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OPEN ACCESS JOURNALS

Archives of Clinical & Experimental Dermatology

Mini Review | Vol 6 Iss 1
ISSN: 2583-6374
https://dx.doi.org/10.46527/2583-6374.154

Roles of Glial Cells in Itch Modulation of Skin Diseases

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Received: March 18, 2024; **Accepted:** March 27, 2024; **Published:** April 06, 2024

Abstract

Itch is a subjective sensation experienced in the skin and some mucous membranes and is defined as an unpleasant sensation that makes one want to scratch. Normally, itching is a physiological sensation that prompts scratching behavior to remove foreign enemies or foreign substances such as insects on the skin, and is a biological defense mechanism. Without this sensation, harmful substances may penetrate the skin, leading to potential life-threatening situations. Similar to pain, itch serves as a biological warning signal alerting us to abnormalities in the body. While acute itch, like that from insect bites, is temporary, chronic itch persists and is often refractory to treatment significantly impacting quality of life. Elucidating its pathogenesis, and development of prevention and treatment strategies for chronic itch is a global aspiration. Previous research has identified numerous itch mediators and receptors. However, the mechanisms of itch potentiation remain largely unknown. Glial cells, a component of the nervous system, have emerged as key players in itch modulation. This mini-review focuses on the role of glial cells in modulating the itch sensation, with an emphasis on skin diseases, where the role of glial cells in itch has been studied in recent years.

Keywords: ***Astrocytes; Chronic itch; Microglia; Spinal cord***

Citation: Tominaga M, Morita M, Takamori K. Roles of Glial Cells in Itch Modulation of Skin Diseases. Arc Clin Exp Dermatol. 2024;6(1):154.

1. Abbreviations

ACD: Allergic contact dermatitis; AD: Atopic dermatitis; AEW: Acetone and diethylether followed by water; CD11b: Cluster determinant 11b; CX3CL1: Chemokine CX3C ligand 1; CX3CR1: Chemokine CX3C receptor 1; DNFB: 1-fluoro-2,4-dinitrobenzene; DRG: Dorsal root ganglion; GRP: Gastrin-releasing peptide; GRPR: Gastrin-releasing peptide receptor; GFAP: Glial fibrillary acidic protein; GNTI: 5'-guanidinonaltrindole; Iba-1: Ionized calcium-binding adapter molecule 1; IL: Interleukin; IMQ: Imiquimod; IP3R1: IP3 receptor type 1; LCN2: Lipocalin-2; NLRP3: NOD-like receptor thermal protein domain-associated protein 3; Npr1: Natriuretic peptide receptor 1; p-p38: Phospho-p38; LPS-RS: Lipopolysaccharide from the photosynthetic bacterium rhodobacter sphaeroides; PD-1/PD-L1: Programmed cell death receptor/ligand 1; STAT3: Signal transducer and activator of transcription 3; s.c.: Subcutaneous; TLR4: Toll-like receptor 4

2. Introduction

Itch is a common sensation experienced by everyone, but its manifestation involves diverse and complex mechanisms. These include the presence of numerous mediators that induce itch and the production of modulators that exacerbate it *in vivo* during pathological conditions [1]. The simultaneous presence of these factors often leads to severe and persistent itch, which can progress to chronic itch (lasting more than 6 weeks). Management of chronic itch is often ineffective with existing remedies, resulting in what is referred to as intractable itch. Chronic and intractable itch also occurs in skin diseases such as atopic dermatitis (AD) and psoriasis or systemic diseases such as kidney and liver diseases [1,2]. Furthermore, in recent years, chronic and intractable itch has been found to significantly diminish patients' quality of life and add to the disease burden [3,4]. In AD, antibody drugs and JAK inhibitors effective against chronic itch have emerged as effective treatments for patients suffering from chronic itch. However, there is still an urgent need to elucidate the mechanisms of chronic and intractable itch and to develop prevention and treatment methods for skin and systemic diseases for which the mechanisms remain unknown.

Glial cells, also known as neuroglia, are a diverse group of cells in the nervous system that provide support, protection, and nourishment to neurons. They encompass various types, including astrocytes, oligodendrocytes, and microglia. These cells perform crucial functions such as metabolizing neurotransmitters, forming neuronal circuits, and regulating the internal environment in the central nervous system, which includes the spinal cord and brain [5].

In the peripheral nervous system, there are primarily two major types of glial cells. First, satellite cells surround neuronal cell bodies, providing nourishment and protection. Second, Schwann cells wrap around peripheral nerve fibers, forming the insulating substance called myelin, which enhances the speed of nerve transmission. These peripheral glial cells play crucial roles in supporting and protecting neurons [5].

