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Cyclic Adenosine Monophosphate Signaling in Inflammatory Skin Disease

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Abstract

The second messenger cyclic adenosine monophosphate (cAMP) regulates numerous key pathways that impact the immune system. Distinct cellular cAMP signaling pathways can lead to both pro- and anti-inflammatory effects depending upon the cell type. When dysregulated, these cAMP pathways can influence the pathogenesis of inflammatory cutaneous diseases, such as atopic dermatitis and psoriasis. In psoriasis and atopic dermatitis, cAMP and/or its effector proteins (e.g., protein kinase A) are downregulated suggesting that elevation of cAMP might be a therapeutic option. cAMP levels are the result of balance between synthesis by adenylyl cyclases and degradation by phosphodiesterases (PDEs). Pharmacologically inhibiting PDEs represents one effective mechanism to raise intracellular cAMP levels perhaps leading to targeted immune suppression. Several drugs have been developed to target PDEs and while some toxicities (e.g., nausea and emesis) exist these drugs are generally well tolerated. Perhaps the best characterized is Apremilast, a PDE4 specific inhibitor, which has been FDA approved for the treatment of psoriasis and shows great promise as a safe and novel immunosuppressive medication. Following on the heels of Apremilast are numerous oral and topical PDE inhibitors in various stages of clinical trials. In this review, we examine the role of cAMP signaling in inflammatory cutaneous diseases and the development of PDE inhibitors as therapeutics.

Keywords: cAMP; PDE; sAC; tmAC; Apremilast

Abbreviations

AC: Adenylyl Cyclase; **AD:** Atopic Dermatitis; **ADSI:** Atopic Dermatitis Severity Index; **ATF:** Activating Transcription Factor; **cAMP:** Cyclic Adenosine Monophosphate; **CLASI:** Cutaneous Lupus Erythematosus Disease Area and Severity Index; **CREB:** cAMP Response Element-Binding Protein; **DLE:** Discoid Lupus Erythematosus; **DQLI:** Dermatology Life Quality Index; **EASI:** Eczema Area and Severity Index; **EPAC:** Exchange Protein Activated by cAMP; **ICER:** Inducible cAMP Early Repressor; **IFN:** Interferon; **IL:** Interleukin; **MIP:** Macrophage Inflammatory Protein; **LP:** Lichen Planus; **NAPSI:** Nail Psoriasis Severity Index; **NF-κB:** Nuclear Factor Kappa B; PASI: Psoriasis Area and Severity Index; **PDE:** Phosphodiesterase; **PGA:** Physician Global Assessment; **PGE:** Prostaglandin; PKA: Protein Kinase A; **PPPGA:** Palmoplantar Psoriasis Physician's Global Assessment; **SAC:** Soluble Adenylyl Cyclase; **SASI:** Sarcoidosis Activity and Severity Index; **SCORAD:** SCORing Atopic Dermatitis; **SPGA:** Static Physician's Global Assessment; **ScPGA:** Scalp Physicians Global Assessment; **Teff cell:** Effector T cell; **tmAC:** Transmembrane Adenylyl Cyclase; **TEWL:** Transepidermal Water Loss; **TLR:** Toll-Like Receptor; **TNF:** Tumor Necrosis Factor; **Treg cell:** Regulatory T cell; **UCR:** Upstream Conserved Region

Introduction

Dysregulated homeostasis of immune responses in the skin is a hallmark of inflammatory skin disease. Disorders such as psoriasis and atopic dermatitis (AD) are characterized by elevated local and peripheral levels of inflammatory mediators and immune cells, most notably T cells, hence the designation of psoriasis and AD as T-cell-mediated skin diseases. Major advances in our understanding of the underlying cellular and molecular mechanisms of these disease processes have implicated numerous signaling pathways in the regulation of skin immunity. Current pathophysiological paradigms of psoriasis and other inflammatory skin diseases recognize both immune cells and resident keratinocytes as players in the pathogenesis of skin inflammation. In particular, it has become clear that the key immunologic role of epidermal keratinocytes in both the acute and chronic phases of skin inflammation is via cytokine production and surface molecule expression [1-3]. Prominent signaling pathways in inflammatory skin disease include the tumor necrosis factor (TNF) and interferon (IFN) pathways, as well as various interleukin pathways (reviewed in [4]). Much less studied is the potential role of the cyclic adenosine monophosphate (cAMP)-signaling pathway, a pathway with proven roles in resident epidermal and dermal immune cells [5], and defined immunosuppressive and anti-inflammatory actions [6]. In addition, there are numerous reports of altered cAMP activity in psoriasis [7-9] and atopic dermatitis [10-13]. Further elevating the importance of cAMP in psoriasis and AD, clinical trials for the treatment of psoriasis with selective phosphodiesterase (PDE) 4 inhibitors, which act on the cAMP pathway, have demonstrated promising results. Here we review the current evidence for a role of cAMP signaling in the pathogenesis of inflammatory skin disease, focusing on psoriasis and AD. We will also provide an overview of novel PDE4 inhibitors currently in clinical trial for the treatment of inflammatory skin diseases.

