Chapter 7
Neuroimmune Interactions in Acute and Chronic Itch

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Abstract Itch is a sensory experience of the skin that is familiar to all humans. Recent studies have established that the immune system and central and peripheral nervous systems engage in extensive interactions termed "crosstalk," which gives rise to both acute and chronic itch pathologies. Peripheral sensory neurons detect itch-triggering stimuli from the environment to transduce pruritic signals. Itch signals travel from nerve fibers in the skin and peripheral nervous system to the spinal cord and brain, eliciting scratch behavior as a response to relieve the irritation caused by itch. The mechanisms underlying itch have also been shown to overlap with molecular circuits involved in pain, suggesting a relationship between the two sensations. We discuss various types of pruritogens, released from immune cells, keratinocytes, neurons, glial cells, and cancer cells, as well as the pruritogen receptors expressed by primary sensory neurons (pruriceptors) and spinal cord neurons. Understanding how neuroimmune interactions modulate acute and chronic itch will be necessary to develop more effective treatments for these pathologies.

Keywords Pruritus · Itch · Neuroimmune interaction · Toll-like receptors (TLRs) · Gastrin-releasing peptide (GRP) · GRP receptor (GRPR) · Glial cells · Skin · miRNA · Lymphoma · TRPA1 · TRPV1

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7.1 Introduction to Itch

Itch (or pruritus) is an unpleasant sensation on the skin that provokes scratching behavior. It is normally a benign, though unpleasant, physiologic response. However, when itch becomes severe, chronic, or occurs with certain medical conditions, it has a significant effect on a patient's well-being. Clinically, itch is considered either acute (lasting less than 6 weeks) or chronic (continuing beyond 6 weeks). Chronic itch is experienced by 15% of the population and negatively affects sleep, mood, and personal relationships, significantly reducing overall quality of life as a result.

Although our understanding of the mechanisms and pathways that carry pruritic stimuli and process itch sensation is still limited, the most well-supported distinction between types of itch is between histaminergic and non-histaminergic itch (Ikoma et al. 2006; Yosipovitch and Papoiu 2008). The different types of itch correspond to differences in disease and treatment responses. Acute itch is coded through a histamine-induced neuronal pathway, whereas chronic itch signaling is non-histaminergic. Chronic itch is the result of interactions between nerves that sense non-histaminergic stimuli, the immune system, and keratinocytes in the skin (Yosipovitch and Bernhard 2013). On the molecular level, pruriceptors, the itch-sensing primary sensory neurons, are responsible for responding to itch-inducing stimuli called pruritogens and modulating itch signaling throughout the nervous system (Ringkamp et al. 2011; Akiyama and Carstens 2013; LaMotte et al. 2014). The sensation of itch results from nerve fiber activation in the dermo-epidermal junction of the skin (Han and Dong 2014). Neuropathic itch can result from damage to the nervous system, including nerve fiber compression or degeneration and glial cell damage (Misery et al. 2014).

The nervous system and the immune system work in tandem to protect and warn individuals of threats by sensing the presence of pathogens as well as injured and dying cells. As a result of their coevolution and overlapping roles, neurons and immune cells respond to both environmental inputs as well as signals from each other. This bilateral interaction tunes the responses of the two systems in different circumstances. Nociceptive neurons express various receptors for soluble mediators produced by the immune system, including ions, amines, lipids, cytokines, and chemokines (see Chap. 2). Conversely, immune cells such as macrophages and mast cells can be directly activated by neuropeptides and other neuromodulators released from the peripheral terminals of activated nociceptors. Therefore, the extensive crosstalk between the nervous and immune systems is being increasingly recognized as an essential aspect of itch-related homeostasis and disease. In the following sessions, we discuss cells, mediators, receptors, and effectors of itch (Table 7.1), with specific focus on neuroimmune and neuroglial interactions.

Table 7.1 Cells, mediators, receptors, and effectors of itch

Resources	Pruritogens	Receptors	Effectors
Neurons	Substance P	NK1R	NK1R
	GRP	GRPR	GRPR
Keratinocytes	NGF	TrkA	TRPV1
	Endothelin-1	ETA	TRPV1
	TSLP1	TSLPR	TRPA1
	BAM8-22 peptide	MrgprC11	TRPV1/TRPA1
	IL-33	IL-33R	TRPV1/TRPA1
	miR-146a	TRPV1	TRPV1
Mast cells	Histamine	H1R/H4R	TRPV1/Nav1.7
	Tryptase	PAR1/2	TRPV1
	Serotonin	5HTR	TRPA1
T cells	IL-31	IL-31R	TRPV1/TRPA1
T cell lymphoma	miR-711	TRPA1	TRPA1
Drugs	Chloroquine	MagprA3	TRPA1/Nav1.7
	β-alanine	MrgprD	TRPA1
	Imiquimod	TLR7	TRPA1
	Morphine	MOR	MOR
Oxidative stress	ROS (H_2O_2)	TRPA1	TRPA1

Itch mediators are secreted from primary sensory neurons, keratinocytes, and immune cells. In addition, commonly used drugs are also known to elicit itch. Furthermore, oxidative stress such as reactive oxygen species (ROS) can also elicit itch via activation of TRPA1 (Liu and Ji 2012)

7.2 Epidermis and Keratinocytes in Itch

Itch is a unique sensory modality, as it is restricted to the skin, mucous membranes, and cornea. No other tissues or organs are capable of experiencing itch (Yosipovitch and Papoiu 2008). It has been demonstrated that removal of the epidermis abolishes the perception of pruritus, but not pain (Schmelz et al. 1997). The sensation of itch originates from the itch-specific nerve fibers located in the epidermis and dermal-epidermal junction, termed pruriceptors. Itch-specific nerve fibers (predominantly C fibers) are characterized by mechano-insensitivity, low conduction velocities, large areas of innervation, and high transcutaneous electrical thresholds (Schmelz et al. 2003). These itch fibers have close relation to epidermal cells such as keratinocytes.

Keratinocytes are a cell type in the skin that form the protective barrier between the body and the external environment (e.g., regulation of water loss, antimicrobial peptide secretion). Keratinocytes contribute to itch by releasing pruritogens, including the alarmin thymic stromal lymphopoietin (TSLP), to directly activate pruriceptive neurons (Schwendinger-Schreck et al. 2015; Wilson et al. 2013; Ziegler et al. 2013). Keratinocytes also express the same receptors expressed on neurons to

mediate pruritus. For example, mast cell proteases not only trigger pruritus via activation of PAR2+ sensory neurons (Schwendinger-Schreck et al. 2015), but they also stimulate the release of TSLP from keratinocytes (Wilson et al. 2013). In addition, TSLP secreted from keratinocytes may indirectly promote skin inflammation and pruritus pathways by activating immune cells. TSLP binds to TSLP receptor (TSLPR) on Th2 cells and type 2 innate lymphoid cells leading to the production of pruritogenic cytokines (Indra 2013; Ochiai et al. 2018; Soumelis et al. 2002). IL-4 and IL-13 produced by immune cells can also stimulate keratinocytes to secrete TSLP (Bogiatzi et al. 2007). Additionally, keratinocytes release nerve growth factor (NGF) in response to neuropeptides substance P (SP) and calcitonin gene-related peptide (CGRP), in order to modulate innervation and leakiness of the skin barrier (neurogenic inflammation). Thus, keratinocyte–neuron interactions create powerful bi-directional feedback loops that can worsen chronic skin conditions.