While the role of glial cells in pain has been extensively studied [6], their relationship to the pathogenesis of itch remains largely unknown. Since 2000, however, the role of glial cells in chronic itch has become increasingly clear in the spinal cord of the central nervous system, particularly in inflammatory skin diseases such as AD and psoriasis. Among these glial cells, astrocytes and microglia have emerged as key players in the pathogenesis of both acute and chronic itch. This mini review describes the roles of glial cells in itch modulation of skin diseases.

3. Glial Cells and Acute Itch

The involvement of astrocytes in acute itch has not been reported. However, several studies have reported interesting findings on the role of microglia (TABLE 1).

TABLE 1. **Summary of the relationship between glial cells and itch.**

Type of itch	Stimuli (e.g. itch mediators)	Diseases	Model	Mouse strain	Type of glia	Description (e.g. mechanisms and treatment)	Ref.
Acute itch	Histamine		$CX3CR1^+$ microglia-deleted transgenic mice	C57BL/6	Microglia	Decreased number of histamine-evoked scratching behavior	6
	Compound 48/80		$CX3CR1^+$ microglia-deleted transgenic mice	C57BL/6	Microglia	Decreased number of compound 48/80-evoked scratching behavior	6
	Chloroquine		$CX3CR1^+$ microglia-deleted transgenic mice	C57BL/6	Microglia	Decreased number of chloroquine-evoked scratching behavior	6
	5'-GNTI-induced scratching		Subcutaneous (s.c.) injection of GNTI (0.3 mg/kg) to the back of the mouse neck.	Swiss-Webster	Microglia	5'-GNTI-induced scratching activates spinal microglia, and preadministration of the KOR agonist nalfurafine decreases microglial activation with a decrease in 5'-GNTI-induced scratching	7
Chronic itch		Xerosis	AEW	C57BL/6	Astrocytes	Involvement of spinal TLR4-expressing astrocytes	9
		Atopic dermatitis	Living mite	NC/Nga	Astrocytes	Enhanced GRP signaling by LCN2 released from active astrocytes	10
		Atopic dermatitis	Dfb	NC/Nga	Microglia	Intrathecal minocycline reduced itching in atopic dermatitis mice in association with a decrease in the number of spinal microglia.	14
		Psoriasis	IMQ	C57BL/6	Astrocytes?	3-oxa-protectin D1 may suppress spinal cord production and astrocyte release of LCN2	19
		Psoriasis	IMQ	C57BL/6	Microglia	Microglia were activated in the spinal cord of psoriasis model mice, and intrathecal minocycline or PLX5622 diet suppressed psoriasis itch	15
		Psoriasis	IMQ	C57BL/6, GRPR-eGFPKO	Microglia	Enhances the activation of $GRPR^+$ neurons through the NLRP3/caspase-1/IL-1β/ IL1R1 axis	17
		Psoriasis	IMQ	C57BL/6	Microglia	Intrathecal PD-L1 suppressed the activation of microglia and psoriatic itch	18
		Psoriasis	IMQ	C57BL/6	Microglia	Sensory neuron contribute to spinal microglial activation	16
		Allergic contact dermatitis	DCP (diphenylcyclopropenone)	C57BL/6	Astrocytes	Enhanced GRP signaling by LCN2 released from active astrocytes	10
		Allergic contact dermatitis	DNFB (dinitrofluorobenzene)	C57BL/6	Astrocytes?	3-oxa-protectin D1 may suppress spinal cord production and astrocyte release of LCN2	19
		Allergic contact dermatitis	DNFB (dinitrofluorobenzene)	C57BL/6	Microglia	Intrathecal PD-L1 suppressed the activation of microglia and itch	18
		CTCL	Intradermal injection of $CD4^+$ MyLa cell line	NOD.CB17-$Prkdc^{scid}$ (immune deficient mice)	Astrocytes?	3-oxa-protectin D1 may suppress spinal cord production and astrocyte release of LCN2	19
Mechanical alloknesis	von Frey filaments	Xerosis	AEW	C57BL/6	Astrocytes	Involvement of spinal TLR4-expressing astrocytes	9
	von Frey filaments	Psoriasis	IMQ	C57BL/6	Microglia	Intrathecal minocycline or PLX5622 diet suppressed mechanical alloknesis	15

