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Calcitonin Gene-Related Peptide: Key Regulator of Cutaneous Immunity

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Abstract

Calcitonin gene-related peptide (CGRP) has been viewed as a neuropeptide and vasodilator. However, CGRP is more appropriately thought of as a pleiotropic signaling molecule. Indeed, CGRP has key regulatory functions on immune and inflammatory processes within the skin. CGRP-containing nerves are intimately associated with epidermal LCs and CGRP has profound regulatory effects on Langerhans cell antigen-presenting capability. When LCs are exposed to CGRP *in vitro*, their ability to present antigen for *in vivo* priming of naïve mice or elicitation of delayed-type hypersensitivity is inhibited in at least some situations. Administration of CGRP intradermally inhibits acquisition of immunity to Th1-dominant haptens applied to the injected site while augmenting immunity to Th2-dominant haptens, although the cellular targets of activity in these experiments remains unclear. Although CGRP can be a pro-inflammatory agent, several studies have demonstrated that administration of CGRP can inhibit the elicitation of inflammation by inflammatory stimuli *in vivo*. In this regard, CGRP inhibits the release of certain chemokines by stimulated endothelial cells. This is likely to be physiologically relevant since cutaneous blood vessels are innervated by sensory nerves. Exciting new studies suggest a significant role for CGRP in the pathogenesis of psoriasis and, most strikingly, that CGRP inhibit the ability of LCs to transmit the human immunodeficiency virus 1 to T lymphocytes. A more complete understanding of the role of CGRP in the skin immune system may lead to new and novel approaches for the therapy of immune mediated skin disorders.

Keywords

calcitonin gene-related peptide; LCs; immunity; inflammation

Introduction

CGRP is a sensory neuropeptide, frequently co-expressed with substance P or somatostatin in sensory neurons (Molander *et al*. 1987). It is a 37 amino acid neuropeptide produced by an alternative splicing of the calcitonin gene (Wimalawansa, 1997). CGRP-containing

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Conflict of interest
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nerves are distributed throughout various tissues and organs (Franco-Cereceda *et al*. 1987) and CGRP is expressed in both the central and peripheral nervous systems (Franco-Cereceda *et al*. 1987, Kresse *et al*. 1995). However, many other cell types, including monocytes/macrophages (Linscheid *et al*. 2004), Langerhans cells (LCs, dendritic antigen-presenting cells that reside within the epidermis) (He *et al*. 2000) and keratinocytes (Hou *et al*. 2011), amongst others, can produce CGRP. There are two isoforms of CGRP, αCGRP and βCGRP that differ by 1 amino acid in the rat and 3 amino acids in humans (Breimer et al. 1988). βCGRP is produced by a separate gene located in the vicinity of the αCGRP gene on the same chromosome (Lips *et al*. 1989). It is believed that αCGRP and βCGRP genes were generated from an ancestor gene by gene duplication (Lips *et al*. 1989). The biological activities of the two isoforms are overlapping (Juaneda *et al*. 2000). Although this review will cover many of the regulatory and anti-inflammatory effects of CGRP, it has long been known to be a mediator of inflammation. It is a potent vasodilator and plays a role in the recruitment of inflammatory cells at sites of inflammation (Huang *et al*. 2011, Li *et al*. 2006, Hartung *et al*. 1989, Merhi *et al*. 1998, Benrath *et al*. 1995). In this regard, CGRP enhances neutrophil adherence to endothelium (Huang *et al*. 2011, Zimmerman *et al*. 1992). This review will summarize the evidence that CGRP is an important regulator of immunity within the skin with implications for the pathophysiology of inflammatory skin disorders.