7.3 Immune Cells and Mediators in Itch

Activation of the immune system can affect neurophysiological, neurochemical, and neuroendocrine activities. Cytokines, chemokines, peptides, micro-RNAs, and other factors produced and released by immune cells may directly act on peripheral neurons, especially pruriceptors (Fig. 7.1 and Table 7.1). We will summarize the interaction among different immune cells and nociceptors below.

Mast cells are the “frontier soldiers” of the immune system. They are involved in the innate and adaptive immune system (Galli et al. 2005; Kubo 2017). Mast cells are found in externally exposed surfaces such as the epithelial lining of the skin, airways of the lung, mucosa of the gastrointestinal tract, and meningeal membrane of the central nervous system (CNS). This feature allows them to induce a rapid immune response to environmental stimuli, such as allergens and pathogens. Increasing evidence has demonstrated that mast cells contribute to various diseases via their interactions with the vasculature and CNS (Aich et al. 2015; Galli et al. 2005; Xanthos et al. 2011). Mast cell degranulation is critical for the innate immune response and allergic reactions. The release of histamine, bradykinin, and other mediators upon degranulation may contribute to itch sensitization in pathological conditions. It has been found that the degranulation of mast cells partly requires interaction between mast cells and peripheral nerve terminals. The process is mediated by the calcium-dependent cell adhesion molecule N-cadherin, which is expressed in both mast cells and nociceptor neurons (Cyphert et al. 2009; Suzuki et al. 2004).

Histaminergic itch is induced through the H1 and H4 receptors on sensory nerves. Combined antagonism of H1 and H4 receptors may be a useful strategy in controlling itch and inflammation in diseases such as atopic dermatitis (AD) and psoriasis (Ohsawa and Hirasawa 2014). Non-histaminergic itch may be associated with several distinct neural pathways. One of them is Proteinase-activated receptor-2 (PAR2), as PAR2+ fibers and the PAR2 agonist tryptase are increased in lesioned

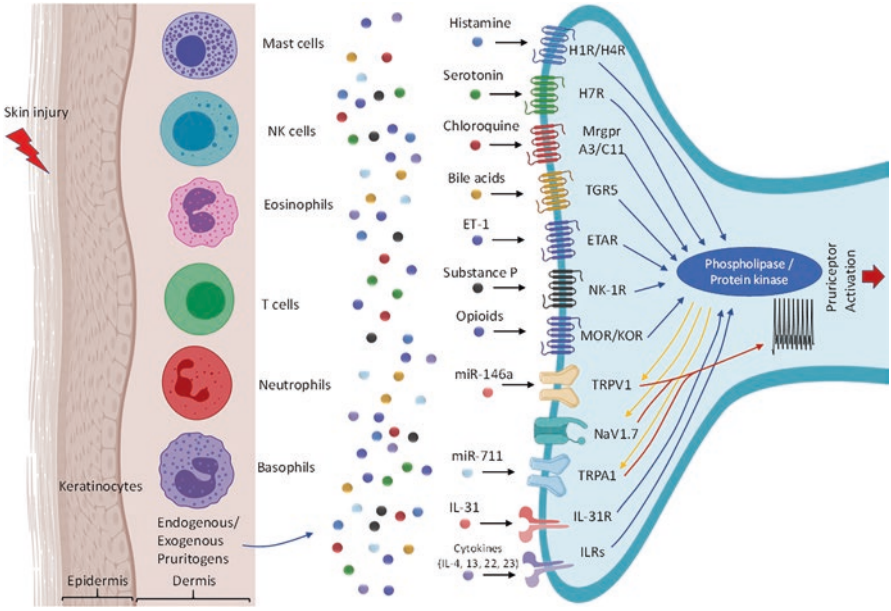

Fig. 7.1 Neuroimmune interactions in the skin for the induction of itch. Following skin injury, keratinocytes and immune cells such as mast cells, NK cells, eosinophils, T cells, neutrophils, and basophils, produce various itch mediators, including histamine released by mast cells and cytokines from immune cells. These pruritogens then bind to specific receptors expressed on pruriceptors (itch-sensing neurons), which can result in the activation of key enzymes (e.g., phospholipase) and protein kinases that can further activate critical ion channels (e.g., transient receptor potential ion channels TRPA1, TRPV1, and TRPV4 and sodium channels Nav1.7). The subsequent propagation of action potentials through the pruriceptive neurons to the central nervous system causes itch sensation. Furthermore, miRNAs, such as miR-711 released from cutaneous T cell lymphoma (CTCL) and miR-146a released from keratinocytes can also induce pruritus via direct activation of TRPA1 and TRPV1, respectively. Additionally, drugs such as opioids (morphine), anti-malaria drug chloroquine, and anti-cancer drug imiquimod also elicit itch via activation of pruriceptors

AD skin. Upon activation of PAR2+ fibers, SP and CGRP are released, leading to the potentiation of neurogenic inflammation (Kempkes et al. 2014; Steinhoff et al. 2003a).

Macrophages are derived from circulating monocytes and recruited within hours of an injury. Regional macrophages take on a phagocytic role almost immediately after injury to remove worn out cells and other cellular debris in both innate and adaptive immune responses. After their activation and recruitment, macrophages release numerous soluble mediators, which sensitize nociceptors/pruriceptors toward pruritus, for instance, during pruritus induced by hydroxyethyl starch (Bork 2005). Mice with pruritic inflammatory skin disease lack heterogeneous nuclear ribonucleoprotein D (hnRNPD), which is a regulator of inflammatory cytokine mRNA stability (Sadri and Schneider 2009).

Skin dendritic cells are antigen-presenting cells (APCs) which initiate the adaptive immune response against invading pathogens by presenting antigens to T cells (Tay et al. 2014). It has been shown that overexpression of the cysteine protease cathepsin S induces elevated PAR2 expression in dendritic cells and the expression of Type 1 helper T cell-(Th1) related cytokines, leading to spontaneous scratching behavior (Kim et al. 2012).

