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Neuroimmunology of psoriasis: Possible roles for calcitonin gene-related peptide in its pathogenesis

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ABSTRACT

The nervous system has a complex interplay with the immune system, especially at barrier sites such as the skin. This allows it to play a role in a variety of cutaneous inflammatory disorders such as psoriasis, exerting effects on various immune cells via effector molecules such as neuropeptides. In this review, we discuss the role of calcitonin gene-related peptide in modulating the immune system and inflammation, with a focus on psoriasis.

1. Neurogenic inflammation, neuropeptides, and the skin

Central to understanding the effects of neuropeptides on inflammatory disorders is the concept of neurogenic inflammation, which broadly refers to inflammatory responses stemming from peripheral stimulation of sensory neurons and driven at least in part by the secretion of neuropeptides (Kilo et al., 1997; Kim and Granstein, 2021). The skin, like other epithelial surfaces with a great degree of exposure to the external environment, is posed to respond rapidly to potential threats from it, owing to dense innervation by various nerve fibers, predominantly sensory but also autonomic, on a time scale much faster than activation of the innate immune system (Chiu et al., 2012; Roosterman et al., 2006). This is driven by the ability of the typically afferent neurons to not only transmit signals/action potentials orthodromically (i.e. to the spinal cord), but also via axonal branch points and their collaterals back to the periphery (i.e. antidromically), which is known as an axon reflex (Choi and Di Nardo, 2018; Sorkin et al., 2018). In the meantime, effectors such as neuropeptides may be released by the nerves, which allows them to communicate with the diverse population of epidermal and dermal cells, as well as blood vessels and adnexa, that are anatomically close to nerve fibers (Roosterman et al., 2006). One outcome of this can be recruitment of immune cells to participate in an inflammatory response to antigens or other insults, or to participate in wound healing (Chiu et al., 2012; Choi and Di Nardo, 2018). Most cells in the skin have neuropeptide receptors, through which they establish feedback loops with nerves by releasing neuropeptides and other signaling molecules themselves (Choi and Di Nardo, 2018). Thus, the nervous system is capable of alerting the immune system to the presence of a threat while simultaneously initiating a response locally. Thus, it follows that through modulating the activity of the immune system, nerves can participate in not only beneficial immune responses (e.g. to infection) but also to deleterious immune processes (e.g. autoimmune/autoinflammatory conditions).

Abbreviations: AM, adrenomedullin; ASIC3, acid-sensing ion channel 3; BMDC, bone marrow-derived dendritic cell; BTX/BoNT, botulinum toxin; CALC, calcitonin (gene); CCL, CC chemokine ligand; CGRP, calcitonin gene-related peptide; CLR, calcitonin-like receptor; cOVA, chicken ovalbumin; CXCL, chemokine ligand; DDC, dermal dendritic cell; DNFB, 1-fluoro-2,4-dinitrobenzene; DRG, dorsal root ganglion; EC, endothelial cell; ERK, extracellular signal-regulated kinase; GATA3, GATA-binding protein 3; GMQ, 2-guanidine-4-methylquinazoline; GPCR, G protein-coupled receptor; HIV, human immunodeficiency virus; HKCA, heat-killed candida antigen; HPA, hypothalamic-pituitary-adrenal (axis); IFN, interferon; IL, interleukin; IMQ, imiquimod; KC, keratinocyte; LC, Langerhans cell; LPC, lysophosphatidylcholine; MAPK, Mitogen-activated protein kinase; NF-κB, nuclear factor-kappa B; NGF, nerve growth factor; NO, nitric oxide; PASI, psoriasis area and severity index; pDC, plasmacytoid dendritic cell; PDK-1, phosphoinositide-dependent kinase 1; pDMEC, primary dermal microvascular endothelial cell; PKA, protein kinase A; RAMP, receptor activity-modifying protein; RORγ, retinoic acid receptor-related orphan receptor gamma; RSK, ribosomal S6 kinase 1; RTX, resiniferatoxin; RvD3, resolvin D3; siRNA, small interfering RNA; SP, substance P; TLR, toll-like receptor; TNF, tumor necrosis factor; TRPV1, transient receptor potential vanilloid 1 (channel); VEGF, vascular endothelial growth factor; VSMC, vascular smooth muscle cell.

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2. Calcitonin gene-related peptide physiology and immunology

2.1. Structure and general functions of CGRP

Calcitonin gene-related peptide (CGRP) is a 37-amino-acid neuropeptide produced via alternative RNA processing of the gene for calcitonin (Amara et al., 1982; Kim and Granstein, 2021). It has 2 forms: αCGRP and βCGRP. In humans, αCGRP is an alternative splicing variant of the CALC I (calcitonin) gene, while βCGRP is derived from a second CALC gene (CALC II), differing from αCGRP by only three amino acids (Brain et al., 1986; Kim and Granstein, 2021). Both are potent vasodilators (Brain et al., 1986; Kim and Granstein, 2021). The sites of expression of αCGRP and βCGRP have considerable overlap (Russo and Hay, 2023). αCGRP is expressed in discrete areas throughout the central (e.g. wide distribution in the spinal cord and brain (Mulderry et al., 1985)) and peripheral nervous systems (e.g. trigeminal and dorsal root ganglia [DRGs]); overall, αCGRP is the predominant form expressed by sensory neurons, whereas intrinsic enteric neurons predominantly express βCGRP (Gibson et al., 1984; Kim and Granstein, 2021; Mulderry et al., 1988; Russo and Hay, 2023).

CGRP binds to receptors that are heterodimers of the calcitonin-like receptor (CLR) and a receptor-activating modifier protein (RAMP), with CLR/RAMP1 being the CGRP receptor, while CLR/RAMP2 is an adrenomedullin (AM) receptor (AM1) and CLR/RAMP3 is the AM2 receptor (McLatchie et al., 1998; Russo and Hay, 2023). βCGRP has some activity at the AM2 receptor, with Hay et al. showing that it was approximately as potent as adrenomedullin and more potent than αCGRP (Hay et al., 2003). CGRP exerts its vasodilatory activity on arterioles, with intradermal injection of femtomolar doses causing increased blood flow and local redness that outlasts histamine in its duration (Brain et al., 1985). This vasodilation can be mediated by both nitric oxide (NO)-independent and NO-dependent pathways (Russo and Hay, 2023). In the former, CGRP binding to vascular smooth muscle cells (VSMCs) induces opening of potassium channels and subsequent relaxation. In NO-dependent pathways, CGRP leads endothelial cells to release NO, which induces relaxation of VSMCs and subsequent vasodilation (Russo and Hay, 2023).

In the skin, CGRP is frequently colocalized with substance P (SP) in epidermal and dermal sensory nerves, with the fingers and toes having the highest number of these fibers (Wallengren et al., 1987). Fibers that are immunoreactive to CGRP can be found as single fibers scattered just underneath the dermoepidermal junction or passing through it into the epidermis, whereas deeper in the dermis they can either be single–especially if they are perivascular or surround the sweat glands–or can form bundles (Wallengren, 1997).

2.2. CGRP and the immune system

$CGRP^+$ nerve terminals have been shown to have a close anatomical relationship with epidermal Langerhans cells (LCs) [dendritic antigen presenting cells closely related to macrophages], with CGRP being found on the surface of a portion of the LCs (Hosoi et al., 1993). CGRP has been shown to have an inhibitory role in the ability of LCs to present antigens for Th1 immune responses while augmenting Th2 responses *in vitro* (Ding et al., 2008; Granstein et al., 2015; Hosoi et al., 1993). Administration of CGRP intradermally followed by immunization at the site of administration to Th1- or Th2-dominant haptens inhibits induction of immunity to the Th1-dominant hapten while enhancing immunity to the Th2-dominant hapten (Asahina et al., 1995a; Asahina et al., 1995b; Ding et al., 2008; Mikami et al., 2011). Additionally, exposure of LCs to CGRP inhibits stimulated production of the Th1 chemokines CXCL9 and CXCL10 but induces release of the Th2 chemokines CCL17 and CCL22 (Ding et al., 2008).