The cAMP signaling pathway

cAMP is an almost ubiquitous second messenger that regulates a plethora of cellular functions, from metabolism to cell shape and gene expression [14]. cAMP signals are generated in response to diverse stimuli and transduced by at least three types of cAMP effector proteins in mammalian cells: protein kinase A (PKA), exchange proteins activated by cAMP (EPACs), and cyclic nucleotide gated ion channels [15]. cAMP is produced by two related but distinct classes of adenylyl cyclases (ACs) in mammalian cells, the well-known transmembrane adenylyl cyclases (tmACs) and the more recently identified non-canonical soluble adenylyl cyclase (sAC) [15,16]. tmACs are located exclusively at the plasma membrane and classically stimulated by various G protein-coupled receptors (GPCRs), while sAC is localized throughout the cytoplasm, within the nucleus, and at the mitochondria and centriole and is uniquely regulated by ATP, bicarbonate and calcium [17]. Once generated, regardless of the source, cAMP is readily degraded by a variety of phosphodiesterases (PDEs), which are spatially organized alongside cAMP effectors. In this way, cAMP is generated in distinct intracellular pools in a precisely regulated manner, allowing for distinct microdomains of cAMP signaling cascades across different cell types [18]. Figure 1 illustrates the current understanding of cAMP signaling transduction cascades in mammalian cells.

The actions of cAMP are highly dependent on cell type and signaling context. With the recent discovery of sAC and its wide expression in tissues [16,19], the physiologic scope and complexity of cAMP signaling has only expanded, spurring new interest in yet undiscovered roles of specific cAMP microdomains. Aside from the before mentioned immune cells, cAMP and its effector proteins, as well as major downstream targets such as cAMP response element-binding protein (CREB), also have established roles in different skin cells, including keratinocytes, melanocytes, and fibroblasts [5]. Both atopic dermatitis and psoriasis are characterized by abnormal growth and regulation of these key skin cells [20]. We will now review how cAMP can influence different cells in the skin to influence the pathogenesis of inflammatory diseases.

cAMP Signaling in inflammatory immune responses

The role of T cells in the pathogenesis of inflammatory skin disorders is incontrovertible. In this context, it should be noted that cAMP itself plays a direct and crucial role in inflammatory pathways through T cells and other immune cells. In T cells and other types of immune cells, elevated intracellular cAMP concentration suppresses the production of various pro-inflammatory mediators [21], including TNF-α [22], IFN- β [23] and -γ [24], interleukin (IL)-12 family cytokines [24-27], inducible nitric-oxide synthase [28], macrophage inflammatory proteins (MIP)-1α and -1β [22], leukotriene B_4 [29], while promoting the release of anti-inflammatory mediators, such as IL-10 [30,31] and suppressor of cytokine signaling-3 [23]. As Figure 1 highlights, there are multiple distinct cAMP signaling microdomains in a mammalian cell and it is currently unknown which microdomain plays a driving role in the immunoregulatory effects of cAMP; however, as discussed below, we are aware of PDEs that play a role [30]. These PDEs promote the release of anti-inflammatory mediators, such as IL-10 [30,31]. In relation to inflammatory skin disease, IL-12 and related cytokines, such as IL-23 and IL-27, which are central to the regulation of T cell responses, have been implicated in the pathogenesis of both psoriasis and atopic dermatitis [32,33]. Multiple substances causing an increase in intracellular cAMP, including cholera toxin [34-37], histamine [38-43], and prostaglandin E2 [44-48], have demonstrated a potent inhibitive effect on IL-12-family cytokine production by different immune cells. Finally, the immunosuppressive and anti-inflammatory actions of cAMP have also been attributed in part to its inhibitory downstream effects on the function of one of the master regulators of inflammation, Nuclear Factor-kappaB (NF-κB) [6,49].