Activation of type 2 helper T-cells (Th2 cells) is important for moderate to severe AD. IL-4 and IL-13 are cytokines required for the development, initiation, and maintenance of the Th2 subset of the T cells. Increased expression of IL-4 and IL-13 are associated with eosinophilic infiltration and increased production of NGF and the NGF receptor TrkA (Leung et al. 2004; Simon et al. 2004). Overexpression of IL-4 and IL-13 in the epidermis of transgenic mice causes AD and pruritus (Chan et al. 2001; Zheng et al. 2009). The expression levels of IL-4 and IL-13 are elevated in human skin samples of AD patients, with IL-13 elevated in the serum (Jeong et al. 2003). Serum levels of IL-13 in turn are correlated with disease severity (Metwally et al. 2004). Recently, researchers found that TRPA1 is linked with IL-13-related pruritus in AD (Oh et al. 2013). Monoclonal antibodies targeting IL-4 and IL-13 can significantly reduce the severity of pruritus in AD patients (Griffiths et al. 2021). IL-33 is a promoter of Th2-mediated inflammation in the pathogenesis of AD (Kroeger et al. 2009; Rankin et al. 2010; Savinko et al. 2012), and the expression of IL-33 is elevated in the skin cells of AD patients (Savinko et al. 2012).

IL-31 is one of the most prominent itch mediators produced by Th2 cells and its receptor (IL-31R) is expressed on keratinocytes, epithelial cells, and primary sensory neurons including nociceptors/pruriceptors (Dillon et al. 2004; Heise et al. 2009; Kremer et al. 2014; Sonkoly et al. 2006). IL-31RA is also localized in small diameter neurons of human DRG (Cevikbas et al. 2014; Sonkoly et al. 2006). IL-31R activation leads to activation of the JAK family of tyrosine kinases, which leads to the activation of transcription factors (STAT-1/5 and ERK-1/2) and an MAP kinase signaling cascade (Cornelissen et al. 2012; Kasraie et al. 2013). IL-31 expression is elevated in many pruritic disorders including AD, allergic contact dermatitis, and cutaneous T-cell lymphoma (CTCL) (Ohmatsu et al. 2012; Raap et al. 2008; Singer et al. 2013; Sonkoly et al. 2006).

Nerve growth factor (NGF) is a neurotrophin which is critical for peripheral nervous system development, growth, differentiation, and regeneration (Yamamoto et al. 2007). It has been demonstrated that serum levels of NGF correlate with the degree of scratching behavior in mice (Yamamoto et al. 2007). Eosinophils serve as a main source of NGF. Thus, NGF is thought to participate in neural hyperplasia (Kanda and Watanabe 2003). In mouse models, NGF stimulates increased levels of substance P and calcitonin gene-related peptide (CGRP), which are factors involved in neurogenic inflammation and the hypersensitization of pruriceptors (Verge et al. 1995). In addition, NGF primes sensory nerves by lowering the threshold for itch sensation. NGF can also induce TRKA activation, which increases the phosphorylation of phosphoinositide 3-kinases (PI3K) and stimulates TRPV1 expression and calcium influx (Nockher and Renz 2006; Zhuang et al. 2004).

7.4 Itch Receptors and Signaling in Itch-Sensing Sensory Neurons (Pruriceptors)

7.4.1 G Protein-Coupled Receptor (GPCR)

To detect external changes, nerve fibers of the pruriceptors (a subset of nociceptors) express specialized receptors. Different receptors are present in different types of nerve fibers to respond to specific ligands (Han and Dong 2014). One common characteristic of these receptors is that they are members of the G protein-coupled receptor (GPCR) family.

Itching and vasodilation can be induced by various types of itch mediators (Fig. 7.1). For example, histamine is released from immune cells due to tissue inflammation and exposure to environmental allergens (Ikoma et al. 2006; Shim et al. 2007; Simons and Simons 2011). There are four histamine receptors, all of which are GPCRs (Simons and Simons 2011). H1R and H4R are expressed in the DRG and have been identified as potential mediators of pruriception (Simons and Simons 2011). H1R is an important receptor for histamine-induced itch reactions, and H1R-specific inhibitors can completely suppress histamine-induced itch in human skin (Simons and Simons 2011). In addition, H4R inhibitors can block itch in a contact dermatitis mouse model, indicating that H4R is another mediator of itch (Rossbach et al. 2009). A novel H4R antagonist (JNJ 39758979) reduced histamine-induced pruritus in a randomized control trial (Kollmeier et al. 2014). Furthermore, H1R and H4R dual blockade was more effective at reducing itch and inflammation than blockade of either alone (Cowden et al. 2010).

Mas-related G protein-coupled receptors (Mrgprs) are a subgroup of GPCRs (Dong et al. 2001). Mice express more than 50 different Mrgprs, while humans express 10 members of the receptor family (Dong et al. 2001; Zylka et al. 2003). Many Mrgprs are expressed by nociceptors in the DRG and the trigeminal ganglia, which project axons into the skin to sense noxious mechanical stimuli and temperature (Dong et al. 2001; McNeil and Dong 2012). Mrgprs are involved in chloroquine (CQ)-induced itch (Liu et al. 2009). In Mrgpr knockout mice, while neither nociception nor histaminergic itch was reduced, but CQ-induced calcium influx and action potentials were abolished (Liu et al. 2009). Further research has revealed that mouse MrgprA3 and human MrgprX1 are involved in CQ-induced itch (Sikand et al. 2011). In a mouse model in which investigators genetically expressed TRPV1 in MrgprA3+ neurons, capsaicin administration resulted in activation of MrgprA3+ neurons and induced itching but not pain (Han et al. 2013). Thus, MrgprA3+ neurons mediate an itch-specific circuit. These critical findings have demonstrated that sensation does not depend on stimulus type but rather on the specific activated neuronal pathway (Han et al. 2013).

Protease-activated receptors (PAR) are another family of itch-related GPCRs found on different cell types, including keratinocytes and pruriceptive neurons in the DRG (Han and Dong 2014). Activation of PAR2 and PAR4 leads to the induction of non-histaminergic itch (Reddy et al. 2008; Vergnolle et al. 2003). PAR2 can

be activated by various endogenous and exogenous proteases, such as cathepsin S, tryptase, dust mites, and Staphylococcus aureus (Reddy et al. 2008, 2010; Soh et al. 2010; Steinhoff et al. 2006). Tryptase, an endogenous agonist of PAR2, is significantly increased in lesioned skin of AD patients (Steinhoff et al. 2003a). More interestingly, histamine levels are not increased in lesioned skin from AD patients compared to healthy controls, further demonstrating that histaminergic nerves are not involved in AD-related itch (Buddenkotte et al. 2005).

