综述

神经免疫紊乱在特应性皮炎中的作用研究进展

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［摘要］特应性皮炎（atopic dermatitis，AD）是全球发病率最高的慢性炎症性皮肤病，临床主要表现为湿疹样皮肤病变、瘙痒和干皮症。近来有研究发现，AD患者的皮损中的感觉神经元可同时与角质形成细胞（keratinocyte，KC）、免疫细胞异常互作，导致神经免疫紊乱的发生。其中，参与神经免疫紊乱的感觉神经元有2类，包括组胺能感觉神经元和非组胺能感觉神经元。在神经免疫紊乱中，KC和免疫细胞可通过分泌白细胞介素-4（interleukin-4，IL-4）、IL-13、IL-31、IL-33、胸腺基质淋巴细胞生成素等促炎细胞因子以及C-X-C模体趋化因子配体12（C-X-C motif chemokine ligand 12，CXCL12）、CXCL10等趋化因子激活感觉神经元以诱发瘙痒，还可分泌神经生长因子、脑源性神经营养因子和神经鞘胚素等神经肽诱导感觉神经元过度生长，以促进神经免疫互作。同时，感觉神经元过度释放的降钙素基因相关肽和P物质等神经肽可作用于KC和免疫细胞，从而加剧皮肤炎症。近年来，诸多靶向神经免疫紊乱的药物处于临床前研究、临床试验等阶段，或已上市用于AD治疗，其中该课题组发现局麻药物利多卡因可靶向神经免疫紊乱并能够在临床上缓解AD患者的瘙痒及皮肤炎症。目前，神经免疫紊乱在AD中的作用鲜少被系统性讨论。基于此，该文围绕参与神经免疫紊乱的感觉神经元种类，KC、免疫细胞及感觉神经元在神经免疫紊乱中的作用，以及靶向神经免疫紊乱的治疗策略进行综述。

［关键词］特应性皮炎；神经免疫；感觉神经元；免疫细胞；角质形成细胞
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Research progress in neuroimmune disorders in atopic dermatitis

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[Abstract] Atopic dermatitis (AD) is a chronic inflammatory skin disease with the highest incidence in the world. The main clinical manifestations are eczema-like skin lesions, pruritus and xeroderma. Recent studies have revealed that sensory neurons in the skin lesions of AD patients can interact abnormally with keratinocytes (KC) and immune cells, leading to neuroimmune disorders. Among them, there are two types of sensory neurons involved in neuroimmune disorders, including histaminergic and non-histaminergic sensory neurons. In neuroimmune disorders, KC and immune cells activate sensory neurons to induce pruritus by secreting proinflammatory cytokines such as interleukin-4 (IL-4), IL-13, IL-31, IL-33, and thymic stromal lymphopoietin, as well as chemokines such as C-X-C motif chemokine ligand 12 (CXCL12) and CXCL10. In addition, neuropeptides such as nerve growth factor, brain-derived neurotrophic factor and artemin secreted by KC and immune cells can induce overgrowth of sensory neurons, thereby promoting neuroimmune disorders. At the same time, the excessive release of neuropeptides such as calcitonin gene-related peptide and substance P by sensory neurons can act on KC and immune cells, thereby aggravating skin inflammation. In recent years, many drugs targeting neuroimmune disorders are in preclinical studies, clinical trials and other stages, or have been marketed for the treatment of AD. Among them, our research group has found that lidocaine, a local anesthetic, can target neuroimmune disorders and relieve pruritus and skin inflammation in AD patients. At present, the role of neuroimmune disorders in AD has not been systematically discussed. Based on this, this article reviews the types of sensory neurons involved in neuroimmune disorders, the role of KC, immune cells and sensory neurons in neuroimmune disorders, as well as the therapeutic strategies targeting neuroimmune disorders.

[Key words] atopic dermatitis (AD); neuroimmune; sensory neuron; immune cell; keratinocyte (KC)