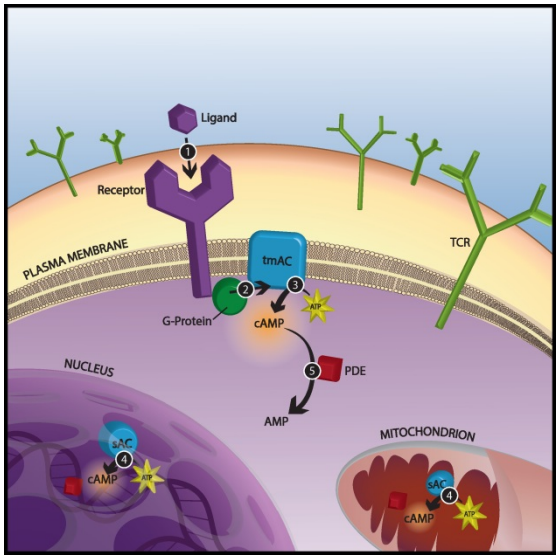

Figure 1: Cyclic adenosine 3', 5' monophosphate (cAMP) signaling microdomains. In response to extra- or intracellular signals, cAMP is formed at discrete intracellular compartments or microdomains including the cell membrane, mitochondria and the nucleus. cAMP microdomains contain an adenylyl cyclase, either a transmembrane adenylyl cyclase (tmAC) or the soluble adenylyl cyclase (sAC), that forms cAMP from adenosine triphosphate (ATP); a phosphodiesterases (PDE) that metabolizes cAMP to adenosine monophosphate (AMP); and a cAMP effector protein such as protein kinase A (PKA), exchange protein activated by cAMP (EPAC) and cyclic nucleotide gated channels. tmAC-dependent signal transduction occurs at the cell membrane when (1) a ligand (e.g., epinephrine) binds its receptor (e.g., ß-adrenergic G-protein coupled receptor) and (2) the heterotrimeric G-protein activates the tmAC (3) to make cAMP. In intracellular microdomains (4) such as the nucleus and the mitochondria, cAMP is produced by sAC in response to changes in metabolism or pH. In either case, the cAMP signal is terminated when cAMP is catabolized to AMP by a PDE (5). Abbreviations: TCR, T cell receptor; tmAC, transmembrane adenylyl cyclase; sAC, soluble adenylyl cyclase; cAMP, cyclic adenosine monophosphate; ATP, adenosine triphosphate; AMP, adenosine monophosphate; PDE, phosphodiesterase.

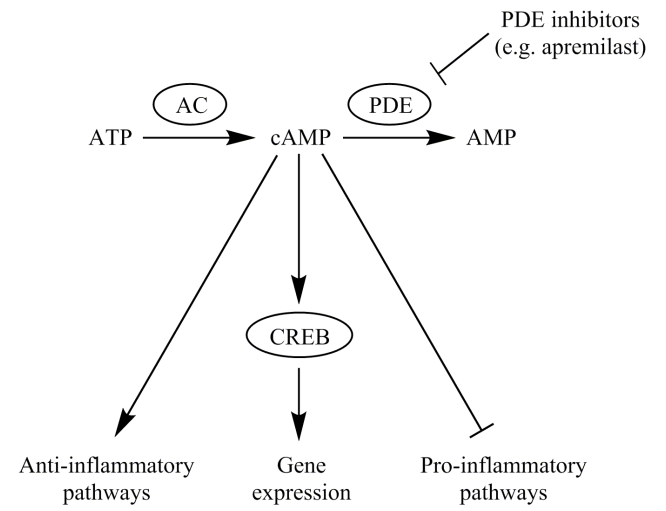

Figure 2: Homeostasis and downstream effects of cAMP signaling in immune cells. The actions of cAMP are highly dependent on cell type, initiating stimulus, and target microdomain and effectors. cAMP signaling pathways commonly exert their effects via gene expression. Of particular importance in inflammatory skin disease, increased intracellular cAMP in immune cells induces anti-inflammatory gene expression while suppressing pro-inflammatory gene expression.

Therefore, it is clear that cAMP signaling pathways lead to a combination of pro- and anti-inflammatory processes (Figure 2), and this apparent conflict is best explained by the existence of multiple cAMP microdomains (Figure 1).

cAMP signaling in psoriasis

Psoriasis is a chronic inflammatory skin disorder that affects an estimated 1-3% of the general population. The disease most commonly manifests as raised, well circumscribed, erythematous plaques with adherent silvery scales, but may also have extradermal manifestations, namely arthritis, termed psoriatic arthritis [20,50]. Psoriatic lesions are characterized by epidermal hyperproliferation with premature differentiation of keratinocytes and predominately dermal infiltration of the skin by dendritic cells, macrophages, and T cells [50]. While much about its pathogenesis remains to be elucidated, psoriasis is increasingly understood to arise from disturbances in the complex interplay between keratinocytes and immune cells from a combination of genetic and environmental factors [51].