7.4.2 Transient Receptor Potential Ion Channels

The transient receptor potential (TRP) family consists of several major ion channels that transmit positively charged ions across the cell membrane. They are important for sensory perception, including itch, and other sensory modalities (Minke and Cook 2002; Moran et al. 2011). Several TRP family members have been implicated in itch including TRPV1, TRPA1, and TRPM8 (Moore et al. 2018).

TRPV1 is expressed broadly in nociceptors, keratinocytes, and mast cells (Han et al. 2013; Shim et al. 2007; Stander et al. 2004). TRPV1 signaling mediates both histaminergic and non-histaminergic itch; especially the former. TRPV1 is activated by various stimuli including capsaicin, high temperature (over 42 °C), acid (pH < 5.9), ATP, and changes in chemical and inflammatory conditions. Histamine-induced TRPV1 activation results in itch (Imamachi et al. 2009; Shim et al. 2007) and requires the activation of phospholipase A2 and 12-lipoxygenase. TRPV1 expression in histamine-sensitive C nerve fibers is correlated with an associated burning sensation of histamine-induced itch (Stander et al. 2004). TRPV1 signaling also causes the release of neuropeptides such as substance P and calcitonin gene-related peptide, leading to neurogenic inflammation (Aubdool and Brain 2011).

TRPA1 is expressed by nociceptors, sensory C fibers, keratinocytes, and fibroblasts (Atoyan et al. 2009; Kwan et al. 2009). TRPA1 responds to pain and itch (Toth et al. 2014). TRPA1 is a mediator of non-histaminergic itch and is involved in Mrgpr-mediated itch (Wilson et al. 2011), as well as pruritus induced by oxidative stress (Liu et al. 2012), miR-711 (Han et al. 2018), and serotonin (Table 7.1). Lesioned skin samples from AD patients have increased TRPA1 expression compared to healthy controls (Oh et al. 2013).

It was found that lymphoma-secreted miR-711 is sufficient to elicit potent pruritus via direct activation of TRPA1 (Han et al. 2018, Fig. 7.2). Unlike conventional activation of TRPA1 from the intracellular side of the channel, miR-711 binds the channel on the extracellular loop and rapidly activates TRPA1, without causing neurogenic inflammation (Han et al. 2018).

TRPM8 is a temperature-sensitive calcium channel expressed by primary sensory neurons, mast cells, and keratinocytes (Denda and Tsutsumi 2011; McCoy et al. 2011). Menthol, eucalyptol, and icillin are the notable ligands of TRPM8 (Valdes-Rodriguez et al. 2013). Activation of TRPM8 causes intracellular calcium influx and a cooling sensation (Patel et al. 2007). TRPM8 is expressed on

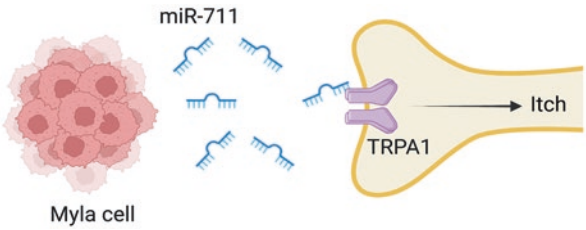

Fig. 7.2 miRNA-mediated cancer itch. Cutaneous T cell lymphoma (CTCL) is a chronic itch condition and CTCL patients suffer from serve pruritus. Inoculation of human Myla cells from CTCL is sufficient to induce lymphoma and chronic itch in immune-deficient mice (Chen et al. 2022). Both mouse and human CTCL produced miR-711, which was shown to induce robust pruritus following intradermal injection. miR-711 directly activates transient receptor potential ankyrin 1 (TRPA1) on sensory neurons. TRPA1 was believed to be activated mainly through intracellular interactions with its ligands; however, recent studies show that it can also be activated extracellularly via RNA-protein interactions (Han et al. 2018). Notably, miR-711 only activates a subset of neurons that also respond to histamine and chloroquine, indicating a population of pruriceptors

myelinated cutaneous nerves and implicated in the transmission of itch signals, accounting for the heterogeneity of symptoms reported by chronic pruritus patients (Ringkamp et al. 2011).

7.4.3 Toll-Like Receptors (TLRs)

Toll-like receptors (TLRs) are pattern-recognition receptors that initiate innate immune responses by recognizing pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) (Akira et al. 2006). Liu et al. showed that TLR7 is expressed in small DRG neurons to mediate itch sensation (Liu et al. 2010). Immunohistochemistry revealed that TLR7 colocalizes with gastrin-releasing peptide (GRP), MrgprA3, and TRPV1 (Liu et al. 2010). Imidazoquinoline derivatives (imiquimod and resiquimod) and guanosine analogs (loxoribine) are ligands for TLR7 (Hemmi et al. 2002). Intradermal injection of imiquimod, resiquimod, and loxoribine induced itch-indicative scratching behavior in wild-type mice, and scratching is reduced in *Tlr7*$^{-/-}$ knockout mice (Liu et al. 2010). Strikingly, bath application of TLR7 ligands on dissociated DRG neurons elicits inward currents and action potentials, and this effect is abolished in *Tlr7*$^{-/-}$ knockout mice (Liu et al. 2010). *Tlr7*$^{-/-}$ knockout mice show a significant reduction in scratching behaviors in response to non-histaminergic pruritogens, including chloroquine, endothelin-1, and SLIGRL-NH2, which is a PAR2 agonist (Liu et al. 2010). However, TLR7 null mice exhibit normal scratching behaviors elicited by histamine, HTMT, or compound 48/80 (Liu et al. 2010). In addition to TLR7, the activation of TLR3 also generates itch, and its expression in DRGs is colocalized with GRP and TRPV1 (Liu et al. 2012). The TLR3 agonist poly (I:C) leads to

excitation of DRG neurons which results in scratching behavior (Liu et al. 2012). Similarly, global deletion of TLR3 abolishes scratching behaviors induced by the TLR3 agonists chloroquine and histamine. Thus, TLR3 is required for histaminergic and non-histaminergic itch, and both TLR7 and TLR3 are critical itch receptors that regulate the excitability of pruriceptive neurons (Liu and Ji 2014). Thus, TLRs may serve as novel targets for therapies against pruritis. Please see Chap. 8 for more details on TLR signaling in pain and itch.