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特应性皮炎（atopic dermatitis，AD）是全球发病率最高的慢性炎症性皮肤病。研究显示，AD在1~12月龄婴儿和1~7岁儿童中的发病率较高，分别为30.48%和12.94%[1]，且在成人中的发病率也高达10%[2]。临床上，AD主要表现为湿疹样皮肤病变、瘙痒和干皮症，可严重影响患者的生活质量[3]。研究[4]发现，2型炎症反应是AD的重要病理生理学机制之一。具体而言，丝聚蛋白基因突变、变应原刺激和金黄色葡萄球菌异常定植等可损伤AD患者的皮肤屏障，诱导角质形成细胞（keratinocyte，KC）释放“警报素”，如白细胞介素-33（interleukin-33，IL-33）和胸腺基质淋巴细胞生成素（thymic stromal lymphopoietin，TSLP）[4]，二者可招募辅助型T细胞2（T helper 2 cell，Th2细胞）和2型固有免疫细胞（group 2 innate lymphoid cell，ILC2）至皮损处分泌IL-4、IL-13等细胞因子，引发2型炎症反应。此外，KC分泌的趋化因子亦可招募上述免疫细胞至皮损中发挥促炎作用[5]。除Th2细胞和ILC2外，嗜酸性粒细胞（eosinophil，EOS）和肥大细胞（mast cell，MC）也能够在AD中诱导2型炎症反应的发生[4]。

在机体组织中，外周神经和免疫细胞互作广泛存在并参与机体的正常生理过程，而因其异常互作形成的神经免疫紊乱则与诸多疾病的发生、发展相关[6]。随着神经免疫领域的不断发展，对AD的病理生理学的研究不再局限于皮肤中的免疫微环境，转而向神经免疫紊乱进行拓展[7]。在AD患者的皮肤中，感觉神经元的活动较为活跃且分布密度较高，其可同时与KC、免疫细胞异常互作导致神经免疫紊乱发生。其中，KC和免疫细胞可分泌促炎细胞因子和趋化因子激活感觉神经元并诱发瘙痒，还可分泌神经肽诱导感觉神经元过度生长；同时，感觉神经元过度分泌的神经肽亦可诱导KC和免疫细胞产生炎症反应，进而导致AD的发生发展[7]。近年来，靶向神经免疫紊乱的治疗策略已在临床中取得了良好的抗AD疗效[7]。基于以上内容，本文围绕参与神经免疫紊乱的感觉神经元种类、KC、免疫细胞及感觉神经元在神经免疫紊乱中的作用、靶向神经免疫紊乱的治疗策略进行综述，以期为研究者拓宽对AD的病理生理学机制的理解，并为AD的基础和临床研究提供新方向和思路。

1 参与神经免疫紊乱的感觉神经元

感觉神经元分为组胺能感觉神经元和非组胺能感觉神经元。组胺是研究最多的瘙痒原，其可与组胺能感觉神经元上的组胺1型受体（histamine 1 receptor，H1R）和H4R结合，以激活神经元释放神经肽［如降钙素基因相关肽（calcitonin gene-related peptide，CGRP）和P物质（substance P，SP）］，从而增加局部血管通透性并促使MC脱颗粒[8]。虽然靶向H1R的抗组胺药物可缓解组胺诱发的急性荨麻疹瘙痒，但并不能显著改善AD患者的皮肤炎症和瘙痒等临床症状[9]。另有研究发现，组胺可通过激活皮肤中组胺能感觉神经元的H4R诱导AD的瘙痒症状，H4R拮抗剂则在AD动物模型和临床试验中被证明具有止痒和抑炎的作用；继而提示，H4R是介导组胺能感觉神经元参与神经免疫紊乱的重要受体[10-11]。

在神经免疫紊乱中，非组胺能感觉神经元也发挥了关键作用。有研究发现，AD患者皮肤中的KC和免疫细胞产生的促炎细胞因子能激活非组胺能感觉神经元上的G蛋白偶联受体，进而打开瞬时受体电位阳离子通道亚家族（transient receptor potential cation channel subfamily，TRP）V1和TRPA1等通道致使膜去极化，继而使电压门控钠离子通道（voltage-gated sodium channels，Na_Vs）打开并产生动作电位，最终激活大脑中投射神经元，产生瘙痒-搔抓反射[12]。与组胺能感觉神经元一样，非组胺能感觉神经元也能够通过过度分泌神经肽作用于皮肤的KC和免疫细胞，从而加剧皮肤炎症[12]。

2 KC和免疫细胞在神经免疫紊乱中的作用

近年来的研究发现，在AD中KC和免疫细胞通过释放IL-4、IL-13、IL-31、TSLP和IL-33等促炎细胞因子以及趋化因子来诱发皮肤炎症、激活感觉神经元产生瘙痒，因此这些因子发挥了促炎和促痒的双重作用。此外，KC和免疫细胞还可分泌神经生长因子（nerve growth factor，NGF）、脑源性神经营养因子（brain-derived neurotrophic factor，BDNF）和神经鞘胚素（artemin，ARTN）等神经肽来诱导神经元生长，从而促进神经免疫互作。通过文献检索，我们对