The effects of CGRP on LCs are not limited to antigen presentation. LCs are among the first dendritic cell subtypes to become infected with HIV before transmitting it to T-cells, as their epidermal location makes them one of the first subsets to encounter the virus (de Witte et al., 2007; Harman et al., 2013). Dendritic cells express pattern recognition receptors known as C-type lectins, which can bind to HIV via its gp120 glycoprotein and allow for viral entry into the dendritic cell, which allows the virus to then infect $CD4^+$ T-cells much more efficiently than directly infecting the T-cells themselves. In LCs, this C-type lectin is known as langerin. As opposed to other C-type lectins expressed on other dendritic cells, which partially protect HIV from degradation, langerin internalizes HIV into Birbeck granules, where the virus is degraded. At high viral loads, however, langerin can become saturated with HIV, thus allowing the virus to bypass it and productively infect T-cells (de Witte et al., 2007; de Jong and Geijtenbeek, 2009). Ganor et al. found that CGRP may play a protective role in HIV transmission from LCs to T-cells (Ganor et al., 2013; Granstein et al., 2015). When LCs were treated with CGRP prior to infection with HIV, the transfer of the virus to T-cells was inhibited in a dose-dependent and time-dependent manner. When T-cells were pretreated with CGRP prior to coculture with infected LCs, this did not occur. CGRP also increased langerin expression on LCs, decreased intracellular HIV and decreased the already inefficient replication of the virus in LCs (Ganor et al., 2013). CGRP's effects on inhibition of HIV transfer from LCs to T-cells was determined to be specifically via the CGRP receptor, as an antagonist of the receptor ($CGRP_{8\text{-}37}$, composed of a fragment of the CGRP peptide) blocked its effects, and an agonist of the amylin receptor, which CGRP also binds, did not affect the response to CGRP (Ganor et al., 2013; Granstein et al., 2015). Additional recent work indicates that, for herpes simplex virus type 1 (HSV-1) infection of LCs, entry is mediated via the HSV-1-specific receptor 3-O sulfated heparan sulfate (3-OS HS) in a pH-depended manner with CGRP down-regulating expression of 3-OS HS; CGRP also abrogates the pH dependency (Cohen et al., 2022). HSV-2 infection of LCs involves langerin-mediation and this process is pH-independent, while CGRP induces expression of atypical langerin double-trimer oligomers on the cell surface (Cohen et al., 2022). These findings suggest that CGRP inhibits HSV infection in mucosa by acting on LCs to differentially modulate subtype-specific entry mechanisms (Cohen et al., 2022). The authors speculate that CGRP might be useful to prevent HSV infection and HSV/HIV-1 co-infection mediated by LCs (Cohen et al., 2022). It should be noted, however, that recent work by Bertram et al. describes a subset of CD11c + DCs that are also present in the epidermis, especially in anogenital tissues, which are infected more easily with HIV and that transmit it more efficiently to T-cells, as up to 80% of these cells express langerin; Bertram et al. hypothesized that it is possible that some earlier work describing LCs in these tissues may have been looking at a mix of LCs and this newly described group of DCs (Bertram et al., 2019). In this regard, two types of activated human LCs, LC1 and LC2 have been defined (Liu et al., 2021). LC1s were described as "classical" LCs, predominantly involved in innate immunity and antigen processing while LC2s were found to be monocyte- or myeloid dendritic cell-like, acting in leukocyte activation/immune responses (Liu et al., 2021). LC1s were found to be stable under inflammatory conditions while LC2s could be activated and expressed increases in immuno-suppressive molecules (Liu et al., 2021). Interestingly, LC2s and migratory LCs were found to be more abundant in psoriatic lesions compared to normal skin, but this was not the case for LC1s (Liu et al., 2021). The significance of this for the pathophysiology of psoriasis would be an important area for investigation.

CGRP has also been demonstrated to have effects on T-cells. The AM2 receptor (CLR/RAMP3) on T-cells, through binding CGRP, was found by Hou et al. to enhance the Th1 antiviral response in mice infected with lymphocytic choriomeningitis virus (Hou et al., 2024). Neurons were also found to have increased CGRP expression during viral infection, with the antiviral response being decreased when $TRPV1^+$ $CGRP^+$ neurons were inactivated with resiniferatoxin (RTX), a potent casaicin analogue that selectiely ablates TRPV1 nociceptors (Iftinca et al., 2021) or when RAMP3 was deleted on T-cells (Hou et al., 2024). This together suggested that a circuit between CGRP-releasing neurons and T-cells

exists via RAMP3 on the T-cells themselves that can modulate antiviral responses in infected tissues (Hou et al., 2024). Innate lymphoid cells (ILCs) have also been shown to respond to CGRP, with type 2 ILCs (ILC2s) in the lungs producing more IL-5 upon exposure and possibly contributing to the pathophysiology of asthma (Sui et al., 2018).

CGRP can induce mast cell histamine release but is not particularly effective at doing so compared to substance P; per Lowman et al. the concentration at which release is significant for CGRP is 30 times higher than for substance P (Lowman et al., 1988). CGRP also potentially acts on neutrophils, with coculture resulting in significantly increased adhesion to human umbilical vein ECs (Zimmerman et al., 1992). However, it has also been shown to inhibit neutrophil recruitment by preventing endothelial cell chemokine release (Baral et al., 2019).

CGRP's effects on the immune system can also be seen by its effects on how the body responds to various pathogens, and can either be beneficial or detrimental. Pinho-Ribeiro et al. suggested a mechanism by which *Streptococcus pyogenes* takes advantage of CGRP's immunomodulatory activity to sustain infection in a mouse model of necrotizing fasciitis. By releasing the compound streptolysin S, *S. pyogenes* activates nociceptors to release CGRP, which can act on neutrophils to suppress myeloperoxidase and thus impair phagocytosis and clearance of infection (Pinho-Ribeiro et al., 2018). CGRP was also shown to impair immunity in a mouse model of *Staphylococcus aureus* pneumonia, with inhibition of CGRP improving survival (Baral et al., 2018, 2019). In a mouse model of polymicrobial septic peritonitis, defense in the early stages was improved in mice with a nonfunctional CGRP receptor, likely through the prevention of CGRP-mediated IL-10 release from macrophages (Jusek et al., 2012; Baral et al., 2019). Thus, CGRP's wide range of immune effects makes it well-positioned to play a role in both normal immune responses as well as autoimmune and autoinflammatory conditions.

3. Brief review of psoriasis and the role of the nervous system

3.1. Clinical, and histopathological overview

Psoriasis is a chronic inflammatory skin disease affecting approximately 3% of individuals over 20 years of age in the United States (Armstrong et al., 2021). The most common variant is plaque psoriasis, which comprises over 80% of cases (Armstrong and Read, 2020). It is characterized by erythematous, scaly patches and/or plaques that often appear on extensor surfaces, but can also be seen in nails, intertriginous areas, and palmoplantar skin. In severe cases, it can involve large areas of the skin surface. It does not have a predilection for any one gender and most commonly affects adults, with a bimodal distribution of the age at which it presents (18–39 years and 50–69 years) (Armstrong and Read, 2020). Histologically, psoriasis is characterized by epidermal thickening (acanthosis) with downward lengthening of the rete ridges and epidermal thinning above the papillary rete ridges and a thinner or absent stratum granulosum (Griffiths et al., 2021). There are also infiltrates of inflammatory cells, with dendritic cells, T-cells and macrophages in the dermis, along with some T-cells in the epidermis (Nestle et al., 2009). Additionally, the blood vessels in developed plaques exhibit dilation and tortuosity, which, combined with the thinning of the epidermis above the rete ridges, leads to characteristic erythema (Murphy et al., 2007; Nestle et al., 2009). There is hyperproliferation and premature cornification of keratinocytes (KCs), the latter of which leads to retention of nuclei in these cells when they become part of the stratum corneum (parakeratosis) (Nestle et al., 2009). The scale characteristic of psoriatic lesions is the macroscopic manifestation of this hyperproliferation and parakeratosis (Nestle et al., 2009).

3.2. Overview of psoriasis pathogenesis

The pathogenesis of psoriasis is still in the process of being elucidated, but it is known that in the initial phase, myeloid dendritic cells are activated by cytokines released by several cell types, including immune cells (macrophages, plasmacytoid dendritic cells, natural killer T-cells) and KCs (Armstrong and Read, 2020). The antimicrobial peptide LL-37 is thought to aggregate with self-DNA released by KCs (for example during injury) and activate toll-like receptors (TLRs) on/in plasmacytoid dendritic cells, which triggers increased secretion of interferon alpha (IFN-α) (Lande et al., 2007). Self-RNA can also bind LL37 and activate toll-like receptor 7 in endosomes of pDCs, activating them and triggering IFN-α secretion (Ganguly et al., 2009). pDCs are also triggered to present antigens to $CD8^+$ T-cells, which activate them and lead to their clonal expansion (Greb et al., 2016). The IFN-α activates myeloid dendritic cells (mDCs), which then secrete IL-12 and IL-23 (E. Lee et al., 2004). The former leads to differentiation of naive $CD4^+$ T-cells to Th1 cells, and the latter helps support the survival and proliferation of Th17 and Th22 cells (Fig. 1) (Armstrong and Read, 2020). Self-RNA-LL37 complexes can also activate bind TLR8 in mDCs and lead to their activation and maturation, along with release of IL-6 and tumor necrosis factor α (TNF-α) (Ganguly et al., 2009). There is also an increase in blood flow, and this may be the one of the first changes that occurs microscopically prior to the appearance of a visible plaque; this was determined by examining the edges of extending plaques and suggests that diffusible vasodilatory molecules may play a role (Hull et al., 1989). A brief graphic summary of key steps in psoriasis pathogenesis is illustrated in Fig. 1.