7.5 Neuroimmune Interactions in Skin Diseases and Chronic Itch

The skin is the largest organ of the human body, with vital roles in maintaining homeostasis, providing a protective barrier, and defending against foreign invaders and pathogens. Nerve fibers innervating the skin are located in the vicinity of keratinocytes, fibroblasts, endothelial cells, Schwann cells, and resident immune cell populations. The cutaneous sensory nerve fibers (CSNFs), which innervate the dermis and epidermis, represent the majority of nerve fibers in the skin. CSNFs originate from the dorsal root ganglia (DRG) and the trigeminal ganglia. The afferent fibers of DRG neurons extend outwards to the body's skin, and stimuli at these projections send signals back to the sensory neuron cell bodies within the DRGs. These signals are then delivered to the dorsal horn of the spinal cord and upwards to the brainstem and thalamus (Fig. 7.3a). Trigeminal ganglia neurons innervate the skin of the head and face.

The autonomic nervous system also innervates the skin but makes up a small overall percentage of the nerve fibers. These nerves are only found in the dermal layer and innervate hair follicles, blood vessels, lymphatic vessels, apocrine and eccrine glands, and erector pili muscles. The resident dermal immune population ensures both protection against pathogens and maintenance of tolerance against innocuous antigens. The skin is highly innervated, and neuroimmune interactions are important for communicating with and responding to the external environment.

Abnormal neuroimmune interactions have consistently been shown to cause a number of inflammatory skin conditions. Neuroimmune interactions play a key role

Fig. 7.3 (continued) expressing neuropeptide Y (NPY), which inhibits mechanical itch. The properties of the excitatory neurons involved in mechanical itch are still not fully understood. Primary sensory neurons of DRG are activated in response to chemical pruritogens and release glutamate, natriuretic polypeptide B (NppB), and gastrin-releasing peptide (GRP). NppB activates natriuretic peptide receptor A (Npra) to release GRP. GRP then activates GRP receptor (GRPR) to transduce the signal to projection neurons (PN) in the dorsal horn. In chronic itch, astrocytes can interact with GRPR-expressing neurons with secreting neuromodulators. Scratching sends signals to inhibitory neurons that express basic helix-loop-helix B5 (Bhlhb5). These interneurons release inhibitory neurotransmitters like dynorphin, glycine, and gamma-aminobutyric acid (GABA) that negatively act upon GRPR-positive neurons. This results in attenuation of the itch sensation

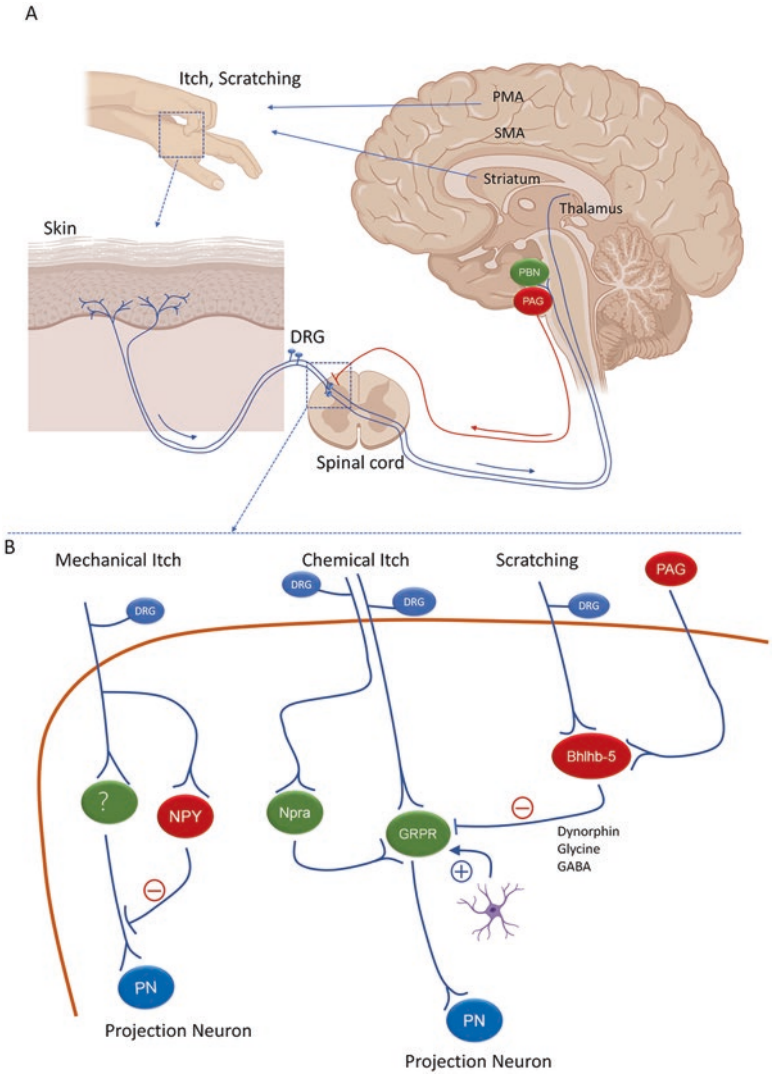

Fig. 7.3 Itch pathways for chemical and mechanical itch (**a**) Ascending and descending pathways of itch. Itch signals are peripherally detected in the skin by itch-sensing primary sensory neurons (pruriceptors), with their cell bodies resided in dorsal root ganglia (DRG). Then, the itch signals are transduced to the spinal cord, ascend through the spinothalamic tract to the thalamus, and finally to the sensory cortex, eliciting itch sensation (pruritus). Pruritic signals also travel through the spinoparabrachial pathway to reach the parabrachial nucleus (PBN). Once itch signals have reached the brain, they are further projected to the premotor area (PMA), supplementary motor area (SMA), and striatum. These areas play a role in sending signals to initiate scratching behavior as a motor reflex. Furthermore, the descending control from the periaqueductal gray (PAG) can also modulate the spinal cord itch circuit. (**b**) Spinal cord neurocircuits for mechanical itch and chemical itch and mechanism of itch relief by scratching. Mechanical itch stimuli from TLR5-expressing primary sensory neurons project onto spinal cord neurons

in the pathogenesis of allergic contact dermatitis (ACD), atopic dermatitis (AD), and psoriasis.

ACD is a T-cell-mediated hypersensitivity reaction caused by allergens and haptens, which causes itchy, inflamed skin. Cutaneous sensory nerves control the immune response via interactions with antigen-presenting cells. Recently, TRPV1 and TRPA1 were found to have different roles in contact hypersensitization in a mouse ACD model caused by treatment with squaric acid dibutylester (SADBE). While SADBE directly activated both TRPV1 and TRPA1 channels on neurons to produce itch, only TRPV1 ion channels played a role in inflammation (LaMotte et al. 2014). This was demonstrated when the removal of TRPV1+ neurons or genetic deficiency in TRPV1 led to increased inflammation. On the other hand, TRPA1 mediates both itch and inflammation (edema, leukocyte infiltration, keratinocyte hyperplasia) in ACD mouse models using urushiol (poison ivy component) and oxazolone, and interestingly, TRPV1 channels were not involved (Liu et al. 2013).