Reports of abnormal cAMP signaling in psoriasis date back to the early 1970s [7]. However, the role of cAMP signaling in the pathogenesis of psoriasis remains controversial, largely due to conflicting literature surrounding how cAMP signaling influences psoriasis. Initial studies reported a significant decrease in cAMP in psoriatic epidermis when compared to uninvolved and control epidermis [52-54], and that pharmacologic elevation of intracellular cAMP could suppress epidermal proliferation [55-57]. Later investigations, however, were not consistent, with some finding no difference in cAMP levels in psoriatic epidermis compared to normal epidermis [58,59] and still others confirming prior studies that did find a difference. Yet, further studies revealed a difference in responsiveness to β-adrenergic stimulation between psoriatic and normal epidermis suggestive of aberrant cAMP production [60] and that β-adrenergic rather than prostaglandin (PGE) E2 stimulation [61] was affected. These observations are not limited to β adrenergic signaling; differences in intracellular cAMP accumulation induced by various tmAC agonists (e.g., cholera toxin, forskolin) were also observed in psoriatic versus uninvolved or normal epidermis [62]. In addition, several studies have also reported deficiencies in cAMP effectors, including decreased expression of and cAMP binding to PKA in psoriatic fibroblasts and erythrocytes [9], which appears responsive to retinoid treatment [63,64] and has been hypothesized to result from altered posttranslational modification of PKA [65,66] or oxidative states in these cells [67]. Further, highly decreased binding of cAMP to PKA in erythrocytes was found by one group to be specific for active psoriasis [68].

New insights in the last decade have revealed additional evidence supporting a role for cAMP signaling in psoriasis. In 2005, it was demonstrated that altered expression of c-Jun and JunB, two key keratinocyte transcription factors regulated by CREB, is sufficient to induce a psoriasis-like phenotype in mice [69]. Correspondingly, upregulated levels of both Jun proteins have also been found in lesional psoriatic skin compared with perilesional skin from patient samples [70]. Upstream of the Jun proteins, increased activation of CREB in association with expression and activation of its upstream activators mitogen- and stress-activated protein kinase 1 (MSK1) and 2 (MSK2) have been demonstrated in both lesional psoriatic epidermis and psoriatic keratinocytes, further strengthening the implication of cAMP signaling in psoriasis pathogenesis [71,72].

Of additional note, the discovery of sAC, a largely unexplored player in disease, introduces new potential routes through which cAMP signaling may influence psoriasis. Recent work has revealed striking differences in sAC localization between keratinocytes in normal skin as compared to certain hyperproliferative skin diseases, including psoriasis. While sAC is diffusely cytoplasmic in normal keratinocytes, in psoriasis, sAC was consistently found almost exclusively in the nuclei of keratinocytes concomitantly with phosphorylated (i.e. activated) CREB. Using a model of epithelial differentiation, it was established that nuclear migration of sAC marks the reentry of differentiated cells into the cell cycle [73]. Taken together with the results of previous work that nuclear migration of sAC can activate PKA-dependent CREB phosphorylation [74], these findings support the hypothesis that nuclear sAC may contribute to psoriasis pathogenesis via modulation of gene expression. Given that all previous studies of cAMP signaling in psoriasis were performed using reagents affecting only the tmAC class of ACs, further studies on sAC in psoriasis and other inflammatory skin disorders hold particular promise.

cAMP Signaling in Atopic Dermatitis

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disorder characterized by pruritic blisters and/or scaly plaques whose distribution and presentation vary with age. The disease affects 15%-30% of children and 2%-10% adults, and is commonly associated with other atopic conditions, such as allergic rhinitis and asthma. AD usually begins in infancy and early childhood with erythematous, scaly, weeping (acute) and/or crusted (chronic) lesions of the face, scalp, and extensor surfaces. In adolescence and adulthood, lesions tend to involve the flexures, especially the antecubital and popliteal fossae. Histologically, acute lesions reveal epidermal intercellular

edema (spongiosis), as well as dermal perivascular infiltration by lymphocytes, monocytes, macrophages, dendritic cells, and some eosinophils. Lichenified plaques display epidermal thickening and hypertrophy and prominent hyperkeratosis [20,75]. As with psoriasis, both genetic and environmental factors contribute to the development of AD. Both immune dysregulation and epidermal barrier dysfunction have been implicated in AD pathophysiology, where structural and functional abnormalities of the stratum corneum confer greater permeability to allergens, irritants, and infection [75].