KC和免疫细胞分泌的促炎细胞因子、趋化因子和神经肽参与神经免疫紊乱的具体机制进行整理并阐述如下。

2.1　IL-4和IL-13

IL-4和IL-13主要由Th2细胞、ILC2和MC等免疫细胞分泌，研究发现过表达IL-4和IL-13可诱发小鼠皮肤炎症，并提高小鼠的搔抓频率[13-14]。感觉神经元表面存在IL-4受体和IL-13受体，可被IL-4和IL-13以TRPV1依赖性钙内流方式直接激活[15]。虽然皮下注射IL-4和IL-13不能导致小鼠的急性搔抓行为，但可激活蛋白酪氨酸激酶（Janus kinase，JAK）/信号转导和转录激活因子（signal transducer and activator of transcription，STAT）信号通路，从而降低皮肤感觉神经元对TSLP和IL-31等瘙痒原的反应阈值，导致小鼠的慢性搔抓行为；而敲除感觉神经元的IL-4受体α亚基基因（*Il4ra*）或*Jak1*基因，则可显著降低AD小鼠的搔抓频率并缓解皮肤炎症[15]。

2.2　IL-31

IL-31是参与AD发病的重要促炎细胞因子，由Th2细胞、EOS和MC等免疫细胞分泌[16-17]。研究[17-18]显示，感觉神经元可高度表达IL-31受体，且其表达水平与皮肤淀粉样变患者的慢性瘙痒程度密切相关。此外，皮下注射IL-31可直接诱发小鼠急性搔抓行为，进一步对其机制研究发现该过程为IL-31直接激活TRPV1$^+$/TRPA1$^+$感觉神经元所致[19]。上述研究均提示，感觉神经元可被IL-31激活，从而产生急性和慢性瘙痒。

2.3　TSLP

研究[20]显示，受损的皮肤屏障中的KC可在AD发病过程中发挥促炎免疫功能。而在该过程中，由KC分泌的TSLP是引发Th2型免疫反应的“警报素”之一[21]。TRPV1$^+$神经元可被TSLP直接激活从而诱导小鼠的急性搔抓行为[22]，提示TSLP能够诱发AD相关急性瘙痒。临床上，干皮症是AD的主要表现之一。在干皮症小鼠模型中，TSLP可通过TRP通道依赖性钙内流方式激活感觉神经元，以诱发自发搔抓行为和皮肤干燥[23]。此外，AD患者的过度搔抓行为会损伤皮肤屏障，而该损伤会进一步促进KC分泌瘙痒原TSLP，从而形成“瘙痒-搔抓循环”[24]。

2.4　IL-33

IL-33也是AD患者受损皮肤屏障中KC释放的“警报素”[25]，近年来多项研究[26-29]发现IL-33也可通过激活感觉神经元介导AD的瘙痒症状。一项体外研究[26]显示，IL-33可通过结合其受体直接激活皮肤感觉神经元。在接触性皮炎小鼠模型中，皮下注射IL-33能够通过激活致癌抑制因子2（suppression of tumorigenicity 2，ST2）信号通路来诱导急性搔抓行为的发生[27]。此外，TRIER等[28]发现在不明原因慢性瘙痒小鼠模型中，敲除感觉神经元的IL-33受体（interleukin-33 receptor，IL-33R）基因*Il1rl1*可显著降低搔抓频率。尽管在AD小鼠中敲除感觉神经元*Il1rl1*基因的改善瘙痒作用是轻微的[28]，但在AD患者的皮损中IL-33的表达水平与慢性瘙痒程度呈正相关[29]。

2.5　趋化因子

研究[7]显示，AD相关趋化因子也可通过C-X-C模体趋化因子配体12（C-X-C motif chemokine ligand 12，CXCL12）/C-X-C模体趋化因子受体4（C-X-C motif chemokine receptor 4，CXCR4）、CXCL10/CXCR3、C-C趋化因子配体2（C-C chemokine ligand 2，CCL2）/C-C趋化因子受体2（C-C chemokine receptor 2，CCR2）等信号通路直接激活感觉神经元，从而诱发瘙痒。

2.6　NGF

AD患者皮损中的KC、EOS和MC均可过度分泌NGF，该因子通过激活其受体即原肌球蛋白受体激酶A受体（tropomyosin receptor kinase A receptor，TrkA）来诱导感觉神经元生长，从而促进神经免疫互作[30]；同时，NGF还可敏化感觉神经元，从而降低AD患者的瘙痒阈值[31]。基于NGF在神经免疫紊乱中的重要作用，有学者针对NGF受体拮抗剂进行研究，结果发现该拮抗剂可显著抑制AD小鼠的皮损中感觉神经元生长，继而减少神经免疫互作，最终降低小鼠的搔抓频率并缓解皮肤炎症[32]。