Calcitonin gene-related peptide and Langerhans cells

Within the skin, epidermal LCs are anatomically associated with CGRP-containing nerves (Hosoi *et al*. 1993). LCs are dendritic antigen-presenting cells that reside in the suprabasalar portion of the epidermis. Classically, LCs were believed to be potent antigen-presenting cells important for the initiation of immune responses in the skin (Inaba *et al*. 1986, Grabbe *et al*. 1991). However, many of the experiments examining LC function used cells that have been cultured ex vivo where they would mature during the culture process (Schuler *et al*. 1985). In the maturation process, LCs upregulate many signaling molecules including CD80, CD86, CD54, CD40, CD83, DC-LAMP, IL-12p40 and CCR7 while downregulating langerin (Madva *et al*. 2013, Nakagawa *et al*. 1999, Berthier-Vergnes *et al*. 2005). Macropinocytosis also is downregulated with maturity (Madva *et al*. 2013, Sparber *et al*. 2010). More recent evidence, however, suggests that in the steady state, LCs may serve to downregulate or limit immunity and, perhaps, induce immunologic tolerance (Kaplan et al. 2005, Igyártó et al. 2010). Teleologically, this activity may serve to prevent unwanted immune reactivity against beneficial or commensal organisms. We speculate that chronic/repetitive exposure to CGRP from the associated nerves may play a role in maintaining LCs in an immature state *in situ* in the absence of a danger signal (see below).

CGRP has long been known to be present in epidermal nerves and has been reported to be associated with Merkel cells [mechanosensitive cells that function in touch sensation (Woo et al. 2014)] within the epidermis (Berthier-Vergnes *et al*. 2005, Sparber *et al*. 2010, Kaplan et al. 2005, Igyártó et al. 2010, Cheng-Chew *et al*. 1996, Vaalasti *et al*. 1988). With regard to a possible association with LCs, Singaram and colleagues reported that LCs in the esophagus showed CGRP immunoreactivity and staining for CGRP was markedly increased in the setting of esophagitis (Singaram *et al*. 1991). Within the skin, it was determined that LCs are very closely associated anatomically with CGRP containing epidermal nerves

(Hosoi *et al*. 1993). Of particular importance, it was found that CGRP could inhibit murine LC antigen-presenting function by several criteria (Hosoi *et al*. 1993). Exposure of mouse epidermal cells to CGRP inhibited their ability to present alloantigen in the mixed epidermal cell-lymphocyte reaction and dose-dependently suppressed their ability to present antigen to a responsive Th1 T-T hybridoma (Hosoi *et al*. 1993). When epidermal cells (containing LCs) were exposed to CGRP *in vitro* followed by pulsing with antigen and use for eliciting delayed-type hypersensitivity to that antigen in previously immunized mice, pretreatment with CGRP dose-dependently inhibited the ability to elicit the immune response (Hosoi *et al*. 1993). Additionally, CGRP treatment of epidermal cells pulsed with antigen inhibited their ability to prime naïve mice to the antigen by subcutaneous injection (Asahina *et al*. 1995a). Subsequent experiments confirmed that CGRP treatment of highly-enriched populations of LCs (up to ∼95%) inhibited the ability to present antigen for Th1-type responses (Asahina *et al*. 1995b, Ding *et al*. 2008). Furthermore, and surprisingly, it was found that CGRP treatment of murine LCs enhanced their ability to present antigen to a Th2 clone and, upon presentation of a fragment of chicken ovalbumin to T cells from DO11.10 chicken ovalbumin T cell receptor transgenic mice, pretreatment with CGRP resulted in increased IL-4 production accompanied by decreased interferon-γ production (Ding *et al*. 2008). CGRP also inhibited stimulated production of the Th1 chemokines CXCL9 and CXCL10 but induced production of the Th2 chemokines CCL17 and CCL22 (Ding *et al*. 2008). Thus, CGRP appears to shift LC antigen function away from the Th1 pole toward the Th2 pole.

In accordance with these findings, intradermal administration of CGRP to naïve mice followed by immunization at the injected site by topical application of a hapten leads to an inhibited contact hypersensitivity response to Th1-dominant haptens but an enhanced contact hypersensitive response to Th2-dominant haptens (Asahina *et al*. 1995a, Mikami et al. 2011).