LCs have also been proposed to contribute to psoriasis pathogenesis. While various studies have produced conflicting results suggesting either pro-inflammatory, anti-inflammatory, or non-contributory roles, Liu et al., in elucidating the heterogeneity of LC populations in the skin, proposed that the variety of subsets may underlie the inconsistency of results (Liu et al., 2021). Further work by Zhou et al. showed a diverse set of LCs in the skin of patients with psoriasis and identified a subset of CCR2+ LCs with a high level of CD11c expression that were not only capable of producing IL-23, but also were only found in the perilesional and lesional epidermis (Zhou et al., 2022).

In addition to conventional T-cells, subsets of γδT-cells may also play a role in psoriasis pathogenesis. While it is known that mouse skin has a large population of these cells and that they form a relatively small percentage of the T cell compartment in human skin, there has been research implicating their involvement in cutaneous immune responses including psoriasis. In addition to suggested roles in tissue immune surveillance and re-establishment of homeostasis in stressed skin, they have been proposed to initiate and/or propagate the inflammatory cycles in psoriasis, as they can release the relevant cytokines IL-17A, IFNγ, and TNFα (Laggner et al., 2011).

3.3. Roles for the nervous system in psoriasis

There is evidence of nervous system involvement in psoriasis—Farber et al., observing that the disease is characterized by symmetric lesion distribution and tends to worsen after stressful life events, speculated that the nervous system may be involved via neuropeptides secreted by nerve endings in the skin. This was further supported by the improvement of psoriasis observed in denervation of skin sites bearing the disease (Farber et al., 1986). There have been several cases described of psoriasis improving after denervation injuries—whether through peripheral nervous system damage (e.g., surgical or self-inflicted nerve severance or mechanical injury of nerves/plexuses, drug blockade, infection) or central nervous system injury (e.g., cerebrovascular accidents)—unilaterally on the side affected by the denervation (Zhu et al., 2016). The duration of improvement was also dependent on the degree of damage to the nerves, with patients who had some recovery of sensation eventually having some recurrence in that area (Zhu et al., 2016). Studies have also reported more severe and extensive psoriasis in groups with high stress compared to groups with low stress (Harvima et al., 1993).

Twenty-four hours after acute psychological stress (Trier test),

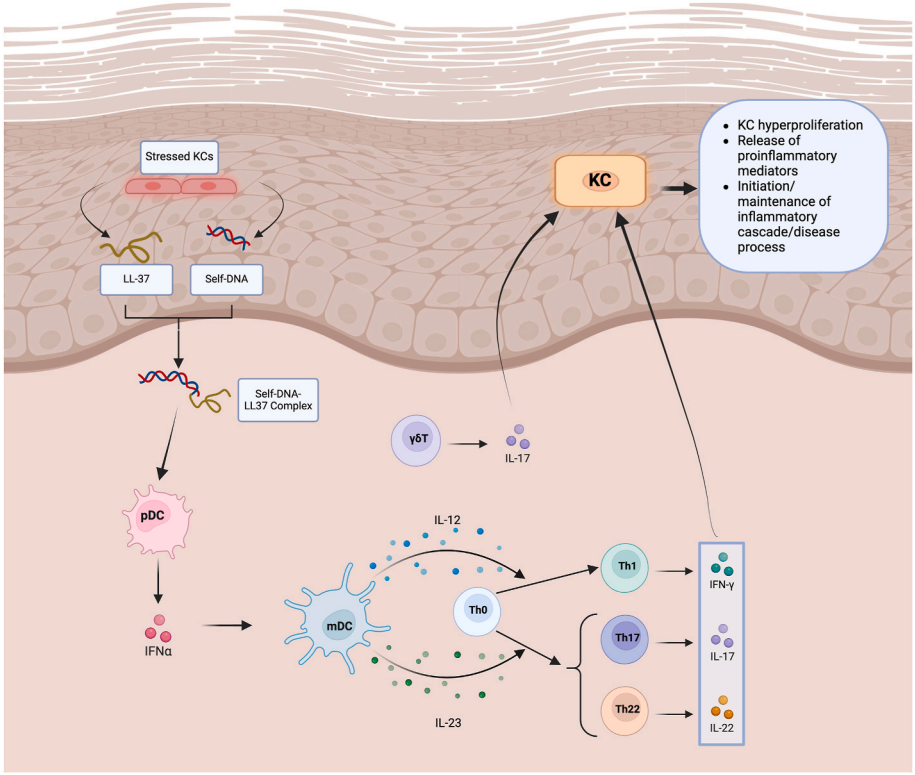

Fig. 1. Overview of psoriasis pathogenesis. Stressed keratinocytes release antimicrobial peptide LL-37 and self-DNA, which form a complex that activates pDCs to produce IFN-α, which promotes the differentiation of Th1 cells by activating mDC secretion of IL-12 and Th17/Th22 cells via secretion of IL-23. Through secreting mediators such as IFN-γ, IL-17 and IL-22, the inflammatory cascade of psoriasis is promoted, with keratinocyte-released mediators also taking part. Abbreviations: mDC, myeloid dendritic cell; KC, keratinocyte; pDC, plasmacytoid dendritic cell. Created in BioRender. Kotlyar, J. (2025) https://BioRender.com/m79w236.

biopsy showed significant decrease in cutaneous CGRP + nerve fibers compared to non-stressed controls. The authors speculated that this may be due to CGRP having been released. At this time point, epidermal LC counts also showed a significant decrease. Taken together, the authors concluded that this is evidence for a "brain-skin" axis (Kleyn et al., 2008).

Chemical denervation's impact on psoriasis has been demonstrated in several studies. When botulinum toxin B (BTX-B) was injected into mice during application of imiquimod to induce psoriasiform dermatitis, there was a significant decrease in erythema, scaling and cumulative scoring of lesion severity (Amalia et al., 2021). Overall, the authors concluded that this could be secondary to blunting of neuropeptide release (Amalia et al., 2021). This is consistent with data that botulinum toxin inhibits stimulated CGRP release (Kim and Granstein, 2021; Rapp et al., 2006). In patients with recalcitrant plaque psoriasis, treatment with onabotulinumtoxin A led to significant improvement in Psoriasis Area and Severity Index (PASI) scores (Aschenbeck et al., 2018). Epidural injection of 1% lidocaine between T12 and L1 at 4 mg/kg body weight in a group of psoriasis patients was followed by improvement in all patients in almost all dermatomes where the lesions were present. PASI scores decreased by 35–70% and improvements held for at least 24 weeks afterwards (Yin et al., 2022). The release of soluble mediators, such as neuropeptides, from neurons is one potential mechanism by which the nervous system can affect disease activity in psoriasis.

4. CGRP and psoriasis

4.1. Circumstantial evidence

Research has demonstrated a higher number of sensory nerve fibers surrounding KCs and immune cells in psoriatic lesional epidermis (Chen et al., 2022). There have also been studies that evaluated the density of CGRP-positive nerve fibers in psoriasis (Kim and Granstein, 2021), with one study revealing via double-labeled immunofluorescence (anti-MAP2 for nerves followed by anti-CGRP antibodies) that the density of $CGRP^+$ nerve fibers in psoriatic lesional epidermis was 2.5 times greater than in the epidermis of healthy individuals (Jiang et al., 1998). Furthermore, there was a significantly higher number of $CGRP^+$ fibers in lesional skin when compared to both non-lesional skin and the skin of healthy patients (Jiang et al., 1998). Another study found that the expression of CGRP and its receptors was higher in psoriasis patients in their intraepidermal nerve fibers (not observed in healthy controls in this report); the expression of its receptor was also found to be elevated, although neither elevation was statistically significant (Kubanov et al., 2015). Additionally, several studies have shown increased serum/plasma CGRP in psoriasis (Li et al., 2016; Narbutt et al., 2013; Wiśnicka et al., 2004), and CGRP has been found on LCs and ECs in psoriatic plaques (He et al., 2000).

Thirteen psoriasis patients were divided into low and high stress groups based on clinical examination/questioning and the results of appropriate questionnaires (Harvima et al., 1993). A higher proportion of patients in the high-stress group exhibited CGRP positive nerve fibers in the papillary dermis of their plaques compared to the low-stress group (3 out of 6 vs. 1 out of 7) (Harvima et al., 1993).

Mature psoriatic lesions had significantly increased contact between mast cells and $CGRP^+$ nerve fibers in the papillary dermis as well as with both these fibers and the basement membrane, when compared to non-lesional skin (Naukkarinen et al., 1996). In psoriatic lesions induced by tape stripping (Koebner phenomenon), contacts between $CGRP^+$ nerve fibers and mast cells were increased (Naukkarinen et al., 1994). This difference was only significant between non-lesional skin and mature lesions, but not between the former and developing lesions. This difference was larger for SP in the papillary dermis, and the authors suggested that SP might be a more important vasodilator in psoriasis, since

the increased number of tryptase-positive mast cells is increased in mature psoriatic lesions, and this enzyme degrades CGRP; also, SP decreases the duration of CGRP's vasodilatory action (Naukkarinen et al., 1994). The overall lack in significant change in contacts between neuropeptide-positive nerve fibers and mast cells in developing lesions, in contrast with mature lesions, led the authors to speculate that neuropeptides may play more of a role in maintaining psoriatic lesions (Naukkarinen et al., 1994).