Evidence for cAMP signaling involvement in AD is closely associated with data supporting a possible role for adrenergic pathway dysregulation. The first clues to cAMP pathway involvement in AD stem from observations surrounding the pharmacologic hypersensitivity to β-adrenergic blockade seen in atopic patients and animal models of atopy. In 1968, Szentivanyi postulated that the clinical features of atopic diseases, such as the exaggerated activity of arteriolar and pilomotor smooth muscle observed in the skin of AD patients, might be attributed to β-adrenergic hypo-responsiveness due to an inherited or acquired abnormality in the β-adrenergic receptor-AC system [76]. Supporting this theory, subsequent investigations reported increased cutaneous reactivity in immediate hypersensitivity skin tests [77] and to histamine [78] in atopic patients with β-adrenergic stimulation and diminished reactivity with β-adrenergic blockade. Later, however, attention was turned to immune cells, when one group noted decreases in both the rise of intracellular cAMP in and physiologic response of leukocytes from AD patients exposed to β-adrenergic agonists but not PGE1. Of note, the investigators also demonstrated normal elevation in intracellular cAMP in atopic epidermis despite failure to evoke normal inhibition of mitosis of basal cells from AD patients in response to β-adrenergic stimulation [79]. Subsequent work further revealed reduced pharmacologic cAMP responsiveness and abnormally elevated PDE activity in peripheral blood leukocytes and monocytes in AD [10-13, 80, 81], giving rise to alternative immunologic-based hypotheses regarding cAMP signaling involvement in AD pathogenesis. Indeed, pharmacologic PDE inhibition has been found to reduce the abnormal release of key inflammatory mediators in AD, including histamine [82], immunoglobulin E (IgE) [83], IL-4 [84, 85], PGE E2, and IL-10 [85], by atopic leukocytes (Figure 2).

While cAMP dysfunction in immune cells clearly has a role, there is evidence to suggest cAMP signaling in keratinocytes may also play a role in the pathogenesis of AD. Several reports point to altered catecholamine synthesis and degradation in atopic epidermis leading to decreased intraepidermal cAMP and ultimately keratinocyte hyperproliferation [86-88]. In particular, Schallreuter and colleagues observed a significant decrease in the density of β2 receptors in both keratinocytes and peripheral blood lymphocytes from AD patients [87], leading to the investigation and subsequent discovery of structural and functional alterations of the β2 receptor associated with a single point mutation found in nine patients with AD [89]. Although continued investigation is necessary to clarify the significance of these findings-along with the role of β-adrenergic signaling in AD-the potential implications are certainly intriguing from a mechanistic and therapeutic standpoint. Overall, the evidence for aberrant β-adrenergic cAMP signaling at the epidermal level in AD is particularly compelling considering the importance of the signaling pathway in keratinocyte proliferation, differentiation, and, importantly, immune function [90]. Moreover, the role of the non-canonical sAC pathway in AD may reveal additional insights into AD pathogenesis.

Phosphodiesterases as therapeutic targets

Since the discovery in 1958 of phosphodiesterases and their role in cyclic nucleotide metabolism, at least 21 phosphodiesterase genes have been identified. Due to the near ubiquitous presence of these key cyclic nucleotide regulators and the importance of cyclic nucleotides (cAMP and cGMP) in numerous biological processes, pharmaceutical companies have developed PDE inhibitors to treat a variety of diseases. Probably the most well-known examples are the drugs that inhibit PDE5, a cGMP-specific PDE, for the treatment of erectile dysfunction [91]. PDE3, a high-affinity enzyme that degrades both cAMP and cGMP, has been targeted for vascular and airway smooth muscle relaxation, inhibition of platelet aggregation, and positive inotropy for the treatment of intermittent claudication and heart failure. While several PDE families exist, only PDE4, PDE7 and PDE8 specifically degrade cAMP. Of these, type-4 phosphodiesterase (PDE4) has demonstrated a significant role in immune activation.

Type 4 Phosphodiesterases and their role in chronic inflammation

Type-4 phosphodiesterases make up a family of at least 35 isozymes coded for by four separate genes sharing a highly conserved catalytic domain and two upstream conserved regions (UCR1 and 2) unique to type-4 PDEs [92,93]. Evidence suggests that as cells differentiate, PDE4 isoform expression also changes. The UCR domains have been shown to both affect enzyme activity and facilitate binding to scaffolding molecules, allowing PDE4 to localize to various parts of the cell [94].One important example of intracellular organization is in airway epithelial cells where PDE4 isoforms serve as a firewall to prevent cAMP diffusion from apical adenosine A2B receptors [95]. Multiple distinct PDE4 isoforms are used in a cell to generate cAMP microdomains. PDE4D isoform variants PDE4D8 and PDE4D9, as compared to PDE4D5, are associated with either the ß1 or ß2 adrenergic receptor signal transduction pathways, respectively. This latter finding further supports isoform variant localization to highly specific subcellular microdomains [96].

PDE4s are the predominant mechanism for cAMP degradation in a majority of immune cells, including T- and B-lymphocytes, eosinophils, neutrophils, dendritic cells, monocytes and macrophages along with structural cells including keratinocytes, chondrocytes, epithelial and endothelial cells [97-100]. In both Jurkat T-cells and human peripheral blood T-cells, prostaglandin E2 is capable of inducing PDE4 activity with increased transcription of several PDE4 isoforms [101]. PDE4D3 and PDE4D5 are more highly expressed in monocytes, but with differentiation of these cells to macrophages, there is a downregulation of these isoforms, which are replaced by the PDE4B2 and PDE4A10 long isoforms [102]. Several other isoforms of PDE4 are expressed in human circulating CD4+ T-cells in response to anti-CD3 and anti-CD28 antibodies or in monocytes in response to lipopolysaccharide.