The molecular and cell biologic changes responsible for these effects are only partly understood. CGRP appears to inhibit stimulated NFκB signaling in murine LCs and, indeed, an inhibitor of NFκB signaling inhibits the ability of LCs to present antigen to a Th1 clone (Ding *et al*. 2007). CGRP also inhibited the expression of IL-12p40 and IL-1β by murine macrophages and a murine-LC-like cell line induced by treatment with lipopolysaccharide while augmenting the expression of interleukin-10 (Torii *et al*. 1997). It also inhibits the induction of CD86 expression (Torii *et al*. 1997).

Consistent with these findings, CGRP has also been found to inhibit antigen presentation by human peripheral blood mononuclear cells, by human blood-derived dendritic cells (Fox *et al*. 1997, Carucci *et al*. 2000) and by murine bone marrow-derived dendritic cells (Mikami *et al*. 2014). To our knowledge experiments examining CGRP effects on dermal dendritic cells or mucosal LCs other than an effect of CGRP on increasing LC langerin expression in human adult inner foreskin explants (discussed below) (Ganor *et al*. 2013) have not been reported.

Calcitonin gene-related peptide and human immunodeficiency virus (HIV)

Infection with HIV most commonly occurs through sexual activity. In this regard, there is substantial evidence that dendritic cells (DCs) in mucosa transmit HIV-1 to T cells, thus establishing infection within the T cell compartment (Harman *et al*. 2013). It is believed that HIV-1 entry onto DCs is facilitated by interactions with C-type lectins (Harman *et al*. 2013, de Witte *et al*. 2007). Since LCs reside in the epidermis of genital mucosa, they are believed to be the first dendritic cell-type to encounter HIV-1 (Harman *et al*. 2013). Abundant evidence demonstraes that human LCs can become infected with HIV-1 and transmit the virus to T cells *in vitro* (Harman *et al*. 2013). Interestingly, data has been reported that langerin may play a role in preventing HIV-1 transmission by LCs (de Witte *et al*. 2007, Ganor *et al*. 2013). Langerin, a C-type lectin, is believed to recognize mannose, fucose and *N*-acetylglucosamine structures on a number of microorganisms (Lee *et al*. 2011). It appears to bind to HIV-1 with the virus internalized into Birbeck granules and then degraded (de Witte *et al*. 2007). Inhibition of langerin binding to HIV-1 through the use of a blocking antibody or mannan (that binds to C-type lectins), resulted in enhanced transmission of HIV-1 to T cells (de Witte *et al*. 2007). The authors hypothesize that langerin protects LCs from infection with the virus and, thus, subsequent transmission to T cells (de Witte *et al*. 2007). de Witte *et al* concluded that LCs actually function as a protective mechanism in intact mucosa working to prevent HIV-1 infection (de Witte *et al*. 2007). However, this protective effect was observed only with relatively low concentrations of HIV-1; at high doses the protective effect is lost.