CGRP has also been shown to be able to modify the virulence of *Staphylococcus epidermidis*, the interaction of the two made more likely by the fact that neuropeptides including CGRP have been found in sweat (Cizza et al., 2008; N'Diaye et al., 2016). CGRP-pretreated *S. epidermidis* had increased cytotoxicity against KCs and stimulated the secretion of LL-37 by KCs *in vitro*; this could potentially encourage the formation of LL-37-nucleic acid complexes, but the significance of this behavior of *S. epidermidis in vivo*, specifically on psoriasis pathogenesis, remains to be further investigated (N'Diaye et al., 2016).

There have been several studies linking migraines and psoriasis, suggesting a possible connection, as CGRP is implicated in migraine pathophysiology, with several CGRP receptor antagonists available for treatment and prevention (Ailani et al., 2021; Edvinsson et al., 2018). A study in South Korea using a national cohort showed a significant increase in migraine frequency in psoriasis patients compared to controls matched for age, sex, medical history, socioeconomic status and region; this was especially prominent in men aged 40–59 years (Min et al., 2019). Furthermore, a Danish nationwide cohort study also demonstrated an increased risk of migraine development in psoriasis patients, which correlated with disease severity; this risk was independent of cardiovascular risk factors such as hypertension, hyperlipidemia and diabetes mellitus, as well as socioeconomic status (Egeberg et al., 2015).

4.2. Relationship between CGRP and IL-23/IL-17 axis

The IL-23/IL-17 axis is an important component of the pathophysiology of psoriasis (Lowes et al., 2013), with several monoclonal antibodies (mAbs) targeting this pathway on the market for treatment such as guselkumab (targeting the p19 subunit of the IL-23 receptor), ixekizumab (targeting IL-17A), and secukinumab (targeting IL-17 receptor A) (Hawkes et al., 2018). Studies suggest that CGRP can modulate this axis. For example, Peng et al. showed that CGRP upregulated IL-23 mRNA and protein in LCs, via phosphoinositide-dependent kinase 1 (PDK1) signaling with induction of ribosomal S6 kinase 1 (RSK); when γδT-cells were co-cultured with LCs and CGRP, they had increased IL-17A and IL-22 secretion, which was not the case when they were cultured with CGRP alone, suggesting action via LCs (Peng et al., 2022). In a model of *Candida albicans* infection, against which IL-17 is an important defender (as evidenced by the increase in chronic mucocutaneous candidiasis in individuals with IL-17 signaling mutations and the increased risk of candidiasis among patients treated with IL-17 inhibitors (Davidson et al., 2022; Okada et al., 2016)), Kashem et al. found that heat-killed *Candida albicans* (HKCA) was able to activate most TRPV1$^+$ nociceptors. In addition, cultured DRG neurons released significantly more CGRP upon exposure to HKCA than control neurons not exposed to HKCA (Kashem et al., 2015). Mice with TRPV1 ablated by resiniferatoxin (RTX) had significantly lower IL-23, higher fungal burden, and decreased numbers of IL-17+ γδT-cells. Zymosan (derived from yeast cell walls) also directly activated DRG neurons. The authors suggested that this implied that TRPV1$^+$ neurons can be directly activated by *C. albicans*. Denervation of half of the lateral dorsum prior to *C. albicans* infection was followed by lower IL-23A and IL-17A mRNA expression and higher fungal burden, highlighting the importance of sensory nerves for IL-23 and IL-17 responses that defend against *C. albicans* (Kashem et al., 2015). Intradermal injection of αCGRP into infected, RTX-denervated mice restored IL-23 expression and decreased fungal burden to control mouse levels. However, when mice with depleted CD301b$^+$ dDCs were treated with CGRP, the effect on RTX-denervated mice was not replicated, indicating that the restoration of the IL17/23 axis was more likely to have occurred with CGRP operating upstream from IL-23 production (rather than via direct antimicrobial activity, as a decrease in fungal burden would have been expected if dendritic cells were not necessary for CGRP to exert a downstream antifungal effect) (Kashem et al., 2015). This, with the fact that CGRP reversed the post-denervation inadequate antifungal response, suggests that modulation of the IL23/17 axis by TRPV1$^+$ sensory nerves occurs at least in part by CGRP activating dendritic cells to produce IL-23, which activates γδT-cells to produce IL-17. The importance of IL-23 in modulating the production of IL-17 by γδT-cells (and therefore acting upstream of them) was further emphasized by the fact that IL-23p19-deficient mice had significantly lower γδT-cell numbers compared to wild-type controls and lower IL-17 production by dermal γδT-cells. This was reversible by exogenous IL-17 administration, which decreased the fungal burden to wild-type mouse levels. Furthermore, the authors found that IL-23 was needed for adequate γδT-cell proliferation and for their production of IL-17A. This pathway suggests a possible mechanism by which CGRP can contribute to the development of psoriasis via modulating the IL-23/17 axis.

CGRP has also been shown to influence the IL-17 pathway via ECs (Ding et al., 2016). When primary dermal microvascular endothelial cells (pDMECs) were pre-treated with CGRP prior to coculture with LCs, responsive T-cells (engineered to spontaneously respond to a fragment of chicken ovalbumin, cOVA $_{323\text{-}335}$), and cOVA$_{323\text{-}335}$, the T-cells responding to antigen presentation were found to have increased intracellular expression of IL-17A and release of IL-17 and IL-6 along with inhibition of IFNγ, IL4 and IL-22 release compared to cocultures with pDMECs treated with only medium. CGRP$_{8\text{–}37}$ blunted these effects, which, in tandem with the presence of RAMP1 and CLR on pDMECs, further supported that CGRP was mediating these effects on cytokine production (Ding et al., 2016). Compared to antigen-presenting cultures without pDMECs, addition of pDMECs treated with only medium was followed by a small but significant increase in CD4$^+$ T cell RORγT (a Th17-associated transcription factor) mRNA, but cocultures with CGRP-pretreated pDMECs led to a much more substantial increase (Ding et al., 2016). Whereas there was a small but significant increase in T-bet (a Th1-associated transcription factor (Szabo et al., 2000)) mRNA in T-cells with medium treated pDMECs, CGRP completely suppressed this (Ding et al., 2016). There was a small but significant decrease in GATA3 (transcription factor important for Th2 differentiation (Zheng and Flavell, 1997)) mRNA in T-cells cocultured with medium-treated pDMECs, and it further decreased significantly with CGRP-treated pDMECs. Based on IL-6 siRNA pre-treatment of pDMECs, induced IL-6 release by pDMECs appeared to play a role in the effect of CGRP on all cytokines except IL-4 (Ding et al., 2016). Contact between pDMECs and endothelial cells, and/or pDMECs cells and T-cells, was not needed for the effects of CGRP on cytokine production to take place (Ding et al., 2016). All of this taken together provided evidence *in vitro* that CGRP could bias antigen presentation towards the Th17 pole by acting on endothelial cells (Ding et al., 2016).

The Th17-biasing ability of CGRP through actions on endothelial cells was further demonstrated *in vivo*. When BALB/c mice were pretreated with CGRP via intradermal injection before immunization with the hapten 1-fluoro-2-dinitrobenzene (DNFB) at the site of CGRP administration, non-specific stimulation of T-cells from their draining lymph nodes with anti-CD3 and anti-CD28 produced significantly more IL-17A, but significantly less IFNγ and IL-22 compared to control mice injected with medium alone (without CGRP) before being immunized with DNFB (Ding et al., 2016). However, IL-4 release was enhanced; the direction of IL-4 change differed between these *in vitro* and *in vivo* experiments. Of course, in the *in vivo* experiments, the site of action of the CGRP is unknown. In this regard, it may be of interest that we have previously reported that LC treatment with CGRP enhances their ability to stimulate IL-4 responses (Ding et al., 2008) and this may account for the result seen in vivo. When percutaneous immunization to DNFB was

conducted with inducible, conditional endothelial cell RAMP1 knockout (EC RAMP1 KO) mice (i.e. without functional CGRP receptors on endothelial cells), the stimulated $CD4^+$ T-cells from draining lymph nodes expressed significantly less IL-17A and significantly more IFN-γ, IL-4 and IL-22 at the protein and mRNA levels (Ding et al., 2022). EC RAMP1 KO mice also expressed significantly less mRNA for RORγT while mRNA for T-bet and GATA3 were significantly increased in responding T-cells, overall demonstrating biasing of immunity towards the Th1 pole in mice unable to respond to CGRP via ECs. Overall, these data suggest that CGRP exerts immunologic effects *in vivo* through actions on endothelial cells, namely a bias of Th cell differentiation towards the Th17 pole and away from the Th1 pole (Ding et al., 2022).