A previous study using transgenic mice to selectively deplete $CX3CR1^+$ microglia and peripheral macrophages together (whole depletion), or selectively deplete microglia alone (central depletion), showed that acute itch responses to histamine, compound 48/80 and chloroquine were all significantly reduced in mice with either whole or central depletion [7]. Furthermore, spinal c-fos mRNA assays and further studies revealed that histamine and compound 48/80, but not chloroquine, elicited primary itch signal transmission from dorsal root ganglion (DRG) to spinal natriuretic peptide receptor 1 (Npr1)- and somatostatin-positive neurons, relying on the microglial CX3CL1-CX3CR1 pathway. These findings suggest that spinal microglia are involved in multiple types of acute chemical itch transmission. Additionally, the underlying mechanisms for histamine-dependent and independent itch transmission may differ, as the former requires the CX3CL1-CX3CR1 signal pathway [7].

A previous study has reported that scratching may activate microglia in the mouse spinal cord [8]. Histologically, it was observed that the complement receptor 3, also known as cluster determinant 11b (CD11b) - a cell surface marker of microglial

cells - was upregulated in the spinal cord 10 to 30 min after a subcutaneous (s.c.) injection of compound 48/80 or 5'-guanidinonaltrindole (GNTI), a κ-opioid receptor antagonist, to the back of the mouse neck [8]. The study also noted numerous intensely labeled CD11b-immunoreactive cells, resembling hypertrophic reactive microglia, distributed throughout the gray and white matter [8], while weakly labeled CD11b-immunoreactive cells were observed in the spinal cord of mice injected with saline [8]. Further analysis through Western blotting showed that CD11b expression levels significantly increased in spinal cords of mice following s.c. injection of compound 48/80 or GNTI to a peak in about 30 min and declined to about the basal level in the ensuing 60 min [8]. In addition, the levels of phospho-p38 (p-p38), which is phosphorylated and activated, were upregulated in spinal cords of mice injected with compound 48/80 or GNTI, with a time course parallel to that of CD11b expression [8]. Pretreatment of the mice with nalfurafine, a κ-opioid receptor agonist that has been shown to suppress scratching, reduce CD11b and p-p38 expression induced by compound 48/80 or GNTI [8]. These findings raise the possibility that physical stimulation by scratching contributes to microglial activation in the spinal cord.

4. Glial Cells and Chronic Itch

In recent years, there has been increasing knowledge and evidence of the role of glial cells in the pathogenesis of chronic itch associated with skin diseases (TABLE 1).

4.1 Glial cells and dry skin-induced itch

There are limited reports of glial cells involved in dry skin itch, particularly regarding the contribution of spinal astrocytes (TABLE 1).

In pain research, mounting evidence suggests that Toll-like receptor 4 (TLR4) plays a significant role in spinal cord glial activation and the sensitization of chronic pain [9]. Considering this, Liu *et al.* investigated the involvement of TLR4 in both acute and chronic itch models in male mice, utilizing transgenic and pharmacological methods [10]. They found that *Tlr4*-knockout mice displayed normal acute itch responses to compound 48/80 and chloroquine but exhibited substantial reductions in scratching behavior in chronic itch models induced by dry skin, through the application of acetone and diethylether followed by water (AEW) on the neck [10]. Inhibiting TLR4 in the spinal cord with lipopolysaccharide from the photosynthetic bacterium Rhodobacter sphaeroides (LPS-RS), a TLR4 antagonist, had no effect on acute itch but attenuated AEW-induced chronic itch. Additionally, injection of compound 48/80 and AEW treatment induced mechanical alloknesis in wild-type mice, which was suppressed by intrathecal administration of LPS-RS and *Tlr4* deletion [10]. Furthermore, repeated application of AEW led to persistent upregulation of *Tlr4* mRNA and increased TLR4 expression in glial fibrillary acidic protein (GFAP)-expressing astrocytes in the spinal dorsal horn [10]. AEW treatment also induced TLR4-dependent astrogliosis (*i.e.* GFAP upregulation) in the spinal cord. Intrathecal injection of the astroglial inhibitor L-α-aminoadipate reduced AEW-induced chronic itch and mechanical alloknesis without affecting acute itch (TABLE 1) [10]. Notably, the researchers found that AEW-induced astrogliosis was mitigated by the application of Elizabethan collars to prevent scratching the itchy skin [10]. This suggests that scratching may play a crucial role in spinal astrogliosis. These findings indicate that TLR4 signaling is crucial for spinal astrocyte activation and astrogliosis, potentially contributing to mechanical alloknesis and chronic itch in AEW-treated dry skin mice. However, the involvement of spinal microglia in the pathogenesis of dry skin itch remains unclear.