Most interestingly, a recent paper reports a possible role for CGRP in inhibiting LC-mediated HIV-1 transmission (Ganor *et al*. 2013). In this study, monocyte-derived human LCs (MDLCs) were utilized. When MDLCS were pre-treated with CGRP, a dose and time-dependent inhibition of HIV-1 transfer to T cells *in vitro* was observed (Ganor *et al*. 2013). Maximal inhibition was seen with treatment for 24 hours with 100 nM CGRP; this resulted in an inhibition of approximately 73% compared to controls not treated with CGRP (Ganor *et al*. 2013). Interestingly, pre-treatment of T cells with CGRP, instead of MDLCs, had no effect on transmission. CGRP was found to exert its ability to inhibit HIV-1 transfer via its receptor as the antagonist $CGRP_{8–37}$ prevented the CGRP effect while blockade of the amylin receptor had no activity (Ganor *et al*. 2013). Of interest, CGRP treatment significantly increased langerin expression on MDLCs and decreased expression of certain integrins (Ganor *et al*. 2013). Furthermore, inhibitors of the NF-κB pathway abrogated the inhibition of HIV-1 transfer, suggesting that activation of NF-κB is involved in this CGRP effect (Ganor *et al*. 2013). CGRP treatment of human adult inner foreskin explants also increased langerin expression on resident LCs (Ganor *et al*. 2013). These authors also found that CGRP treatment decreased viral replication within MDLCs (Ganor *et al*. 2013). CGRP pre-treatment of MDLCs decreased expression of CD29, CD49e and CD50 (Ganor *et al*. 2013) and, in accordance with this finding, CGRP treatment of MDLCs inhibited the proportion of cells adhering to fibronectin-coated plates and also decreased the percentage of conjugates formed between MDLCs and T cells *in vitro*. In a subsequent study, the same group found that LCs in the basal state secreted low basal levels of endogenous CGRP,

which increased markedly following CGRP treatment (Ganor *et al*. 2014). CGRP exposure also enhanced expression of its cognate receptor on LCs (Ganor *et al*. 2014).

Also of interest, these investigators found that CGRP levels in blood were significantly decreased in a group of HIV-1 infected individuals compared with healthy controls and in a group of HIV-1 infected persons receiving highly active anti-retroviral therapy, CGRP levels normalized (Ganor *et al*. 2013). These observations may relate to the earlier finding that infection is associated with loss of cutaneous innervation and reduced epidermal nerve fiber density (Ganor *et al*. 2013, McCarthy *et al*. 1995, Zhou *et al*. 2007).

These quite interesting findings, of course, suggest that CGRP may play a protective role *in situ* against LC-mediated HIV-1 infection and suggest an important new area of investigation with obvious clinical implications.

Calcitonin gene-related peptide inhibits inflammation

Many studies have reported that systemic or local administration of CGRP to animals inhibits the magnitude of an induced inflammatory stimulus in the animal. For example, Gomes and collaborators reported that intraperitoneal administration of CGRP inhibited by approximately 50% the number of neutrophils found in mouse blood and in the peritoneal cavity 4 hours after injection of the peritoneal cavity with lipopolysaccharide (Gomes *et al*. 2005); lipopolysacchride (also known as endotoxin) is an inflammatory component of the membrane of gram-negative bacteria (Rhee 2014). Strikingly, pretreatment of mice with CGRP protected against a lethal dose of lipopolysaccharide (Gomes *et al*. 2005). The protective effect could be inhibited by the CGRP receptor antagonist $CGRP_{8–37}$ and a protective effect of CGRP correlated with inhibition of tumor necrosis factor alpha (TNFα) while inducing serum levels of IL-6 and IL-10 (Gomes *et al*. 2005). Furthermore, CGRP enhanced IL-10 production production by peritoneal macrophages *in vitro* while inhibiting TNFα secretion (Gomes *et al*. 2005).

In another study, hamster cheek pouches were treated topically with CGRP or were not treated followed by application of histamine [a mast cell mediator that, amongst other physiologic functions, causes vasodilitation and increases permeability capillaries; it is involved in urticaria and some other inflammatory skin disorders (Greaves *et al*. 205)] and assessment of capillary leakage (Raud *et al*. 1991). Pretreatment with CGRP reduced the total leakage significantly. CGRP treatment had to be before histamine; in co-administration experiments CGRP had no effect. In another experiment, CGRP was administered by sub-plantar injection into a rat paw while the other paw was injected with the vehicle only (Raud *et al*. 1991). Twenty minutes later, both paws were challenged with subplantar injections of 5-hydroxytryptamine and paw swelling assessed. Paw swelling was markedly suppressed on the CGRP-treated side compared to the control paw (Raud *et al*. 1991). Most interestingly, human volunteers received an intradermal injection of CGRP in one arm and dilulent alone in the other arm (Raud *et al*. 1991). Subsequently, each site was injected intradermally with histamine and the wheal and flare responses quantified. CGRP significantly suppressed the histamine-induced wheal but had no effect on the flare reaction (Raud *et al*. 1991). Injection of CGRP by itself produced a flare but no wheal.