2.7　BDNF

研究[33]显示，BDNF能促进感觉神经元生长。在AD患者的外周血中，显著浸润的EOS水平与BDNF水平呈正相关，提示EOS可能通过分泌BDNF

参与AD的发生发展[34]。而后，GUSEVA等[35]发现AD患者的皮损中浸润的EOS可通过分泌BDNF诱导感觉神经元生长，并观测到大量$BDNF^+$ EOS与感觉神经元共定位，继而提示EOS和感觉神经元在AD患者的皮损中存在互作。

2.8 ARTN

ARTN是参与神经免疫紊乱的重要神经肽之一。在AD患者的皮损中，成纤维细胞可分泌过量的ARTN，以促进感觉神经元生长并降低皮肤的温热依赖性瘙痒阈值，从而促进神经免疫互作并加剧AD患者在温热环境下的瘙痒症状[36]。HIDAKA等[37]进一步发现，激活芳香烃受体可使KC过度表达*Artn*基因并分泌过量的ARTN，继而导致AD小鼠的皮肤中$TRPV1^+$感觉神经元过度生长，最终促进了AD的发生与发展。

3 感觉神经元在神经免疫紊乱中的作用

在AD中，感觉神经元可通过过度分泌神经肽参与神经免疫紊乱[7]。研究显示，AD患者的皮损中存在被异常激活并过度生长的$CGRP^+$和SP^+感觉神经元[38]，二者能够过度分泌神经肽，使得在AD患者的皮损及外周血中均可检测到较高的CGRP和SP水平，且该水平与AD的严重程度呈正相关[39-40]。当应用肉毒毒素抑制感觉神经元释放CGRP和SP后，AD小鼠的皮肤炎症缓解且搔抓频率降低，继而提示CGRP和SP在神经免疫紊乱中存在重要作用[41]。下文就感觉神经元通过分泌CGRP、SP和其他神经肽参与神经免疫紊乱的具体机制进行阐述。

3.1 CGRP

感觉神经元过度分泌的CGRP具有促炎作用。相关研究[42]显示，银屑病大鼠的皮损中感觉神经元过度分泌的CGRP可促进树突状细胞分泌IL-23，继而诱发皮肤炎症。而两项体外研究表明，CGRP可通过促进KC过度增殖导致表皮增厚[43]，还可诱导KC分泌IL-1β和肿瘤坏死因子-α（tumour necrosis factor-α，TNF-α）等促炎细胞因子，在AD的发生与发展中发挥重要作用[44]。由于AD患者的皮损中的KC可表达更高水平的CGRP受体，使得KC对CGRP更为敏感[43]。此外，CGRP还可促进皮肤记忆T细胞转向Th2表型，从而促进该细胞分泌IL-13，加重AD的皮肤炎症[45]。相反，腹腔注射CGRP受体拮抗剂BIBN4096可降低AD小鼠的皮损中IL-13等促炎细胞因子的水平，从而降低皮损区域淋巴细胞募集和表皮异常增厚，降低搔抓频率[46]。

3.2 SP

感觉神经元过度分泌的SP能够通过激活神经激肽-1受体（neurokinin-1 receptor，NK-1R，即SP受体）诱导KC和成纤维细胞分泌IL-1β和IL-8，从而加剧皮肤炎症[47]。随后，SHI等[44]发现SP还可通过激活细胞外信号调节激酶1/2（extracellular regulated kinase 1/2，ERK1/2）和JNK信号通路来诱导KC分泌TNF-α、IL-6等促炎细胞因子。同时，SP可抑制AD患者外周血来源的EOS凋亡，以提高EOS在AD患者中的系统性浸润[48]。FRIEDMAN等[49]发现，SP还可通过激活NK-1R或NK-2R来诱导EOS脱颗粒释放NGF和IL-31。且有研究[50]证实，在AD小鼠的皮损中，SP^+感觉神经元的周围存在大量的脱颗粒EOS。此外，SP还可激活MC中Mas相关G蛋白偶联受体成员B2，从而诱导MC脱颗粒释放蛋白酶、IL-4和IL-13等，使AD小鼠的皮损处发生2型炎症反应[51]。