4.3. CGRP and keratinocytes

There is also molecular evidence suggesting a role for CGRP in the hyperproliferation of KCs that occurs in psoriasis, as shown in Fig. 2 (Yu et al., 2009). KCs have been shown to express CLR and RAMP1, suggesting that there is a complete CGRP receptor on these cells, which could respond to CGRP in the surrounding environment (Shi et al., 2013). In fact, when rat KCs were cultured with CGRP for 3 h the amount of CGRP the KCs themselves produced was significantly increased 21 h later (Shi et al., 2013). The response to CGRP coupled with an amplification of production suggest the ability of CGRP to influence KCs in an autocrine and/or paracrine fashion (Shi et al., 2013). In these cells and in an immortalized human KC line (HaCaT), CGRP also led to increased KC proliferation in a concentration-dependent manner (Shi et al., 2013) (Yu et al., 2009). Culture of KCs with CGRP also led to increased expression of TNF-α, IL-1β, IL-6 and nerve growth factor (NGF) at the gene and protein levels in a concentration-dependent manner, and this was abrogated for all mediators except NGF by addition of the CGRP antagonist $CGRP_{8\text{-}37}$ (Shi et al., 2013). Selectively inhibiting ERK1/2 MAPK significantly decreased the CGRP-stimulated increase in TNF-α, NGF and IL-6 mRNA levels, but did not have much of an effect on IL-1β (Shi et al., 2013). Selective p38 inhibition only reduced IL-6 expression, reducing the CGRP-stimulated IL-6 mRNA back to the level of it in KCs not exposed to CGRP at all (Shi et al., 2013). Collectively, this suggests a role for ERK1/2 in CGRP-stimulated increase in TNF-α and NGF expression and a role for p38 (in addition to ERK1/2) in CGRP's effects on IL-6 expression (Shi et al., 2013). The lack of effect of inhibiting ERK1/2 and p38 MAPK on CGRP-stimulated IL-1β expression was suggested to possibly indicate that a different pathway plays a role for this cytokine (Shi et al., 2013).

Culture of HaCaT cells with CGRP also led to an enhancement in serum-induced cell proliferation, which was assessed due to serum's known richness in mitogenic substances (Yu et al., 2009). Given that inflamed skin typically hosts an abundance of cytokines capable of acting as mitogens for KCs (KCs), these findings suggest that CGRP might amplify cytokine-mediated mitogenic effects (Yu et al., 2009). There was also a significant increase in phosphorylated ERK1/2 and MAPK in CGRP-exposed HaCaT cells; this, along with the proliferation increase being abrogated by the inhibitors of these proteins, suggested a role for this pathway in mediating an increase in KC proliferation upon exposure to CGRP (Yu et al., 2009). Ye et al. also found increased phosphorylation of p38 and ERK 1/2 upon incubation of HaCaT cells with CGRP, which decreased with inhibition of CGRP, suggesting that CGRP influences the phosphorylation of these proteins (Ye et al., 2017). Another study demonstrated that when treated with CGRP, HaCaT KCs had concentration-dependent increases in vascular endothelial growth factor (VEGF) expression and release that were significantly abrogated with CGRP and ERK1/2 inhibitors, which suggests a mechanism by which CGRP could influence angiogenesis in psoriasis (Yu et al., 2006).

Ye et al. demonstrated that through activating the MAPK and NF-κB pathways in immortalized HaCaT KCs, CGRP can promote KC secretion

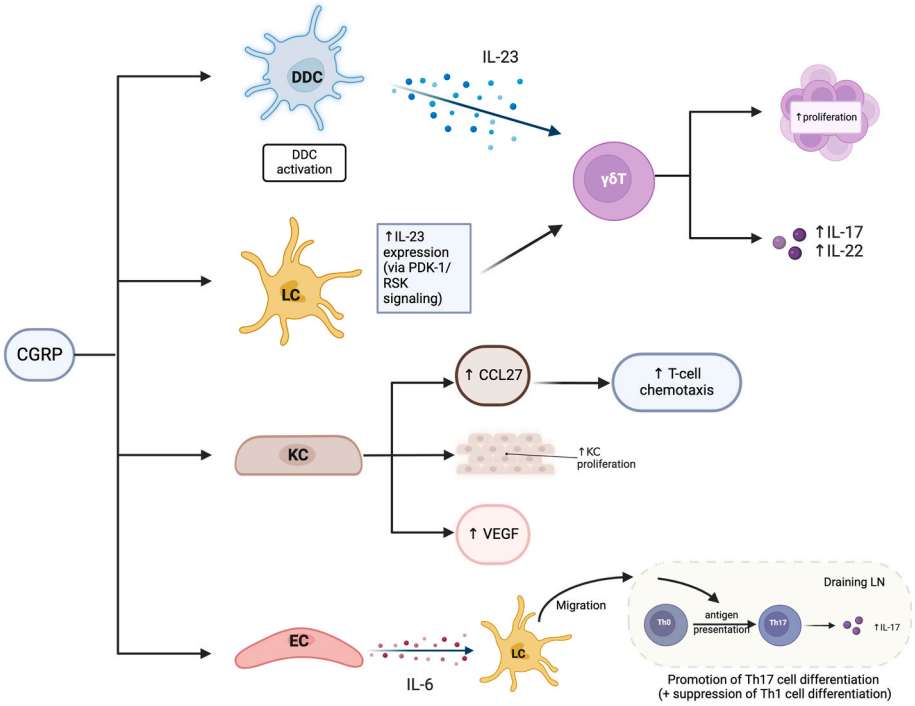

Fig. 2. CGRP acts on various cell types, resulting in downstream effects that could promote psoriatic inflammation. It can activate DDCs to produce IL-23, which promotes the proliferation of γδT-cells, which secrete IL-17 and IL-22. LCs can also be driven by CGRP to produce IL-23 via PDK-1/RSK signaling, which also promotes γδT-cell activity. CGRP action on KCs leads to increased CCL27, which promotes T-cell chemotaxis, as well as increased KC proliferation and VEGF secretion, the latter of which may contribute to angiogenesis in psoriatic lesions. In addition, CGRP can indirectly bias antigen presentation by LCs away from the Th1 pole and towards the Th17 pole, via ECs acting as bystanders, which involves release of IL-6. Abbreviations: CGRP, calcitonin gene-related peptide; DDC, dermal dendritic cell; LC, Langerhans cell; KC, keratinocyte; EC, endothelial cell; VEGF, vascular endothelial growth factor; PDK-1, phosphoinositide-dependent kinase 1; RSK, ribosomal S6 kinase 1. Created in BioRender. Kotlyar, J. (2025) https://BioRender.com/w24k433.

of CCL27, which stimulates T cell chemotaxis (Ye et al., 2017). Specifically, there is evidence that the p38-MAPK and ERK1/2 pathways, in addition to NF-κB, are involved in this promotion of CCL27 release by KCs. This was in part determined by analyzing the chemotactic index (CI) of T-cells from patients with psoriasis (a measure of the ability of HaCaT cells to modulate chemotaxis of by using a porous double well system containing T-cells in one well and either HaCaT cell supernatant or HaCaT-unexposed control medium in the other and calculating the ratio of migrated T-cells between the two cultures after a set time). At baseline, the CI of T-cells from patients with psoriasis was significantly higher than in non-psoriatic patients (i.e. chemotaxis of T-cells is related to psoriasis onset). When incubated with supernatants from CGRP-treated HaCaT cells, the T-cells from psoriatic patients had a significantly increased CI. This increase was blunted by treatment of HaCaT cells with $CGRP_{8-37}$ prior to culture with CGRP. The post-CGRP CI increase after was also blunted by the addition of inhibitors of p38-MAPK, ERK1/2, and NF-κB to HaCaT-CGRP cultures, suggesting a role for the MAPK and NF-κB pathways in the modulation the ability of KCs to influence T-cell chemotaxis after CGRP exposure. There was also a dose-dependent increase in CCL27 expression and secretion with increasing CGRP concentration, which was blunted by CGRP antagonist exposure and by p38-MAPK, ERK1/2, and NF-κB inhibitors. This overall suggested that CGRP led to HaCaT cells secreting CCL27 via the MAPK and NF-κB pathways (Ye et al., 2017). CGRP treatment of HaCaT cells led to degradation of IκBα, which is an inhibitor of NFκB signaling. The CGRP inhibitor $CGRP_{8-37}$ prevented IκBα degradation thus inhibiting the NF-κB pathway, suggesting a role for it in the CGRP-to-psoriatic inflammation pathway (Ye et al., 2017). A summary of the effects of CGRP on KCs *in vitro* is shown in Fig. 2. The data on CGRP's effects on keratinocytes taken together suggests possible contributions to psoriasis pathogenesis via increased KC proliferation, release of pro-inflammatory cytokines and chemokines, and promotion of angiogenesis.

4.4. Animal models suggesting roles for CGRP in psoriasis

4.4.1. Imiquimod model

One animal model of psoriasis that supports a potential role for CGRP in the condition is the imiquimod model. Imiquimod (IMQ) is a toll-like receptor (TLR)-7-activating immunomodulatory molecule used in the treatment of human papilloma virus infections (warts), actinic keratoses and superficial basal cell carcinomas (Edwards, 1998; Geisse et al., 2002; Jurk et al., 2002; Szeimies et al., 2004). It has been known to induce/exacerbate psoriasis in people, including those with no history of the disease who were applying it for basal cell carcinomas or actinic keratoses (Patel et al., 2011). In mice, imiquimod induces a dermatitis resembling psoriasis clinically (skin scaling, thickening and erythema), histopathologically (acanthosis, parakeratosis), and immunologically (T cell, neutrophil, dendritic cell, and pDC infiltration) (van der Fits et al., 2009).