CGRP demonstrated anti-inflammatory activities in two additional *in vivo* models. When croton oil was applied to the ears of mice (producing irritant contact dermatitis) followed by application of CGRP topically, CGRP significantly inhibited the inflammatory response induced (Clementi *et al*. 1994). Systemic administration of CGRP also inhibited peritoneal exudation induced by intraperitoneal administration of acetic acid (Clementi *et al*. 1995). This inhibition was observed when the CGRP was given 5 minutes before administration of acetic acid but no effect was seen when it was given 30 or 60 minutes after acetic acid. Topical treatment of mouse ears with CGRP also inhibited inflammation induced by subsequent treatment of the ears with topical croton oil, arachidonic acid or tetradecanoylphorbol acetate (Clementi *et al*. 1995).

Calcitonin gene-related peptide and endothelial cells

Recent experiments suggest a novel mechanism by which CGRP produces its anti-inflammatory effects. When the human microvascular endothelial cell line HMEC-1 or primary human dermal microvascular endothelial cells (pHDMECs) were treated with CGRP *in vitro*, it was found that CGRP treatment inhibited lipopolysaccharide-induced production of the chemokines growth-related oncogene-1 (GROα ,CXCL1), monocyte chemotactic protein-1 (MCP1, CCL2) and IL-8 (CXCL8) (Huang *et al*. 2011). This inhibition could be blocked by antagonists of the CGRP receptor and both cell types were found to express components of the CGRP and adrenomedullin receptors (Huang *et al*. 2011). Furthermore, CGRP was found to inhibit lipopolysaccharide-induced activation of NFκB and Bay 11–7085, an inhibitor of NFκB activation and the phosphorylation of IκBα, also inhibited lipopolysaccharide-induced release of these chemokines (Huang *et al*. 2011). These results strongly indicate that the NFκB pathway is involved in CGRP-mediated suppression of chemokine production. In accord with these findings, pre-treatment of HMEC-1 cells with CGRP prior to stimulation with lipopolysaccharide significantly suppressed the ability of these cells, or of supernatants conditioned by these cells, to chemoattract human mononuclear cells or neutrophils (Huang *et al*. 2011). Presumably this is due to inhibition of release of chemokines by pretreatment with CGRP. Thus, some of the in-vivo effects of CGRP may be mediated by binding to receptors on endothelial cells and, thereby, decreasing production of certain chemokines.

Calcitonin gene-related peptide and inflammatory skin diseases

Psoriasis

Psoriasis is a common papulosquamous disease of the skin characterized by scaly, red papules and plaques (Di Meglio *et al*. 2014). Recent evidence suggests a link to the metabolic syndrome (Di Meglio *et al*. 2014). A growing body of evidence supports the idea that nerves play an important role in the pathogenesis of this disorder. It has long been known that the denervation of skin bearing psoriasis leads to its improvement or resolution (Dewing 1971, Raychaudhuri *et al*. 1993). Additionally, intralesional injection of local anesthetics improves psoriatic lesions (Perlman 1972). Recently two animal models have supported the involvement of nerves in psoriasis. In one model, mice are engineered to overexpress the receptor tyrosine kinase Tie2 in keratinocytes (Wolfram *et al*. 2009, Ostrowski *et al*. 2011). These animals develop a psoriasiform dermatitis characterized by the