4.2 Glial cells and atopic itch

Here we describe the involvement of glial cells in the pathogenesis of itch of AD (TABLE 1). Several studies have shed light on the relationship between AD-induced itch and astrocytes or microglia, with a particular focus on the role of astrocytic activation in the spinal dorsal horn and its contribution to chronic itch conditions. In 2015, Shiratori-Hayashi *et al*. reported for the first time that astrocytes activated in the dorsal horn of the spinal cord play a role in chronic itch in AD [11]. They observed that reactive astrogliosis depended on the activation of signal transducer and activator of transcription 3 (STAT3) in mouse models of AD [11]. Disruption of astrocytic STAT3 conditionally suppressed chronic itch, while pharmacological inhibition of spinal STAT3 ameliorated developed chronic itch [11]. Furthermore, intrathecal administration of gastrin-releasing peptide (GRP) in AD mice increased itch-related scratching behavior, which was normalized by suppressing STAT3-mediated reactive astrogliosis [11]. Additionally, they identified lipocalin-2 (LCN2) as an astrocytic STAT3-dependent upregulated factor crucial for chronic itch, demonstrating that intrathecal administration of LCN2 to normal mice increased spinal GRP-evoked scratching [11]. These findings suggest that STAT3-dependent reactive astrocytes act as amplifiers of atopic itch by enhancing spinal itch signals through LCN2. Moreover, a recent study has elucidated the mechanisms underlying the persistent activation of astrocytic STAT3 in chronic itch conditions such as AD [12]. In that study, knockdown of IP3 receptor type 1 (IP3R1) in astrocytes suppressed interleukin (IL)-6-induced persistent STAT3 activation and expression of LCN2 [12]. Furthermore, IP3R1-dependent astrocytic Ca^{2+} responses involved Ca^{2+} influx through the cation channel transient receptor potential canonical (TRPC), which was necessary for persistent STAT3 activation evoked by IL-6 [12]. Additionally, IL-6 expression was upregulated in DRG neurons of AD mice. Notably, DRG neuron-specific IL-6 knockdown, spinal astrocyte-specific IP3R1 knockdown, and pharmacologic spinal TRPC inhibition attenuated LCN2 expression and itch-related scratching behaviour [12]. Thus, these findings suggest that IP3R1/TRPC channel-mediated Ca^{2+} signals elicited by IL-6 in spinal astrocytes are essential for persistent STAT3 activation, LCN2 expression, and chronic itch.

In our more recent study, utilizing a mouse model of AD induced by repeated applications of *Dermatophagoides farinae* body extracts, we observed that the expression level of LCN2 in satellite glial cells surrounding the cell bodies of DRG neurons was higher compared to that in the spinal cord [13]. We also found that the increased expression of LCN2 in DRG neurons preceded its upregulation in the spinal cord during the onset of AD [13]. Moreover, administration of a neutralizing antibody against LCN2 did not exhibit an antipruritic effect but instead suppressed dermatitis [13]. While it is plausible that the frequency and duration of antibody administration were inadequate, this observation raises the possibility that LCN2 may play distinct roles in the pathogenesis of AD at peripheral and central levels. Previously, we reported that accumulation of immunoglobulin G against *D. farinae* tropomyosin in DRG, particularly within satellite glial cells, of NC/Nga mice with AD [14]. The mechanism by which this IgG accumulation in satellite glia contributes to the pathogenesis of itch in AD remains unclear. However, there is growing evidence suggesting a correlation between peripheral glial cells and AD symptoms.

As attention was drawn to the role of spinal cord astrocytes in the development of chronic itch in AD, we observed an increased number of microglia in the spinal cord of mice with AD [15]. Remarkably, intrathecal administration of minocycline, a microglial inhibitor, reduced the elevated number of microglia in the spinal cord of AD mice, alleviated itching, and improved dermatitis [15]. Hence, in addition to the aforementioned astrocytes, it has been suggested that spinal microglia are at least partially involved in the pathogenesis and processing of atopic itch.

4.3 Glial cells and psoriatic itch

Like other itch models, psoriasis-induced itch is known to entail the activation of glial cells. Xu *et al*. reported a significant increase in the expression of Iba-1, a marker for microglia, in the dorsal horn of the cervical spinal cord following treatment with imiquimod (IMQ). Moreover, they found that intrathecal administration of the microglial inhibitor minocycline or a PLX5622 diet suppressed spontaneous itch, mechanical alloknesis, and microglial activation [16]. These findings suggest that the activation of spinal cord microglia plays a role in the pathogenesis of psoriatic itch.