More specifically, TCR and CD28 stimulation in human peripheral T-cells has been shown to recruit PDE4A4, PDE4B2, PDE4D1, and PDE4D2 in complex with ß-arrestin to oppose TCR-induced cAMP production [103]. A subsequent study showed that PDE4D plays a prominent role in various T-cell functions, and its activity is sufficient to inhibit T-cell proliferation. In contrast, PDE4A or PDE4B seem to have little to no effect on T-cell proliferation [104].

As described above, cyclic AMP is known to play an important role in inflammatory diseases [97]; therefore, elevation of cAMP would be

predicted to have anti-inflammatory effects [6]. Due to their presence in immune cells, the PDE4 family of enzymes represents a potential therapeutic target to induce immune suppression [105-108]. Thus, the PDE4 family of enzymes represents a promising target in the treatment of cutaneous inflammatory conditions [109]. For these reasons, PDE4 inhibitors have been developed for the treatment of atopic dermatitis and psoriasis in addition to a variety of other inflammatory conditions such as psoriatic arthritis [110-112].

A PDE4 inhibitor for the treatment of psoriasis

Of the PDE4 inhibitors developed to treat dermatologic conditions, none is more studied than Apremilast (CC-10004, Otezla.). A selective PDE4 inhibitor, apremilast has been shown to block pro-inflammatory cytokines including TNF-α, Interferon-γ, IL-12, IL-17 and IL-23 with a reduction in psoriasiform biology in humans [113]. By binding to the catalytic site and blocking PDE4 mediated enzymatic degradation of cAMP, apremilast leads to increased cAMP mediated PKA activation and subsequent phosphorylation of CREB. Incubation in apremilast also leads to activation of Activating Transcription Factor (ATF)-1 and inhibition of the transcriptional activity of NF-κB, resulting in alterations in cellular activity downstream of type-4 toll-like receptor (TLR-4) in both T-cells and monocytes [114] (Figure 2).

Three phase III trials have evaluated the safety and efficacy of apremilast compared to placebo. The ESTEEM 1 and ESTEEM 2 trials, two randomized, placebo-controlled trials studying the safety and efficacy of apremilast, studied 844 and 413 patients, respectively, with moderate to severe plaque psoriasis. The patients were included based on a Psoriasis Area and Severity Index (PASI) score ≥ 12, a Static Physician's Global Assessment (sPGA) score ≥ 3, and a body surface area of ≥ 10%. Nail Psoriasis Severity Index (NAPSI), Scalp Physicians Global Assessment (ScPGA) and Palmoplantar Psoriasis Physician's Global Assessment (PPPGA) were also evaluated [115,116].

Results demonstrated significant improvements in achieving a 75% reduction in Psoriasis Area and Severity Index (PASI-75) and a 50% reduction in Psoriasis Area and Severity Index (PASI-50) in both trials with apremilast 30 mg BID ($P<0.0001$) at the study's primary end point of week 16. In the ESTEEM 1 trial, PASI-75 was achieved in 33.1% of the apremilast 30 mg BID treatment group versus 5.3% of the placebo-treated group.

sPGA of 0-1 was achieved in 21.7% of those receiving apremilast 30 mg BID compared to 3.9% of the group receiving placebo ($P<0.0001$) [115]. At week 16, the ESTEEM 2 trial showed 28.8% achievement of PASI-75 compared to 5.8% in placebo and 55.5% achievement of PASI-50 compared to 19.7% in placebo. sPGA of 0-1 was achieved in 20.4% receiving drug compared to only 4.4% of patients receiving placebo ($P<0.0001$) [116].

The phase IIIb LIBERATE trial compared apremilast 30 mg BID to both Etanercept 50 mg QW and placebo in patients with moderate to severe plaque psoriasis. This study supported the efficacy of apremilast in achieving significant improvements in the PASI-75 response in patients receiving either apremilast 30mg BID or etanercept 50mg QW when compared to placebo ($P<0.0001$). However, no statistically significant differences were seen between the apremilast and etancercept treatment groups. DLQI scores were significantly improved in the first 16 weeks in both the apremilast 30 mg BID (-8.3) and the etanercept 50 mg QW (-7.8) compared to placebo (-3.8) [117]. Current studies are evaluating the safety, tolerability and pharmacokinetics of apremilast in pediatric patients with moderate to severe plaque psoriasis and apremilast in combination with narrowband UVB in plaque psoriasis [118, 119]. This drug was approved by the FDA for the treatment of both psoriasis and psoriatic arthritis in 2014 following the above phase III clinical trials for psoriasis and psoriatic arthritis [117,120-123].