presence of Th17 cells, involvement of the IL-17 family of cytokines, and improvement in the dermatitis with many of the therapies effective in human psoriasis (Wolfram *et al*. 2009). Of particular interest, denervation of the skin leads to improvement in the psoriatic phenotype (Ostrowski *et al*. 2011). It has been reported, however, that after denervation if CGRP is administered systemically the improvement in the psoriatic phenotype, particularly acanthosis, is blunted (Ostrowski *et al*. 2011). Similarly, administration of substance P systemically after denervation inhibits the resolution of the inflammatory cell infiltrate associated with the psoriasiform dermatitis (Ostrowski *et al*. 2011). Of course, this suggests that CGRP and substance P may be products of nerves relevant to maintenance of the psoriasiform dermatitis. In a second model, application of imiquimod [a TLR7 agonist used clinically to enhance innate immunity for the treatment of viral neoplasms of the skin (e.g. warts) and certain skin malignancies and pre-malignancies (Hemmi *et al*. 2002)] to mouse skin daily for 5–6 days also induces psoriasiform hyperplasia (Van Belle *et al*. 2012). In this model also, innervation is required for expression of the rash (Baerveldt *et al*. 2012).

Recent preliminary work from out laboratory suggests that CGRP may play a role in biasing immune responses towards the Th17 pole through actions on endothelial cells which, in turn, influence the outcome of Langerhans antigen presentation to T cells (Granstein *et al*. 2014). If confirmed, this may suggest a mechanism by which CGRP may contribute to the psoriasis phenotype as Th17 cells and the IL-17 family of cytokines appear to be important in psoriasis pathogenesis. Additional circumstantial evidence that CGRP may be involved in psoriasis through actions on endothelial cells comes from the observation that endothelial cells in dermal blood vessels in psoriatic lesions can be found to have CGRP on their surface (He *et al*. 2000) and that CGRP containing nerves are increased in the epidermis of lesions of psoriasis (Jiang *et al*. 1998). Furthermore, plasma concentrations of CGRP are significantly elevated in psoriatic individuals compared with healthy controls (Reich *et al*. 2007).

Atopic dermatitis

Atopic dermatitis (“eczema”) is a common disorder characterized by itching of the skin with dryness, erythema and excoriations (Thomsen, 2014). The pathogenesis of this disorder involves aberrant immunity in a manner only partially understood. The disease is associated, in at least some patients, with a mutation affecting a skin protein important to normal skin barrier function (Thomsen, 2014). Circumstantial evidence exists linking CGRP to atopic dermatitis. As mentioned above, CGRP biases antigen presentation towards the Th2 pole (Asahina *et al*. 1995b, Ding *et al*. 2008) and atopic dermatitis, in part, is a Th2-mediated disease. In this regard, CGRP-bearing nerve fibers are increased in lesions of atopic dermatitis (Järvikallio *et al*, 2003) and, additionally, circulating levels of CGRP are elevated in these patients (Hodeib *et al*. 2010). Investigators have shown, using an *in vitro* innervated skin model, that neurons induce the proliferation of keratinocytes through release of CGRP and CGRP enhanced keratinocyte proliferation and epidermal thickness in these models (Roggenkamp *et al*. 2013). Keratinocytes from atopic individuals exhibited higher expression levels of CGRP receptor components in innervated skin models employing atopic keratinocytes and had a thicker epidermis and a higher neurite density than those with keratinocytes from healthy controls (Roggenkamp *et al*. 2013). Furthermore, suction blister

roofs from patients with atopic dermatitis had higher levels of mRNAs for CGRP receptor components *ramp1* and *rcp* compared with healthy skin (Roggenkamp *et al*. 2013). Suction blister fluids obtained from atopic skin also contained more CGRP than healthy controls (Roggenkamp *et al*. 2013).

With regard to other inflammatory mechanisms, CGRP has been reported to induce mucosal mast cell degranulation (De Jonge *et al*. 2004). On the other hand, in a mouse model where a spontaneous mutation results in induction of an atopic dermatitis-like rash in mice housed under conventional conditions but not when housed in specific pathogen-free conditions, the CGRP concentration in the skin lesions was found to be lower than in non-affected skin in these mice (Katsuno *et al*. 2003). Of course, it remains unknown how closely this model represents human atopic dermatitis.