Nociceptive sensory neurons have been implicated in psoriasis pathogenesis via this model. Riol-Blanco et al. (Riol-Blanco et al., 2014) demonstrated that when mice were pretreated with resiniferatoxin (RTX, a highly potent capsaicin analogue that selectively ablates $TRPV1^+$ nociceptors (Iftinca et al., 2021)) prior to IMQ application to their ears, the protein levels of IL-17A, IL-17F and IL-22, as well as the number of $IL\text{-}17F^+$ and $IL\text{-}22^+$ γδT-cells, were significantly lower in their ear skin after IMQ challenge than in IMQ-exposed control mice with intact nociceptors. In addition, the mRNA levels for both subunits of IL-23 (IL-23p19, IL-23p40) and protein levels of p40, were significantly lower in RTX-pretreated mouse ear skin after IMQ application than in control mice. This led the authors to speculate that nociceptors played a role in IMQ-induced production of IL-17F and IL-22 by γδT-cells, as well as in the IMQ-induced production of IL-23 in the skin. Mice with selectively deleted $Na_v1.8$ channels (which are co-expressed with TRPV1 on many sensory neurons, shown in Fig. 3) were found to have significantly lower IL-17A, IL-17F and IL-22 and IL-23p40 in their ear skin upon exposure to IMQ compared to control mice. Since there was still some TRPV1 transcription in DRGs in $Na_v1.8$-knockout mice, the authors concluded that the nociceptors driving IMQ-induced psoriasiform inflammation were the $Na_v1.8^+TRPV1^+$ subset. Intradermal injection of IL-23 resulted in increased production of IL-17A and IL-17F regardless of nociceptor presence/ablation, suggesting that nociceptors act upstream of the IL-23-mediated activation of γδT-cells to produce IL-17A/F and this pathway is what nociceptors influence to mediate psoriasiform dermatitis. The primary producers of IL-23 in the skin were determined to be dermal DCs (DDCs), most of which were found to be near or in direct contact with sensory neurons; this distribution was found to be biased when compared to contacts with other numerous structures in the skin, namely blood and lymph vessels. These results led the authors to propose a model in which $Na_v1.8^+TRPV1^+$ nociceptors influence the IL-17/23 axis by inducing nearby DDCs to produce IL-23, which stimulates γδT-cells to produce IL-17 and IL-22, which in turn recruits neutrophils and monocytes to promote psoriatic inflammation (Riol-Blanco et al., 2014).

Zhang et al. (2021) further elucidated the role of CGRP in this process. RTX denervation was followed by decreased DRG expression of CGRP mRNA as well as almost complete loss of nerve fiber CGRP secretion (Zhang et al., 2021). In innervated, IMQ-treated mice, DRG

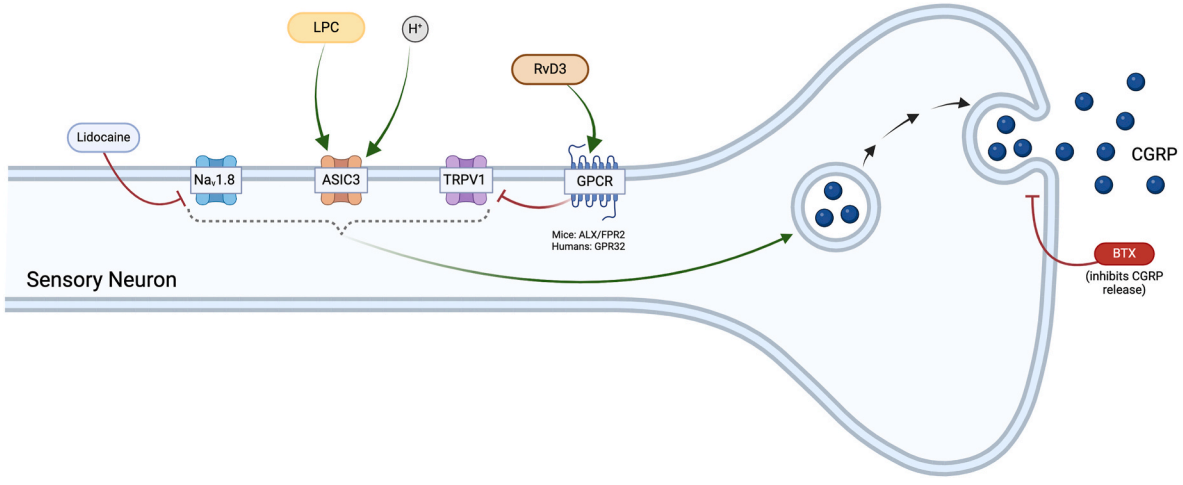

Fig. 3. Sensory nerve terminal receptors and ion channels implicated in psoriasiform dermatitis via release of CGRP. Abbreviations: ASIC3, acid-sensing ion channel 3; BoNT, botulinum toxin; CGRP, calcitonin gene-related peptide; LPC, lysophosphatidylcholine; RvD3, resolvin D3; TRPV1, Transient Receptor Vanilloid 1 channel. Created in BioRender. Kotlyar, J. (2025) https://BioRender.com/o07n141.

expression of CGRP mRNA was significantly increased by 6 h after the first IMQ application, but a gradual decrease in CGRP levels in the skin was seen over the entire application period, leading the authors to suggest that the CGRP increase in IMQ-induced psoriasiform dermatitis happened early and was transient, with the gradual decrease in CGRP possibly being due to vesicle depletion, especially given the decrease in density of CGRP + nerve fibers over this time period (Zhang et al., 2021). The transient increase in CGRP expression in RTX-pretreated mice was significantly lower than in innervated mice. RTX-denervated, IMQ-exposed mice had significantly decreased IL-23 and IL-17A expression in skin (both at the mRNA and protein levels) compared to innervated, IMQ-exposed controls; in tandem, there was a significantly lower number of IL-17A$^+$ γδT-cells. Notably, treatment with CGRP reversed the diminution of IL-23 following denervation, suggesting a link between the CGRP expression and IL-23 expression in IMQ-induced psoriasiform dermatitis. There was significant reduction in the development of psoriasiform dermatitis in denervated, IMQ-treated mice (decreased erythema and decreased skin thickening days 3–5 and decreased scale day 4–5) and the histopathologic scores of these mice (determined by psoriasis hallmarks) was significantly lower than in their innervated counterparts. There was a reduction in nociceptive behavior induced by IMQ (e.g. scratching) in RTX-pretreated mice as well. Similar clinical effects happened with application of IMQ to the ear—since this area is difficult to scratch or lick, the authors suggested a protective role of denervation in psoriasiform dermatitis independent of reduction of nociceptive behavior (Zhang et al., 2021). Injection of recombinant IL-23 during IMQ application reversed the decrease in IL-17A mRNA expression seen with denervation, while also leading to development of psoriasiform dermatitis uninfluenced by RTX denervation. All of this taken together suggests that sensory denervation with RTX, by means of decreased CGRP from the neurons, suppresses the Th17 response in IMQ-induced psoriasiform dermatitis by decreasing an initial imiquimod-induced uptick in IL-23 expression, thus suggesting a nociceptor-dendritic cell-γδT-cell axis by which CGRP can influence the development of psoriasis (Zhang et al., 2021).

Studies with botulinum toxin in the imiquimod model further support the role of CGRP in modulating psoriasiform inflammation. In mice treated with IMQ, the expression of CGRP mRNA in whole skin samples was significantly enhanced compared to control mice, while in mice treated with BTX-B intradermally 24 h prior to imiquimod exposure at the injected site, this increase in CGRP expression was significantly lower than in vehicle-treated mice. The number of CGRP$^+$ cells by immunostaining was significantly lower in BTX-treated mice than in vehicle-treated mice. The number of nerve fibers in BTX-treated mice was also lower, leading the authors to suggest that BTX-B might mediate a decrease in the production/release of neuropeptides from and the elongation of nerve fibers in psoriasiform dermatitis (Amalia et al., 2021). $CGRP_{8\text{-}37}$ significantly blunted the development of IMQ-induced psoriasiform dermatitis, with significant decreases in erythema, scaling and acanthosis. Mice also had significantly fewer infiltrating CD4$^+$ T-cells and CD11c$^+$ DDCs and significantly lower IL-17A/F (Amalia et al., 2021) mRNA in skin. This suggested that CGRP release may be a component of IMQ-induced psoriasiform dermatitis, by potentially promoting dermal T cell and dendritic cell infiltration and IL-17 production, and BTX-B may lead to improvement via preventing CGRP release from nerve terminals in the skin (Amalia et al., 2021). The authors also speculated that CGRP itself may play a role in the IL-23/17 axis since CGRP receptor antagonist administration led to a greater suppression of IL-23 than BTX-B and thus the former treatment might target that pathway more strongly (Amalia et al., 2021). The authors proposed a model wherein by inhibiting neuropeptide (including CGRP) secretion, BTX-B leads to decreased inflammatory cell infiltration and IL-17 production with blunting of development of psoriasiform dermatitis, which may possibly be helped by decreased nerve fibers in the skin (Amalia et al., 2021). In mice with IMQ-induced psoriasiform dermatitis, there was a higher fluorescence of CGRP in their dorsal root ganglia when compared with control mice. Pretreatment with BTX-A led to significantly lower CGRP secretion in the IMQ-exposed mice, with the percentage of CGRP$^+$ DRG neurons being lower as well (Chen et al., 2022).