Recent studies have identified key molecules involved in the activation of microglia in psoriatic itch. One study demonstrated the essential role of primary sensory neurons in activating spinal microglia in IMQ-induced psoriatic itch, Ablation of sensory neurons resulted in reduced scratching behavior and fewer activated microglia in the spinal dorsal horn [17]. Another study revealed that the NOD-like receptor thermal protein domain-associated protein 3 (NLRP3) inflammasome and IL-1β activate gastrin-releasing peptide receptor $(GRPR)^+$ neurons in the spinal cord [18]. Under chronic itch conditions such as allergic contact dermatitis, psoriasis, dry skin and AD, the NLRP3 inflammasome is activated, and IL-1β expression is increased in spinal microglia near $GRPR^+$ neurons [18]. Blocking microglial activation, the NLRP3/Caspase-1/IL-1β axis, or IL-1β or IL1R1 signaling effectively attenuated psoriatic itch and neuronal activation in IMQ mice [18]. These findings suggest that microglia enhance the activation of $GRPR^+$ neurons through the NLRP3/Caspase-1/IL-1β/IL1R1 axis.

In their study, Xu *et al*. investigated the mechanism underlying itch induced by programmed cell death receptor/ligand 1 (PD-1/PD-L1) inhibitors, commonly used in cancer treatment [19]. They identified the presence of the PD-1 receptor in the spinal cord of mouse models for chronic itch conditions, including dry skin, psoriasis, and allergic contact dermatitis [19]. Notably, intrathecal administration of PD-L1 specifically suppressed the activation of microglia in the spinal dorsal horn, thereby alleviating psoriatic itch [19]. These findings suggest that the activation of spinal PD-1 plays a crucial role in the activation of microglia during the pathogenesis of psoriatic itch.

Recent reports have implicated spinal astrocytes in the pathogenesis of psoriasis itch [20]. Behavioral analysis revealed that intrathecal administration of n-3 docosapentaenoic acid, particularly 3-oxa-protectin D1, effectively reduced psoriatic itch in IMQ mice [20]. The potential mechanisms underlying itch suppression by 3-oxa-protectin D1 may involve the regulation of excitatory and inhibitory synaptic transmission and the inhibition of LCN2 secretion by astrocytes [20]. This suggests that not only microglia but also astrocytes may play a role in processing psoriasis itch in the spinal cord. This idea is further supported by our data indicating that serum LCN2 levels positively correlate with the degree of itchiness in patients with psoriasis [21].

4.4 Others

Shiratori-Hayashi *et al*. have demonstrated that astrocytes in the spinal dorsal horn become reactive in a model of allergic contact dermatitis (ACD) through activation of STAT3 and play a critical role in chronic itch [11]. Furthermore, *Tlr4*-knockout mice exhibited substantial reductions in scratching in ACD on the neck [10]. These findings, similar to the role of astrocytes in atopic itch, suggest that spinal astrocytes may also contribute to the pathogenesis of itch in ACD (TABLE 1). Moreover, behavioral analyses have shown that intrathecal administration of 3-oxa-protectin D1 reduced itch in 1-fluoro-2,4-

dinitrobenzene (DNFB)-induced ACD and cutaneous T-cell lymphoma (CTCL). Given that 3-oxa-protectin D1 suppresses the production of astroglial LCN2 [20], these findings raise the possibility that astrocytes are also involved, at least in part, in the pathogenesis of itch in ACD and CTCL.

Intrathecal administration of PD-L1 specifically suppressed the activation of microglia in the spinal dorsal horn, thereby alleviating chronic itch induced by DNFB-induced ACD [19]. Such activation of microglia in the spinal dorsal horn was undetected in the AEW-treated mice [19].

5. Conclusion

In conclusion, the modulation and processing of itch intensity by different types of glial cells may vary depending on the specific skin disease state. Future research will primarily focus on elucidating these dynamics, as few studies have explored the interactions of multiple glial cells over time in chronic itch models. Additionally, simultaneous assessment of both itch and pain will be crucial for a comprehensive understanding of sensory processing in these conditions.

6. Funding

This work was partly supported by grants from JSPS KAKENHI [grant numbers 20H03568 and 22H02956].

7. Conflicts

The authors have no conflicts of interest to declare.

8. Acknowledgements

We thank David Price of English Services for Scientists for proofreading the manuscript.

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