While a role for CGRP in the pathogenesis in atopic dermatitis is still speculative at this time, the data collected suggests that additional, detailed studies are warranted to further determine whether CGRP indeed is involved in this disease.

Perspectives

The immune and nervous systems cannot be considered as separate entities. An enormous amount of data demonstrate the regulatory and effector interactions between these homeostatic and protective systems (21). In this regard, the neuropeptide, vasodilator, signaling molecule and immunologic signal CGRP is a key actor (Table 1 and Figure 1). The data summarized herein demonstrate its important functions in regulating immune and inflammatory processes within the skin. Although much of the data is derived from *in vitro* experiments, it is clear that CGRP has a number of important regulatory effects including inhibitory effects on LC (and at least some other dendritic cell) antigen presentation for Th1 responses and augmentation of antigen presentation for Th2 responses. Through effects on endothelial cells, CGRP also inhibits the release of at least some proinflammatory chemokines. The recent report from Ganor *et al* that CGRP may inhibit LC-mediated HIV-1 transmission suggests another potentially important role for this neuropeptide. Of course key questions remain: Are the findings reported with mouse cells indicative of what happens with human cells? Do effects seen *in vitro* faithfully reflect *in vivo* activities? With regard to the possible role of langerin in LC-HIV-1 interactions, can the results of Ganor *et al* be reproduced with LCs derived from mucosa? Perhaps the most important question to be answered is what are the signals that regulate CGRP release or non-release by peripheral nerves? Do such signals arise from psychological factors? If so, CGRP may play a role in psychological stress-induced modulation of inflammatory skin disorders.

Although circumstantial, some of the evidence discussed above indeed suggests that CGRP may be important in the pathogenesis of inflammatory skin disorders and relevant cellular and molecular mechanisms are being delineated. If this proves to be the case, CGRP signaling pathways may prove to be druggable targets. Figure 1 shows several relevant activities of CGRP that have been determined in *in vitro* experiments. A greater understanding of the role of CGRP in immune and inflammatory processes in the skin may

lead to new and novel approaches to prevent or treat skin disorders for the benefit of our patients.

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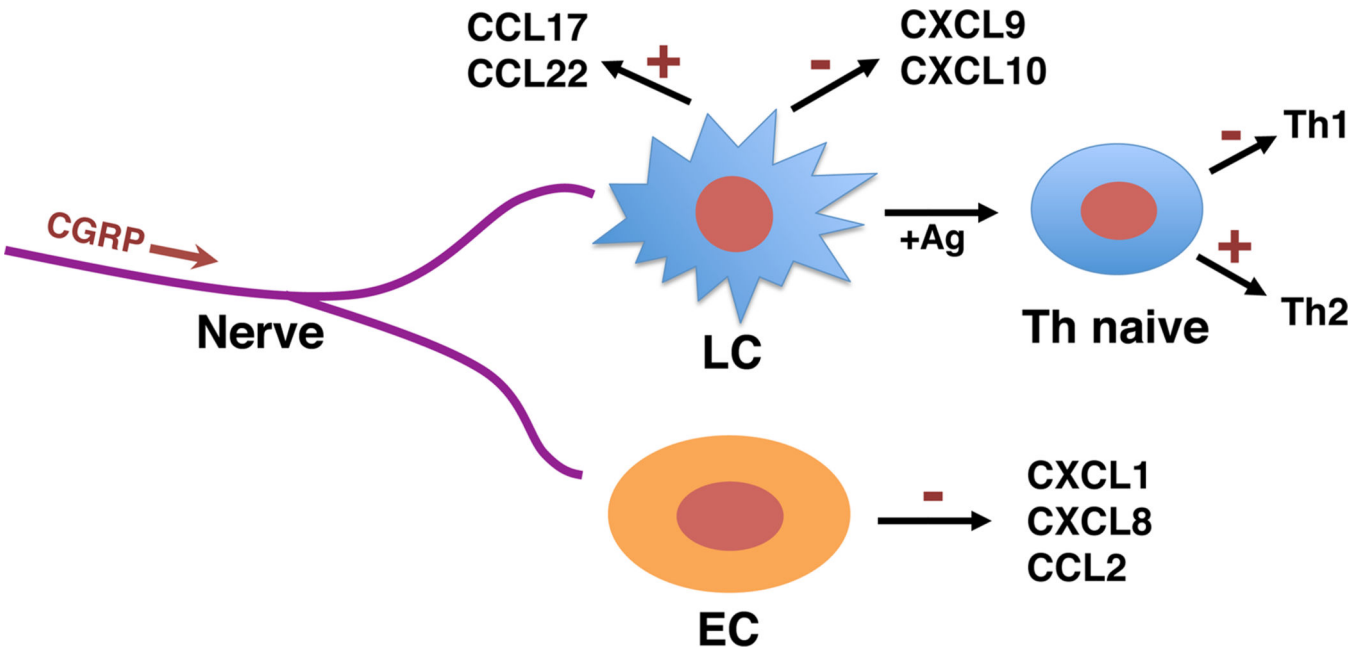