Lidocaine, an anesthetic that blocks voltage-gated sodium channels such as $Na_v1.8$ (Chevrier et al., 2004; Colloca et al., 2017), also led to improvements in imiquimod-induced psoriasiform dermatitis in rats (Yin et al., 2022). Rats treated with 1% lidocaine twice a day via epidural catheter on days 3–6/6 of IMQ application showed significant reduction in acanthosis and hyperproliferation. There was also a significant decrease in inflammation and vascular hyperplasia as shown by decreased CD3$^+$ T cell infiltrates and CD31$^+$ endothelial cells. Rats exposed to IMQ and treated with lidocaine achieved decreases in acanthosis comparable to treatment with an anti-TNF-α monoclonal antibody and with the Janus kinase inhibitor tofacitinib (Yin et al., 2022). In rats treated with lidocaine, the increase in CGRP in skin lysates was suppressed compared to controls, with a significantly lower level of CGRP in rats treated with lidocaine than those treated with saline (Yin et al., 2022). Treatment with CGRP along with IMQ led to worse skin thickening on day 7 of IMQ treatment and increased inflammatory cell infiltration (Yin et al., 2022). However, when rats were instead co-treated with a CGRP receptor antagonist ($CGRP_{8\text{-}37}$), there was a reduction in epidermal acanthosis and skin thickening (Yin et al., 2022). There were fewer CGRP$^+$ neurons in the skin of those rats as well. The expression of CGRP in dorsal root ganglia of IMQ-treated rats was increased, but when treated with lidocaine, it was significantly lower than in rats treated with saline (Yin et al., 2022). In addition, mice that were RAMP1$^+$ showed much higher IL-23A expression than RAMP1$^-$ mice after IMQ treatment (Yin et al., 2022). Rats treated with lidocaine also had significantly lower levels of neuronal marker beta-III tubulin in their skin and significantly improved nerve fiber hypertrophy (as seen via staining for beta-III tubulin). When the DRGs of IMQ-treated rats were treated *ex vivo* with lidocaine, the elongation of their neurons was significantly lower compared to rats treated with IMQ and saline. Overall, this suggested that lidocaine inhibited the disordered sensory nerve elongation and outgrowth that was induced by imiquimod (Yin et al., 2022). These investigators also treated human psoriasis patients with epidural lidocaine which reportedly induced marked improvement lasting “at least” 24 weeks (Yin et al., 2022). The effect of lidocaine in $Na_v1.8^+$ neurons is summarized in Fig. 3.

Co-incubation of sensory neurons with bone marrow-derived dendritic cells (BMDCs) followed by administration of a CGRP receptor antagonist led to significant decreases in IL-23 production; this decrease was abolished by replenishment of CGRP (Yin et al., 2022). When CALCI was knocked out in sensory neurons, leading to knockout of CGRP production, IL-23 production was significantly reduced, and lidocaine administration did not further suppress it; the authors suggested that was an indication that CGRP modulates IL-23 secretion by dendritic cells, and that lidocaine’s effects on IL-23 levels occur via suppressing CGRP release. Furthermore, intravenous lidocaine injection did not improve IMQ-induced psoriasiform inflammation (as opposed to epidural injection), which led the authors to conclude that neuron-derived CGRP is what is responsible for enhanced IL-23 production in the rats with IMQ-induced psoriasiform dermatitis (Yin et al., 2022).

A relationship between CGRP and psoriasis via similar mechanisms was suggested by Lee et al. using resolvin D3 (RvD3), a member of a family of lipid-derived mediators generated by omega-3-polyunsaturated fatty acid metabolism with anti-inflammatory properties, and which have had proposed activity against psoriasis (S. H. Lee et al., 2020; Sawada et al., 2018; Serhan et al., 2002). Mice treated with RvD3 did not develop skin lesions after repeated IMQ application and had significantly blunted stratum corneum thickening and infiltration of inflammatory cells into the skin (Lee et al., 2020). There was also significantly lower transcription of IL-17C and F, as well as IL-23A. There was a dose-dependent decrease in erythema and scaliness.

Concomitantly, DRG transcription of CGRP was found to be significantly lower at day 7 of IMQ application in mice injected with RvD3 vs. vehicle, as were CGRP levels in the skin. Similarly, siRNA targeting of CGRP in DRG neurons (which led to a ~45% decrease in CGRP levels in the skin) was followed by significantly reduced erythema, scaliness and spontaneous itch, as well as significantly blunted stratum corneum thickening and inflammatory cell infiltration. Also, transcriptional expression of IL-17C and F was decreased in the skin, but not that of IL-23, ultimately suggesting an IL-17 modulating role for CGRP in the pathophysiological pathway of psoriasis (S. H. Lee et al., 2020). In human donor DRGs, RvD3 treatment also significantly blunted capsaicin-induced CGRP release similarly to the murine model (S. H. Lee et al., 2020). Cotreatment of mice with RvD3 and capsaicin (a TRPV1 agonist) significantly blunted the increase in transcription and release of CGRP (that capsaicin leads to on its own). It was demonstrated that this could be via RvD3 binding to a GPCR that downstream lead to TRPV1 inhibition, thus blunting CGRP release (S. H. Lee et al., 2020). The murine GPCR, ALX/FPR2 has a cognate (GPR32) that is also expressed in human DRG neurons, suggesting translational relevance (S. H. Lee et al., 2020). A summary of how RvD3 influences CGRP release is shown in Fig. 3.

Further investigation of how TRPV1 activation can modulate psoriatic inflammation via CGRP was conducted by Huang et al. who suggested the importance of acid-sensing ion channel 3 (ASIC3) in nociceptor-mediated, IMQ-induced psoriasiform dermatitis (Huang et al., 2024). ASIC3 is a proton-activated sodium channel in the ENaC/degenerin family that has roles in inflammatory and acidic pain (Deval et al., 2008). Application of IMQ to constitutive ASIC3-knockout mice resulted in significantly lower acanthosis, epidermal proliferation and lesional skin levels of IL-17, IL-22 and IL-23 compared to wild-type mice (Huang et al., 2024). This trend was also seen when ASIC3 was selectively knocked out in $Na_v1.8^+$ nociceptors by Lox-Cre recombination and when it was selectively knocked down via RNA interference (using an adeno-associated viral vector). In the latter mice, when ASIC3 was selectively reactivated using a viral vector, there was a significant worsening of epidermal proliferation, skin thickening, and significant increases in lesional skin levels of IL-17, IL-22 and IL-23 (i.e. a full recapitulation of the psoriasiform phenotype). The authors found that there is a large degree of co-expression of ASIC3 and TRPV1 in DRG neurons and afferent neurons in the skin, and when they induced selective chemical denervation using RTX, the results were the same as those seen with elimination of ASIC3 activity, showing the importance of ASIC3 in TRPV1-mediated psoriasiform dermatitis. However, intradermal injection of IL-23 led to psoriasiform dermatitis in both wild-type and ASIC-3 knockout mice, with no significant differences between the two groups in terms of histologic changes and cytokines, showing that ASIC-3, and by extension nociceptors, are dispensable in IL-23-triggered psoriatic inflammation (consistent with results shown by Riol-Blanco et al.), and suggesting that the ASIC-3-triggered pathway is upstream of IL-23 activation (Huang et al., 2024).

Additionally, only mice with intact ASIC3 showed a decrease in acanthosis, KC proliferation and attenuation of IL-17, IL-22 and IL-23 with local subcutaneous BTX-A injection around the site of IMQ inflammation, demonstrating that the ASIC3-dependent psoriatic inflammation was likely through molecules released by sensory neurons in vesicles. Given the studies showing CGRP's role in IMQ-induced psoriatic inflammation and in type 17 inflammation, the authors sought to investigate whether the active molecule in the vesicles was CGRP. When DRG neuron cultures were acidified to pH 5.5, the concentration of CGRP in the media increased significantly, but only in ASIC3-intact cultures. The increase was reversible with amiloride (an ASIC3 antagonist (Kellenberger and Schild, 2015)) and BTX-A. A non-proton agonist of ASIC3, 2-guanidine-4-methylquinazoline (GMQ) (Yu et al., 2010), also resulted in significantly higher CGRP concentrations in media of wild-type DRG cultures compared to ASIC-3 knockout cultures. CGRP levels in the skin of mice painted with IMQ was also tested, which showed a higher concentration of CGRP in skin of wild-type mice compared with ASIC3-knockout mice; this, along with the *in vitro* results, demonstrates that ASIC3 plays a role in CGRP release from sensory neurons (Huang et al., 2024). When wild-type mice were injected intradermally with CGRP receptor antagonist BIBN 4096 prior to each IMQ application, there was a significant decrease in KC proliferation and IL-17/22/23 protein levels in skin compared to controls; conversely, when ASIC3 KO mice were injected with CGRP prior to IMQ, proliferation and IL-17/22/23 increased significantly, showing that ASIC3 plays a role in IMQ-induced psoriatic inflammation by modulating CGRP release (Huang et al., 2024). Furthermore, an increase in IL23+ bone-marrow-derived dendritic cells (BMDCs) was seen in co-cultures of BMDCs and DRG neurons at pH 5.5 and was reversible with BIBN 4096, but only in wild type mice and not ASIC3 knockout mice.