AD is a chronic inflammatory skin condition, with symptoms including constant itchiness, thick scaly skin, damaged epidermal barrier function, and a T helper 2 (TH2) cell-skewed allergic response. One major feature of AD lesions is hyperinnervation and penetration of sensory neurons into the epidermis, causing increased itch and release of neuropeptides. Lesions and blood samples from AD patients have been found to contain high concentrations of substance P and NGF, which lead to keratinocyte hyperproliferation. In an innervated skin model, where human AD skin samples were cultured alongside porcine DRGs, sensory nerves caused keratinocyte proliferation that was dependent on CGRP. Isolated AD skin samples used in this model also demonstrated increased innervation and neurite outgrowth, CGRP release, and epidermal thickening compared with healthy control skin samples (Erickson et al. 2021).

Psoriasis is an inflammatory disorder of the skin defined by dysregulation of the IL-17/IL-23 axis, acanthosis (dark discoloration in body folds), hyperkeratosis (abnormal thickening of the skin), and itch. Neuroimmune interactions control the induction of IL-23 signaling and formation of inflammatory lesions. The role of the sensory nervous system in psoriasiform skin inflammation was first demonstrated by cutaneous denervation of a psoriasis mouse model. When the skin was surgically axotomized (axons severed along an axis) in KC-Tie2 psoriasiform mice, acanthosis improved greatly, while CD4+ T cells and CD11c + DCs decreased. These effects were shown to depend on CGRP and substance P, pointing toward the nervous system's major role in psoriasis. In a follow-up study, botulinum neurotoxin A (BoNT-A), a neurotoxin that cleaves SNAP25, was injected intradermally into KC-Tie2 mice. BoNT-A prevented the release of CGRP and substance P, and greatly improved skin inflammation and epidermal hyperplasia (Riol-Blanco et al. 2014). Small-scale human clinical trials have confirmed the effectiveness of BoNT-A in improving plaque psoriasis (Todberg et al. 2018). Using a mouse of psoriasis model driven by TLR7/8 agonist imiquimod, TRPV1+ nerves were found to control IL-23

release via dermal dendritic cells. These dendritic cells control IL-17 expression via γδ T cells in the skin, thus promoting psoriatic inflammation (van der Fits et al. 2009).

Cutaneous T-cell lymphoma (CTCL) is a cancer that causes T-cells to mount an immunological attack against the skin, resulting in dermatological sequelae and the development of tumors. Approximately 88% of CTCL patients are affected by severe pruritus that requires separate treatment from the lymphoma itself. Emollients, topical steroids, and oral histamines fail to relieve the chronic itch, suggesting that CTCL pruritus is not caused by histamines (Cevikbas and Lerner 2020). Researchers, therefore, have sought histamine-independent mediators as possible treatment targets to alleviate chronic pruritus. It was found that CTCL is associated with increased levels of the IL-31 in plasma, which correlate with itch severity (Nattkemper et al. 2016). IL-31 is produced by Th2 cells, particularly those in the malignant population associated with CTCL (Singer et al. 2013). Researchers speculate that IL-31 exerts indirect effects on sensory nerves through T cells and keratinocytes to transduce itch sensations (Nattkemper et al. 2016). Studies have also suggested that IL-31 initiates basophil migration and the release of IL-4 and IL-13. Recently, histamine receptor 4 (H4R) has been observed on CD4+ T-cells. This receptor increases mRNA expression of IL-31. Additionally, a recent study showed no correlation between itch severity and IL-31 levels in the early stages of CTCL, which is dominated by Th1 cells rather than Th2 cells (Malek et al. 2015). Studies involving different treatments at different stages of CTCL indicate additional mechanisms involved in pruritus. Successful treatment with SP receptor antagonism has been reported, and treatment regimens with gabapentin and mirtazapine during advanced stages of CTCL were also proposed (Erickson et al. 2021). To study the mechanisms of CTCL, an animal model of CTCL was developed at Duke University using immune-deficient mice. Inoculation of Myla cells from a CTCL patient resulted in robust tumor growth and chronic pruritus that can last more than 2 months. Lymphoma is highly innervated by nerve fibers and intra-tumoral injection of nerve blockers (C-fibers or A-fibers) or IL-31 neutralizing antibody significantly attenuated pruritus (Chen et al. 2022). Moreover, lymphoma secreted miR-711, which can elicit itch via direct activation of TRPA1 (Fig. 7.2).

7.6 Neurocircuits of Itch

There is considerable overlap between the molecular mediators of pain and itch, and they even coexist in some chronic pathologies (Liu and Ji 2013). However, while there certainly does seem to be some intersections between the two, pain and itch remain separate processes. It is possible to knock out itch-related behaviors in mouse models while retaining symptoms of pain, demonstrating distinct pathways for each sensation (Fig. 7.3a).

7.6.1 Pain and Itch

Two theories of how signals of pain and itch are transmitted throughout the nervous system are the labeled-line coding model and the population-coding model. Labeled-line coding posits that primary afferent sensory neurons specific to either pain or itch will send information to central nervous system (CNS) neurons, which produce the respective sensation (Ma 2010). This theory holds that different sensory modalities are modulated by mutually exclusive neuronal populations (Sun et al. 2017). The labeled-line theory has been challenged by the finding that painful can suppress itch through a specific neurocircuit in the spinal cord involving inhibitory neurons (Fig. 7.3b).

The population-coding model proposes that a subpopulation of neurons receives pain and itch signals through distinct combinations of activated fibers (Akiyama and Carstens 2013; Ma 2010). Upon receiving either type of stimuli, the neurons will transmit a signal for the specific sensation. Population-coding reflects a complex and intricately integrated system of sensory transmission (LaMotte et al. 2014).

Intercommunication between different parts of the nervous system suggests how related etiological processes and mediators cause pain and itch. Chronic pain and itch negatively impact quality of life, and this is compounded by the fact that these pathologies often accompany one another (Liu and Ji 2013). Further studies on the molecular mechanisms underlying these sensations will contribute to the development of more effective treatments.

7.6.2 Neuropeptides as Itch Transmitters

Substance P (SP) is a neuropeptide which is highly involved in afferent neuronal signaling (De Felipe et al. 1998). SP is released by activated sensory neurons and binds to neurokinin receptors (NK1) expressed on mast cells, keratinocytes, and cutaneous nerves, resulting in the release of other itch mediators (Kremer et al. 2014). Intradermal injection of SP results in mast cell activation and histamine release (Jorizzo et al. 1983; van der Kleij et al. 2003). SP also induces itch that is not dependent on histamine, but rather on mast cells. Furthermore, SP-activated mast cells release inflammatory mediators such as leukotriene B4, prostaglandin D2, and TNF-α (Luger 2002; Steinhoff et al. 2003b). In addition to the mast cells, SP also triggers the release of pruritogenic compounds from keratinocytes, endothelial cells, and immune cells (Biro et al. 2007; Kulka et al. 2008). Recently, it was found that SP is an endogenous agonist of Mrgprb2 in mast cells and mediates immune cells' migration via Mrgprb2. SP was shown to activate human mast cells via MRGPRX2 (human homolog of Mrgprb2) for the release of inflammatory cytokines and chemokines (Green et al. 2019).

