comprehensive treatment strategy in the context of chronic itch [401–403].

Patient Education

The effectiveness of any treatment modality, be it topical or systemic, is useful only to the extent that the patient (or caregiver) is able and willing to adhere to the recommended regimen. The concept of patient adherence describes the extent to which a patient, after agreeing to a specific regimen, participates in the agreed upon strategy [404, 405]. Nearly half of all patients treated for a chronic condition stop taking their medications after a year [404–406]. Nonadherence indeed may be the underlying precursor to a significant number of cases of treatment failure, as opposed to nonresponse [407]. In a web-based questionnaire study of 3096 dermatologic patients (43 % of which had AD), patient adherence was low in 66 and 76 % of patients receiving oral and topical medications, respectively [408].

The ability of a patient to adhere to a stated treatment protocol necessarily is predicated upon the assumption that the patient understands both her diagnosis and medications. The reasons behind why patients do not fully comprehend a given therapeutic plan are often multifactorial and include inattentiveness, forgetfulness, and poor explanation, among other causes.

In a study of pediatric patients with AD, poor patient understanding of the chronic nature of their disease accounted for a majority of nonadherence [405, 409]. Patients were unaware of the fact that the goal of treatment was control of their AD, as opposed to a cure [405]. In patients treated with topical corticosteroids (n=200), 73 % of patients expressed reservations about using the prescribed treatment; the most frequent cause for concern was the perceived risk of skin thinning [410]. Less than 5 % of all parents in an uncontrolled study of pediatric patients with AD (n=51) recalled receiving any explanation regarding the cause of their child's eczema or a demonstration of how to apply topical treatments [411]. Repeated education and demonstration of topical therapies by a specialized dermatology nurse resulted in an 89 % reduction in disease severity, which was largely due to a substantial (800 %) increase in the use of emollients [411]. Interestingly, this improvement in disease severity occurred in spite of the finding that there was no increase in the use of topical corticosteroids [411]. Written action plans for AD may increase patient understanding and adherence [412, 413]. Ultimately, patient education is of fundamental importance in the treatment of atopic itch.

For these reasons, we utilize a function of our electronic medical records system that autopopulates patient visit summaries with a verbatim copy of everything written in the assessment and plan portion of visit notes. Such measures ensure that patients leave every visit with documentation of our suspected diagnoses and associated orders with instructions. Furthermore, we provide all patients complaining of itch with instructions regarding "best practices" to reduce itching (e.g.,

limiting time spent in shower, using lukewarm water, etc.), as well as specific recommendations regarding common over-the-counter moisturizers and emollients. The use of short (<10 min), patient-oriented web-based videos is a promising new avenue of patient education that we support.

Drugs on the Horizon

Dupilumab

Dupilumab is a novel monoclonal antibody designed for the treatment of atopic diseases. It binds to and then blocks the actions of interleukins-4 and 13, both of which are key drivers of type 2 helper T-cell-mediated inflammation. In a recent (2013) randomized, double-blinded, placebo-controlled trial involving adults with moderate to severe AD, dupilumab was found to have marked and rapid improvement in all the evaluated measures of AD disease activity. With regard to pruritus, treatment with dupilumab resulted in a significant decrease in itch severity (55.7 versus 15.1 %) [143]. In November of 2014, the FDA granted the manufacturers of dupilumab (Regeneron and Sanofi) breakthrough therapy designation for the treatment of adults with moderate to severe AD not adequately controlled with topical medications and/or for whom topical medications are contraindicated.

Oclacitinib

Oclacitinib (Apoquel) is a novel janus kinase (JAK) inhibitor. The JAK enzymes are vital to cell signaling pathways that are activated by various cytokines, including IL-2, IL-4, IL-6, IL-13, and IL-31 [414]. IL-2, IL-4, IL-13, and IL-31 are all implicated as mediators in itch sensation. In a recent (2014) investigation in dogs, oclacitinib was found to inhibit IL-2, IL-4, IL-6, IL-13, and IL-31 [414]. Thus, oclacitinib represents a novel therapeutic of interest for the treatment of AD and atopic itch.

AN2728

AN2728 is a novel boron-containing topical small molecule being studied for its anti-inflammatory properties [415]. AN2728 is thought to work via inhibition of PDE4 and reduction of proinflammatory cytokines, such as TNF-alpha [416]. Several clinical trials have reported that the topical agent is well tolerated and efficacious [417]. Currently, the manufacturer (Anacor) is performing a phase 3 clinical study in patients with mild to moderate AD. Interestingly, in a recent (2014) randomized, vehicle-controlled, multicenter study, a different topical PDE4 inhibitor, E6005 (Eisai), failed to produce significant reductions in itch severity after 12 weeks of use [418].

Conclusion

Chronic itch is a pervasive problem in atopic dermatitis and is often the defining feature. There is no one catchall cause of itch in these patients. Indeed, atopic itch involves a complex interplay between secreted factors, inflammatory cells, resident skin cells, and neural networks. Dermatologists and allergists possess an arsenal of various treatment modalities to treat atopic itch, ranging from OTC moisturizers, topical prescription medications, oral systemic agents, and alternative treatment strategies. Regardless of which strategy is utilized, patient education is the cornerstone of any effective treatment modality.

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