Adverse effects of Apremilast

Adverse effects of apremilast have been shown to be mild to moderate in severity; with the largest study (ESTEEM) showing the most frequently reported adverse effects to include: diarrhea (18.7%), upper respiratory tract infection (17.8%), nausea (15.3%), nasopharyngitis (13.4%), tension headache (9.6%), and headache (6.5%). Discontinuation rates for diarrhea and nausea were each <2% in the apremilast 30 mg BID group through week 51. Weight loss of up to 10% of body weight were reported in 12% of patients treated with apremilast 30 mg BID for psoriasis compared to 5% in placebo treated patients. Though there were no adverse effects reported as a result of the weight loss, two patients cited weight loss as the reason for discontinuing treatment. Monitoring patients for weight loss is recommended while receiving apremilast [124,125]. Serious adverse effects were low and there was no increase in incidence with long-term exposure to the drug [115,116]. Importantly, compared to current biologic treatment of psoriasis and psoriatic arthritis, there does not appear to be an increased risk for tuberculosis reactivation or lymphomas.

PDE4 inhibitors in the treatment of atopic dermatitis

Compared to treatment of psoriasis and psoriatic arthritis, less is known about the effects of PDE4 inhibitors in the treatment of atopic dermatitis (AD.) The mainstay of therapy for those at risk for AD or with mild disease has traditionally focused on topical moisturizers and good skin care, as well as avoidance of possible irritants [126]. Those patients in whom first-line treatment fails are often graduated to topical corticosteroids, calcineurin inhibitors or systemic immunomodulatory therapies [127]. Since pruritus is often associated with AD, antihistamines have also been prescribed [128,129].

It has been established that patients with AD have increased intra-lesional PDE activity [130]. And since cAMP elevation would presumably have anti-inflammatory effects, PDE4 inhibition seems a reasonable therapeutic option for AD.

Apremilast

Apremilast has been investigated in two studies as a therapeutic for AD. The first, a 12-week trial of 20 mg apremilast BID in ten patients with AD and/or allergic contact dermatitis, showed the drug was ineffective [131]. A second, prospective trial compared 20 mg apremilast BID for 3 months with a 30 mg BID dose for 6 months' duration and found significant improvements in pruritus, DLQI and EASI in both groups with the 6-month group showing a reduction in EASI score greater than 50%. This makes apremilast comparable to other systemic agents currently used for AD. In this study, the most commonly reported side effect was nausea, which was dose-dependent [132]. Another randomized, double-blind, phase 2 study is currently in its accrual stage and aims to evaluate EASI score improvements at 12 weeks [133].

Boron-Derivatives

Phenoxybenzoxaboroles, a family of novel small molecules with a boron atom in the 5-membered ring of a 6,5-bicyclic molecule, have recently shown promise in micromolar concentrations [134,135]. One such compound, crisaborole (AN2728, Anacor Pharmaceuticals, Inc., Palo Alto, CA), a topical PDE4 inhibitor, has shown anti-inflammatory properties both *in vitro* and *in vivo* [135]. Crisaborole reduces the production of TNF-α. It also inhibits other pro-inflammatory cytokines, such as IL-12 and IL-23 [136]. A recent phase IIA randomized, double-blind, bilateral 6-week study of twice-daily application of crisaborole (2% ointment) versus vehicle control in 25 adults with AD demonstrate a greater decrease in the Atopic Dermatitis Severity Index (ADSI) score for crisaborole-treated lesions as compared to vehicle-treated lesions in 68% of patients, while 20% experienced a greater decrease in ADSI score for those lesions treated with vehicle as opposed to crisaborole (P=0.017).Twelve percent of patients had equal decreases in ADSI scores in crisaborole and vehicle treated lesions. A total of 29 adverse effects were reported in 11 of the study's participants, though most were mild. Larger, phase III pivotal trials will aim to assess efficacy and safety of crisaborole [137].

E6005

Another topical PDE4 inhibitor, E6005 (methyl 4-[({3-[6,7-dimethoxy-2-(methylamino)quinazolin-4-yl]phenyl}amino)carbonyl]benzoate), was developed as a novel PDE4 inhibitor with topical application. The molecule has demonstrated selective and effective inhibition of PDE4 and prevents the elaboration of proinflammatory cytokines and adhesion molecules in both lymphocytes and monocytes [138]. E6005 has also demonstrated inhibition of hapten-induced scratching in sensitized mice and spontaneous scratching in mice with chronic dermatitis [138-140]. Preliminary studies of 76 subjects in Japan have established safety and tolerability in healthy volunteers as well as patients with AD [140].