Gastrin-releasing peptide (GRP) is a neuropeptide involved in the sensation of itch. Intradermal or intrathecal injection of GRP elicited itch in mice (Sun and Chen

2007; Kulka et al. 2008). GRP receptor (GRPR) is expressed on spinal cord neurons, and activation of GRPR transmits the itch signal to higher order neurons (Mishra and Hoon 2013; Sun and Chen 2007; Sun et al. 2009). Ablation of GRPR-expressing neurons in the spinal cord results in substantial deficits in scratching behavior in response to all chemical itch stimuli (Sun et al. 2009). In monkey chronic idiopathic pruritus models, the expression of GRP and GRPRs in the spinal cord and skin are significantly increased (Nattkemper et al. 2013).

7.6.3 Spinal Cord Circuits of Chemical and Mechanical Itch

When pruritic neuronal signals are transduced to the spinal cord from primary sensory neurons, there is a circuit in the spinal cord modulating signaling and affecting conscious itch sensation (Fig. 7.3b). Mechanical itch, such as alloknesis (when normal mechanical stimuli are perceived as itchy stimuli) and hyperknesis (excessive itch perception to a pruritic stimuli) are conveyed by an itch-related circuit. It has been demonstrated that neuropeptide Y (NPY) positive neurons have an inhibitory effect on mechanical itch (Bourane et al. 2015). For chemical itch, primary sensory neurons respond to pruritic stimuli by releasing glutamate and natriuretic polypeptide B (NppB). Nppb activates natriuretic peptide receptor A (NPA) to release GRP. In addition, primary sensory neurons may release GRP themselves. Thus, GRP and GRPRs are critical molecules involved in chemical itch (Fig. 7.3b).

In chronic itch models, the chemical itch circuit can be modulated by astrocytes in the spinal cord (Ji et al. 2019). Lipocalin-2 released by astrocytes potentiates GRP signaling (Shiratori-Hayashi et al. 2015). Toll-like receptor 4 (TLR4) is also involved in chronic itch through astrogliosis in the spinal cord (Liu et al. 2016, Fig. 7.4).

To relieve the response from the system, there is a circuit to mitigate pruritus. Pain, cooling, and mechanical stimuli (scratching) can attenuate itch sensation and activate a specific population of inhibitory neurons, which is characterized by their expression of basic helix-loop-helix family member B5 (Bhlhb5) (Ross et al. 2010). These inhibitory interneurons release neurotransmitters such as dynorphin, glycine, and gamma-aminobutyric acid (GABA) to inhibit the activity of GPRP+ neurons (Fig. 7.3b).

After processing in the spinal cord, itch signals are transduced through the spinothalamic tract to the thalamus and through the spinoparabrachial pathway to the parabrachial nucleus (Mu et al. 2017), as shown in Fig. 7.3a. Pruritic signals are then projected to various brain regions such as the primary and secondary somatosensory cortex. These regions contribute to the localization and intensity of itch. Other projected regions are linked with different behaviors or sensitizations related to itch. The midcingulate cortex is linked to perception and motivation; the anterior cingulate cortex (ACC) and insula are associated with unpleasant sensations; the premotor area (PMA), supplementary motor areas, striatum, and cerebellum are

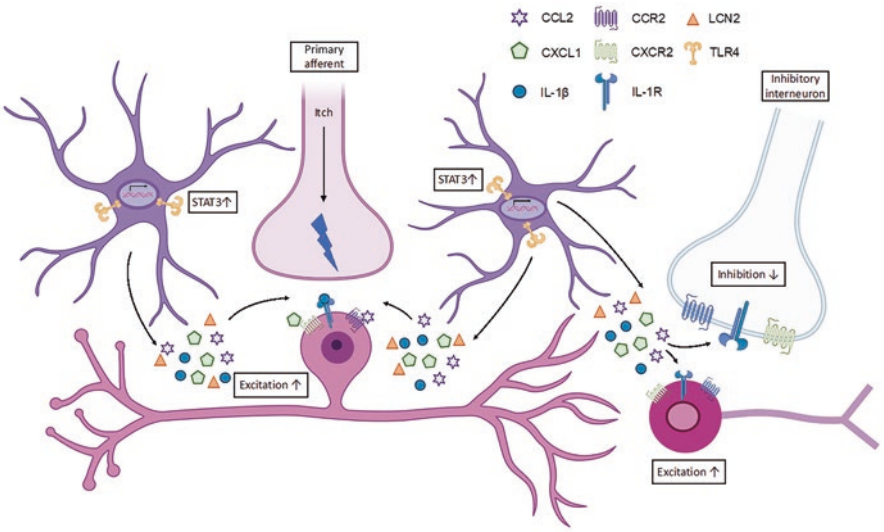

Fig. 7.4 Astrocyte activation drives chronic itch pathology via neuroglial interactions. Chronic itch conditions such as dry skin injury or cutaneous T cell lymphoma result in astroglial reaction in the spinal cord dorsal horn. Increased activity of TLR4 and signal transducer and activator of transcription 3 (STAT3) has been implicated in reactive astrogliosis (Liu et al. 2016; Shiratori-Hayashi et al. 2015). The activation of astrocytes in the spinal cord induces the release of neuroinflammatory signals that lead to itch, such as lipocalin-2 (LCN2). LCN2 potentiates itch symptoms by acting on neurons expressing gastrin-releasing peptide receptor (GRPR). Reactive astrocytes also upregulate the synthesis of inflammatory molecules like C-X-C chemokine ligand 1 (CXCL1), interleukin 1 beta (IL-1β), and C-C motif chemokine 2 (CCL2). CXCL1 binds to C-X-C chemokine receptor 1 (CXCR2), IL-1β binds to interleukin 1 receptor (IL-1R), and CCL2 binds to C-C motif chemokine receptor 2 (CCR2). It is possible that these molecules bind to their receptors and then act on GRP+ interneurons and GRPR+ neurons as well as pruriceptors in the periphery to drive chronic itch symptoms. These astrocyte-derived mediators could increase the excitation of postsynaptic neurons and disinhibition of inhibitory interneurons to drive chronic itch sensation. (Modified from Ji et al. 2019) (Nature Review Neuroscience, Author's own copyright)

involved in controlling and initiating scratching behavior, and the prefrontal area is implicated in decision-making (Fig. 7.3a).