Figure 1.

Effects of CGRP *in vitro*. Pre-exposure of murine LC to CGRP inhibits antigen presentation for Th1 cell generation while enhancing antigen presentation for Th2 cell generation. The simultaneous presence of CGRP inhibits interferon-γ-induced production of the Th1 chemokines CXCL9 and CXCL10 by a LC-like cell line derived form BALB/c epidermis while treatment with CGRP alone induced production of the Th2 chemokines CCL17 and CCL22 (Ding *et al*. 2008). Additionally, CGRP inhibits lipopolysaccharide (LPS)-induced production of CXCL1, CXCL8 and CCL2 by human dermal microvascular endothelial cells (cells were cultured in CGRP and 1 hour later LPS was added without removing the CGRP) (Huang *et al*. 2011).

Table 1

CGRP Effects Relevant to Cutaneous Immunity (refs)

• Inhibits murine LC antigen presentation for Th1 responses (Hosoi *et al*. 1993, Asahina *et al*. 1995b, Ding *et al*. 2008).
• Enhances murine LC antigen presentation for Th2 responses (Ding *et al*. 2008).
• Inhibits murine LC interferon-γ-induced CXCL9 and CXCL10 production while inducing production of CCL17 and CCL22 (Ding *et al*. 2008).
• Inhibits lipopolysaccharide-induced expression of IL-1β and IL-12 p40 by a murine LC-like cell line while enhancing IL-10 expression (Torii *et al*. 1997).
• Inhibits stimulated NFκB signaling in murine LCs (Ding *et al*. 2007).
• Intradermal administration inhibits immunity to Th1 dominant haptens while enhancing the response to Th2 dominant haptens in mice (Asahina *et al*. 1995a, Mikami et al. 2011).
• Inhibits the response to inflammatory stimuli *in vivo* in mice, rats, hamsters and humans (Gomes *et al*. 2005, Raud *et al*. 1991, Clementi *et al*. 1994, Clementi *et al*. 1995).
• Inhibits stimulated production of the chemokines CXCL1, CCL2 and CXCL8 by human dermal microvascular endothelial cells (Huang *et al*. 2011).
• Inhibits stimulated NFκB signaling in murine dermal microvascular endothelial cells (Huang *et al*. 2011).
• Plays in an important role in the Tie2-KC murine model of psorisiform dermatitis (Ostrowski, *et al*. 2011).
• Inhibits human monocyte-derived LC mediated HIV-1 transmission to T cells (Ganor *et al*. 2013).