LEO 29102

A piclamilast derivative, LEO 29102 (2-{6-[2-(3,5-dichloro-4-pyridyl)acetyl]-2,3-dimethoxyphenoxy}-N-propylacetamide), a potent and highly selective PDE4 inhibitor suitable for topical application, has reached phase 2 and has demonstrated clinical efficacy in the treatment of atopic dermatitis. It is currently being evaluated as a low-cost, well-tolerated alternative to other PDE4 inhibitors [141].

Roflumilast

When applied topically to chemically induced murine AD models, roflumilast had beneficial effects on intensity scores and dorsal skin thickness [142]. Currently, topical Roflumilast Cream (0.5%) is still being evaluated in clinical trials. A recently completed three-center randomized, double-blind, placebo controlled German study failed to show a statistically significant improvement in SCORing Atopic Dermatitis (SCORAD) or Transepidermal Water Loss (TEWL) values between the group receiving 0.5% Roflumilast Cream compared to vehicle alone. However, patient assessment of pruritis was significantly improved in the 0.5% Roflumilast treated group (-3.05) compared to vehicle treated group (-1.50) on day 15 of the study (P=0.013) [143].

Isoxazoline derivatives

Finally, isoxazoline derivatives with dual PDE4/PDE7 inhibitory activity have recently been described in patent applications with efficacy demonstrated *in vitro* and possible utility in the treatment of AD. Other PDE4/PDE7 inhibitors based on heterospirocyclic compounds as well as the structurally related isoxazoline spirocycles diminish TNF-α release *in vivo* and in cell-based cultures respectively [144]. Another group of PDE inhibitors containing fused furane cycles including benzo[4,5]furo[3,2-c]pyridine derivatives (Glenmark Pharmaceuticals S.A. Mumbai, India) and structural anologues (Matrix Laboratories, Ltd., Secunderabad, India) have demonstrated whole-blood TNF-α inhibition[144].

PDE4 inhibitors in other inflammatory skin diseases

Because of the immunosuppressive effects of PDE4 inhibitors, preliminary investigations of potential therapeutic effects of selective PDE4 inhibitors in lichen planus (LP), discoid lupus erythematosus (DLE), and cutaneous sarcoidosis have been conducted. A 2012 pilot study of the PDE4 inhibitor apremilast in 10 patients with moderate to severe LP produced at least a 2-grade improvement in the Physician Global Assessment after 12 weeks of therapy in 3 patients, as well as significant clinical improvement in the other 7 [145], suggesting that further study of cAMP signaling in LP may be warranted. Published the same year, an 8-patient pilot study of apremilast in DLE showed marked reductions in CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index) scores in 4 patients who completed the full 85 days of treatment [146]. Finally, a 15-patient study also published in 2012 investigating the efficacy and safety of apremilast in cutaneous sarcoidosis reported statistically significant improvement in both SASI (Sarcoidosis Activity and Severity Index) scores and photographic comparison of cutaneous lesions prior to and after 12 weeks of treatment. Interestingly, 3 patients experienced relapse of cutaneous lesions only partially responsive to prednisone therapy within 3 months of apremilast discontinuation [147].

Other studies have shown apremilast to be effective in the treatment of rosacea with statistically significant improvement on the Physician Global Assessment (PGA) and Physician Overall Erythema Severity, erythematotelangiectatic rating and nontransient erythema [148]. Another case series evaluating apremilast for the treatment of lichen planus demonstrated significant clinical improvement of at least 2-grades in PGA following twelve weeks of treatment with 20 mg apremilast BID [149].

Conclusion

A key second messenger and regulator of numerous inflammatory mediators, cAMP is a prominent player in immune mechanisms underlying inflammatory skin diseases such as psoriasis and atopic dermatitis. Changes in intracellular cAMP via production and/or degradation can profoundly influence immune responses in T cells and other immune cells, where increased cAMP generally suppresses inflammatory mediator production and other immune functions. In a broader cellular context, cAMP plays a pivotal role in cellular proliferation and differentiation as well as gene expression-primary cellular processes whose disruption in skin as well as immune cells may also be involved the pathogenesis of these diseases. The potential significance and contribution of abnormal cAMP signaling in skin cells, especially keratinocytes, in inflammatory skin disorders is far from established but becoming clearer. Regardless, the efficacy of novel

oral and topical PDE4 inhibitors such as apremilast that target cAMP degradation bolsters evidence that cAMP pathways are not only principally involved but also relevant therapeutic targets in these diseases. In addition, the safety and favorable side-effect profiles of this class of drugs makes them particularly attractive for continued development and application in various inflammatory cutaneous diseases. Overall, further studies and a better understanding of cAMP signaling in these diseases are likely to provide new insights into disease pathogenesis as well as other potential therapeutic targets and treatment approaches.

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