7.6.4 Opioid-Induced Itch

Opioid-induced pruritus most commonly occurs following neuraxial administration of opioids, with 30–60% of patients reporting itch symptoms. Pregnant women who receive epidural or spinal morphine are often treated with opioids and are particularly prone to side effects related to itch (Melo et al. 2018; Wang et al. 2021). While itch symptoms are often associated with peripheral mechanisms, opioid-induced itch is primarily mediated by the central mechanisms (Liu et al. 2011). It is

noteworthy that opioid-induced itch is thought to arise through a mechanism largely independent of the analgesic effects of opioids (Wang et al. 2021). In the past, it was believed that opioid analgesia itself unmasked itch. While it was initially proposed that neurons expressing both mu opioid receptor (MOR) and GRPR were responsible for the induction of morphine-induced itch (Liu et al. 2011), recent studies found that there are distinct neuronal populations that express either MOR or GRPR, both of which are involved in the itch circuitry. Strikingly, it was found that pruritus induced by intrathecal injection of the mu opioid receptors agonists (morphine or DAMGO) was totally abolished in mice with a specific deletion of *Oprm1* (gene encoding MOR) in Vgat+ inhibitory neurons (Wang et al. 2021). Furthermore, ablating GRPR-expressing neurons blocked morphine-induced itch, and the administration of a GRPR antagonist successfully eliminates morphine-induced itch. Taken together, these findings suggest morphine inhibits GABAergic neurons with a downstream effect of disinhibiting excitatory GRPR neurons (Wang et al. 2021). Furthermore, it was found that kappa-opioid receptor agonists can alleviate morphine-induced itch without affecting the analgesic properties of morphine in mice (Nguyen et al. 2021). Additionally, opioid receptors in TRPV1-expressing sensory neurons may mediate peripheral opioid-induced itch (Melo et al. 2018). Different types of skin cells, such as keratinocytes, mast cells, fibroblasts, and macrophages, express MORs (Reich and Szepietowski 2012). Further studies are still required to fully characterize the mechanism of opioid-induced itch in both the peripheral and central nervous systems, but notable progress has been made in recent years.

7.7 Glial Cells in Itch

Recent studies have shown that reactive astrocytes in the spinal cord are involved in the pathogenesis of chronic itch. Intrathecal administration of astroglial inhibitors reduces chronic itch, as mouse models of dry skin and cutaneous T-cell lymphoma (CTCL) exhibit astrogliosis in itch-affected areas of the spinal cord (Fig. 7.4).

Astrocytes induce chronic itch by multiple mechanisms. Astrocyte activation is dependent on toll-like receptor 4 (TLR4) and transcription factor signal transducer and activator of transcription 3 (STAT3). Blocking TLR4 signaling and the expression of astrocytic STAT3 inhibits chronic itch, or suppression of STAT3-dependent astrogliosis decreased scratching behavior in chronic itch conditions (Shiratori-Hayashi et al. 2015; Liu et al. 2016; Chen et al. 2022). The activation of spinal astrocytes leads to the release of several immune factors, such as lipocalin-2 (LCN2). Intrathecally administering LCN2 together with GRP increased GRP-induced scratching in mice by acting on GRPR-expressing neurons. However, administering LCN2 alone did not increase itch and neuronal excitability (Shiratori-Hayashi and Tsuda 2021). Mouse models of chronic itch exhibit elevated LCN2 levels in the spinal dorsal horn, and suppressing astrocytic LCN2 activation can block pruritus (Furutani et al. 2022; Shiratori-Hayashi and Tsuda 2021). Astrocytic

LCN2 was also shown to increase the GRP-evoked excitability of GRPR+ postsynaptic neurons in a mouse model of chronic itch (Koga et al. 2020). These findings suggest that chronic itch induced by GRP is heightened by LCN2 release. Persistent STAT3 activation in astrocytes was evoked by IL-6 through inositol trisphosphate receptor type 1 (IP3R1) and transient receptor potential canonical (TRPC) channels (Shiratori-Hayashi and Tsuda 2021). Another cytokine involved in astrocyte-mediated chronic itch is IL-33, which maintains chronic itch through the JAK-STAT3 pathway. ST2, the receptor for IL-33, is highly expressed in astrocytes, and ST2-knockout mice exhibited reduced astrocyte activation and decreased scratching behavior (Du et al. 2019).

The chemokine receptor CXCR3 is also upregulated in the central nervous system of chronic itch models and is involved in astrocyte-mediated chronic itch. CXCR3-knockout mice exhibit normal acute itch symptoms but reduced scratching under chronic itch-inducing conditions, indicating that CXCR3 plays an important role in chronic itch. Administration of a CXCR3 antagonist reduced astrogliosis and chronic itch as well (Du et al. 2022; Jing et al. 2018). While more work is still required to fully understand the mechanisms underlying reactive spinal astrocyte-related chronic itch, it is a promising avenue of study for future therapeutic techniques to treat pruritus.

Activation of mitogen-activated protein (MAP) kinases in chronic itch conditions will lead to the release of pro-inflammatory molecules including C-X-C chemokine ligand 1 (CXCL1), interleukin 1 beta (IL-1β), and C-C motif chemokine 2 (CCL2), which bind to their receptors on GRP-expressing interneurons and postsynaptic GRPR-expressing neurons (Ji et al. 2019; Du et al. 2022). This may result in the disinhibition of inhibitory interneurons and excitation of postsynaptic neurons (Fig. 7.4).

7.8 Conclusion

Recent studies show the important effects of crosstalk between the nervous and immune systems in itch sensitization. Peripheral pruriceptors act as immune sensors and coordinate with immune cells to form a comprehensive, well-organized defense system. Immune-related receptors, such as Toll-like receptors, are expressed in peripheral nociceptors and can be activated by certain ligands and environmental stimuli. Immune cells can also be activated by neuropeptides and modulate peripheral nociceptors. The neuroimmune interaction of peripheral pruriceptors and immune cells play an important role in itch regulation for both physiological and pathological conditions and for future clinical treatments. Research has suggested that the central nervous system is also deeply involved in itch symptoms as itch signals from peripheral neurons are transduced through the spinal cord and brain. Itch circuits in the CNS, such as those for chemical or mechanical itch, are intertwined with the action of glial cells, molecular mediators of chronic pain, opioid receptors, and other circuits. While the nervous and immune systems are distinct

from each other, it is clear that studying their interactions will be critical to further develop clinical therapeutic techniques and improve patient outcomes. As our understanding develops of how these systems work together to generate different pathologies, more effective treatment strategies will be established.

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