3.3 其他神经肽

AD患者的皮损中感觉神经元还可过度分泌生长抑素、脑利钠肽和内皮素-1等神经肽。研究显示，IL-31可促进感觉神经元过度分泌生长抑素，而生长抑素可直接激活感觉神经元诱导瘙痒的发生[52]；脑利钠肽可通过联合糖原合成酶激酶-3（glycogen synthase kinase-3，GSK-3）依赖性途径和c-Jun氨基末端激酶（c-Jun N-terminal kinase，c-JNK）激活途径促进KC分泌CXCL10和IL-17A，从而导致皮肤炎症[53]；内皮素-1可通过ERK1/2信号通路促进KC分泌IL-25，诱导2型炎症反应的发生[53]。

4 靶向神经免疫紊乱的治疗策略

神经免疫紊乱是AD的重要病理生理学机制。当前，已有诸多靶向该机制的药物处于临床前研究、临

床试验等阶段，或上市用于AD治疗。度普利尤单抗（Dupilumab）可靶向IL-13受体、IL-4受体的共享亚基IL4Rα，同时阻断IL-13、IL-4通路，该药物已用于中重度AD患者的临床治疗[54]。小分子药物阿布昔替尼（Abrocitinib）可抑制IL-4、IL-13通路下游的JAK1活性，也已用于治疗中重度AD患者[55]。曲罗芦单抗（Tralokinumab）可高亲和力、特异性地与IL-13结合，以阻断IL-13与其受体相结合，从而抑制IL-13介导的信号通路；该药物的3期临床试验显示其可缓解AD患者瘙痒及皮肤炎症[56]。奈莫利珠单抗（Nemolizumab）是靶向IL-31受体的人源化单克隆抗体，也在3期临床试验中展现出良好的抗AD疗效[57-59]。曲地匹坦（Tradipitant）可拮抗NK-1R，3期临床试验显示该药物可显著缓解轻度AD患者的瘙痒症状并具有良好安全性[60]。H4R拮抗剂JNJ-39758979的2期临床试验显示，其可显著减轻中度AD患者的瘙痒症状[11]。Asivatrep（PAC-14028）可拮抗TRPV1，其乳膏剂型在2期临床试验中可显著改善轻中度AD患者瘙痒和皮肤炎症[61]。特泽鲁单抗（Tezepelumab）是靶向TSLP的人源化单克隆抗体，有关其治疗AD的有效性和安全性的研究尚处于2期临床试验中[62]。TRPA1拮抗剂、IL-33单抗、TrkA拮抗剂Typhostin（AG879）和CGRP受体拮抗剂Olcegepant（BIBN4096）在AD动物模型中均展现出了良好的疗效[32,63-64]。在我国，利多卡因“老药新用”，可以静脉封闭方式治疗中重度AD患者[65-66]。本课题组最近的创新性研究发现利多卡因可靶向神经免疫紊乱，在AD小鼠中能作用于皮肤$Na_V1.8^+$感觉神经元，从而抑制其释放CGRP，以显著降低小鼠的搔抓频率并缓解皮肤炎症[46]。同时，利多卡因还可作用于调节性T细胞（regulatory T cell，Treg细胞），通过激活TGF-β/Smad3信号通路诱导Treg细胞分化，从而抑制2型炎症反应[65-66]。因此，将利多卡因转化用于AD治疗或具有良好的前景。伴随着神经免疫紊乱在AD病理生理学机制中的重要性被逐步发现，更多靶向神经免疫紊乱的药物正在不断地被开发并应用于临床。

5　总结与展望

AD是全球疾病负担和发病率最高的慢性炎症性皮肤病，临床上亟需对其病理生理学机制及有效的治疗方法行进一步的研究及开发[67]。回顾既往研究发现，AD患者的皮损中的感觉神经元（包括组胺能感觉神经元和非组胺能感觉神经元）能够同时与KC、免疫细胞发生异常互作，导致神经免疫紊乱的发生。其中，KC和免疫细胞可通过分泌促炎细胞因子和趋化因子激活感觉神经元诱发瘙痒，还可通过分泌神经肽诱导感觉神经元过度生长；同时，感觉神经元过度释放的神经肽可反过来作用于KC和免疫细胞，从而加剧皮肤炎症。当前，靶向上述神经免疫紊乱的治疗策略在临床上已取得了良好疗效，这也证实神经免疫紊乱在AD病理生理学机制中的重要作用。综上，在本文中我们系统综述了近年来神经免疫紊乱在AD中的研究进展，对神经免疫紊乱的研究或将为AD的病理生理学机制探索提供新的思路和方向，同时也可为AD的临床治疗提供新的靶点和策略。

利益冲突声明/Conflict of Interests

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宣臻全负责撰写论文，宣臻全和陈轩祎参与了论文修改，姚志荣负责论文审阅。所有作者均阅读并同意了最终稿件的提交。
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