While skin pH remained constant in the vehicle-treated mice, it gradually decreased in the imiquimod-treated mice, which the authors suggested could indicate that ASIC3 mediates imiquimod-induced psoriatic inflammation through activation by acidic metabolites (Huang et al., 2024), Fig. 3. This is plausible, based on research which has demonstrated pH to be significantly lower in psoriatic plaques than in healthy control skin (Maroto-Morales et al., 2021).

Lipidome analysis showed an increase in certain subclasses of lysophosphatidylcholine (LPC) with the highest increase in LPC 14:0, which significantly increased CGRP release at pH 7.4 and at pH 6.5 in wild-type DRG cultures, but not in ASIC3 knockout cultures (Huang et al., 2024). Subcutaneous injection of LPC 14:0 led to significant increases in acanthosis, proliferation, and IL-17, IL-22 and IL-23 but only in wild-type mice, with authors proposing that LPC could be a trigger in ASIC3-mediated psoriatic inflammation (Huang et al., 2024). LPC's role is potentially relevant to human psoriasis, where the concentrations of LPC have been shown to be increased in lesions (Ryborg et al., 1995). The results, taken with the observation that cultured HaCaT cell proliferation was increased in a time-dependent manner by CGRP, led the authors to propose a model where acidosis and/or LPC could trigger ASIC3 activation Fig. 3, leading to release of CGRP that stimulates DCs to produce IL-23 and that increases the proliferation of KCs (which are also stimulated by IL-17 and IL-22 released downstream from IL-23) (Huang et al., 2024). ASIC3 KO mice also had a decreased density of nerve fibers positive for CGRP and PGP9.5 relative to wild-type mice (Huang et al., 2024). ASIC3's role in CGRP release as suggested by this study is summarized in Fig. 3.

4.4.2. KC-Tie2 model

Other animal models of psoriasis have also suggested roles for CGRP in psoriasis pathogenesis. Mice in which the angiopoietin receptor Tie2 is overexpressed in KCs (KC-Tie-2 mice) develop a dermatitis that meets the clinical, histological, immunological, and pharmacological criteria for an animal psoriasis model (Wolfram et al., 2009). In addition, surgical denervation has been shown to improve acanthosis and CD11c + dendritic cell numbers in KC-Tie2 mice (Ostrowski et al., 2011). CGRP expression has been found to be significantly elevated (along with substance P) in KC-Tie2 mouse DRG cells (Ostrowski et al., 2011).

In the KC-Tie2 model of psoriasiform dermatitis, one injection of BTX-A was followed by significant improvement (e.g. significantly decreased acanthosis) as early as 2 weeks after the injection (Ward et al., 2012). This was accompanied by significantly lower numbers of CD11c + dendritic cells in the dermis of treated skin and a significant decrease in the number of $CD4^+$ T-cells by week 2 (25%) and week 6 (34%) (Ward et al., 2012).

In KC-Tie2 mice who had unilateral axotomy of thoracic dorsal cutaneous nerves near their entry to the skin, there was significantly less acanthosis and KC proliferation in denervated skin compared to innervated skin (Ostrowski et al., 2011). Intradermal CGRP injection significantly blunted the denervation-associated improvement in acanthosis. The denervated but CGRP-reconstituted side had similar levels of KC proliferation to the innervated side (low post-denervation levels remained after injection with an SP agonist). Intradermal CGRP and SP

agonist injection into denervated skin (which had confirmed $CD4^+$ cell decrease) reconstituted innervated skin levels (Ostrowski et al., 2011). CGRP antagonist injection into innervated KC-Tie2 skin was followed by significant improvements in acanthosis and KC proliferation to a similar degree as surgical denervation (Ostrowski et al., 2011). SP and CGRP antagonist-treated mice had significant decreases in $CD4^+$ cells in the dermis, but only SP antagonist treatment led to significant reduction in $CD11c^+$ dendritic cell numbers. These results suggest an *in vivo* role for CGRP in the hyperproliferation of KCs and skin thickening seen in psoriasis (Ostrowski et al., 2011).

4.4.3. Other models

A mouse model where TRPV1 can be specifically activated using blue light (TRPV1-Ai32) was used by Cohen et al. (Cohen et al., 2019) to demonstrate that TRPV1 activation resulted in a dermatitis resembling IMQ dermatitis at the site of stimulation and generated specifically type 17 inflammation. This was dependent on CGRP, as injection with $CGRP_{8\text{-}37}$ prior to photostimulation inhibited the inflammation. Via the axon reflex, activation of TRPV1 led to diminution of *C. albicans* infection not only at the site of activation but also at adjacent sites (Cohen et al., 2019).

Mice engineered to consitutively express VEGF on a keratin 14 promoter develop psoriasiform dermatitis (Vegas et al., 2018). Interestingly, although chronic social stress was found to increase levels of CGRP and pro-inflammatory cytokines in these mice, lesion development was prevented. This was reversible with glucocorticoid blockade, suggesting that glucocorticoids due to stress play an anti-inflammatory role, and that people whose psoriasis worsens with stress may have a defect in their HPA axis, allowing the pro-inflammatory milieu of stress to be stronger than the anti-inflammatory milieu (Vegas et al., 2018).

5. Potential therapies targeting CGRP in psoriasis

In patients with recalcitrant plaque psoriasis, local treatment with onabotulinumtoxinA, led to significant improvement in PASI scores (Aschenbeck et al., 2018). Although the mechanism(s) by which onabotulinumtoxinA exerts its beneficial effects on psoriasis remain unclear, this observation supports the concept that nerve-derived influences, perhaps including CGRP, play a role in the pathogenesis of psoriasis. Neuromodulators such as botulinum toxin A have potential for treating recalcitrant plaques, which may be more resistant to systemic treatment due to local microenvironmental factors and signals around the recalcitrant areas including involvement of neuropeptides such as CGRP (Gilbert and Ward, 2014). Overall, the evidence suggesting a possible rule for CGRP in psoriasis, indicates that a trial of a CGRP inhibitor in this disease is warranted.

6. Conclusions

Research has shown that CGRP has several potential roles in psoriasis by affecting various mediators of its pathogenesis, notably in promoting type 17 inflammation *in vivo* and enhancing KC proliferation and ability to attract T-cells *in vitro*. Notably, several studies, primarily in rodent models, have shown that CGRP released from nociceptors can modulate dendritic cell function and promote the release of IL-23, which then stimulates γδT-cells to secrete IL-17. CGRP has also been shown to promote IL-23 expression in LCs, which upon co-culture with γδT-cells results in release of IL-17 by the latter. Also, CGRP has been suggested to modulate antigen presentation by LCs to naïve T-cells, promoting the differentiation of Th17 cells and suppressing the differentiation of Th1 cells. This occurs via ECs acting as bystanders and is thought to be modulated by IL-6. The actions of neuropeptides on immune and inflammatory processes have been shown to be impactful for the treatment of several dermatological diseases, such as rosacea, for which erenumab (an anti-CGRP receptor mAb) has recently been shown to be effective (Wienholtz et al., 2024). In addition, botulinum toxin, which inhibits CGRP release, has shown efficacy in treating psoriasis, and has potential for addressing recalcitrant plaques. This approach holds promise for individuals whose biologics are effective except for several select areas; this would absolve the need to discontinue the biologic and start a new one, which avoids several logistical hurdles in addition to the potential of diminution of efficacy.

The results of these studies should also be approached with caution: although IMQ can induce a psoriasiform dermatitis in rodents with histological, clinical and immunological similarity to human psoriasis, the complex nature of the disease in humans could mean that not all aspects of this model may be generalizable. Given the close relationship between psoriasis disease activity and the sensory nerves around active lesions, CGRP's role is likely to be local, at least in part. Also, it must be noted that substance P is frequently co-located with CGRP; further studies to parse out the individual effects of each neuropeptide may be prudent, although it may not be relevant *in vivo* since, if both are released simultaneously, their combined effect holds more importance. Further research examining the roles of various other neuropeptides in psoriasis will allow for a more comprehensive understanding of the brain-nerve-skin axis, especially as it relates to this disease.

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Joshua Kotlyar: Writing – review & editing, Writing – original draft. **Richard D. Granstein:** Writing – review & editing.

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Data availability

No data was used for the research described in the article.

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