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Commentary

Apremilast mechanism of action and application to psoriasis and psoriatic arthritis

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ABSTRACT

Psoriasis and psoriatic arthritis are common clinical conditions that negatively impact health-related quality of life and are linked to serious medical comorbidities. Disease mechanisms involve local and systemic chronic inflammatory processes. Available biologic therapies specifically target single inflammatory mediators, such as tumor necrosis factor-α (TNF-α), in the context of a larger inflammatory signaling cascade. To interrupt this pathological cascade earlier in the response or further upstream, and return pro-inflammatory and anti-inflammatory signaling to a homeostatic balance, the use of a phosphodiesterase4 (PDE4) inhibitor has been explored. PDE4 is the major enzyme class responsible for the hydrolysis of cyclic adenosine monophosphate (cAMP), an intracellular second messenger that controls a network of pro-inflammatory and anti-inflammatory mediators. With PDE4 inhibition, and the resulting increases in cAMP levels in immune and non-immune cell types, expression of a network of pro-inflammatory and anti-inflammatory mediators can be modulated. Apremilast is an orally available targeted PDE4 inhibitor that modulates a wide array of inflammatory mediators involved in psoriasis and psoriatic arthritis, including decreases in the expression of inducible nitric oxide synthase, TNF-α, and interleukin (IL)-23 and increases IL-10. In phase II studies of subjects with psoriasis and psoriatic arthritis, apremilast reversed features of the inflammatory pathophysiology in skin and joints and significantly reduces clinical symptoms. The use of an oral targeted PDE4 inhibitor for chronic inflammatory diseases, like psoriasis and psoriatic arthritis, represents a novel treatment approach that does not target any single mediator, but rather focuses on restoring a balance of pro-inflammatory and anti-inflammatory signals.

1. Introduction

Psoriasis is a chronic inflammatory disease predominantly affecting the skin and is estimated to occur in 2–3% of the population [1,2]. A subset of these psoriasis patients will also develop psoriatic arthritis, a seronegative spondyloarthropathy [3,4]. In psoriasis and psoriatic arthritis, a dysregulation of multiple pro-inflammatory and anti-inflammatory mediators occurs in dendritic cells, monocytes, macrophages, neutrophils, T cells, B cells, keratinocytes, chondrocytes, and synoviocytes [5,6]. The cascade of aberrant immune signaling, triggered by stress, physical injury, drugs, or infection, is believed to underlie the clinical signs of inflammation, pain, and pruritus, as well as the histological signs such as keratinocyte hyperproliferation, scaling, and, in subsets of patients, pustular or guttate plaques and nail and joint involvement [5,7]. Because of the chronic nature of psoriasis and psoriatic arthritis, long-term treatment is often required [8]. Systemic therapies are typically recommended for patients with moderate psoriasis affecting 3–10% of the body surface area, and for severe psoriasis affecting more than 10% of the body surface area, or for patients who experience significant psoriasis-related impairments in quality of life [7–9]. Traditional systemic or disease-modifying antirheumatic drugs (DMARDs) include methotrexate and cyclosporine; however, these agents are associated with serious organ toxicity and adverse effects and require clinical monitoring throughout treatment [9]. Additionally, evidence for the efficacy of methotrexate in psoriatic arthritis is limited, although methotrexateis often used as a first-line therapy because of its oral route of administration and lower cost, compared with the newer, more effective biologic treatments [3]. These biologic therapies include inhibitors of tumor necrosis

Abbreviations: ACR20, 20% or greater improvement from baseline in American College of Rheumatology; cAMP, cyclic adenosine monophosphate; CREB, cAMP-response element binding protein; DMARDs, disease-modifying antirheumatic drugs; IC_{50}, half maximal inhibitory concentration; IFN-α, interferon-αl; IL, interleukin; iNOS, induciblenitricoxidesynthase; NF-κB, nuclear factor kappa B; PDE, phosphodiesterase; PDE4, phosphodiesterase 4; PKA, protein kinase A; Th1, type 1 helper T cell; Th17, type 17 helper T cell; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor.

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factor-alpha (TNF-α), interleukin 12 and 23 (IL-12/IL-23), and antibodies that target B cells or T cells [7,8]. Although biologic therapies represent an advance in the treatment of chronic inflammatory diseases, their use is limited by treatment resistance (including both initial lack of efficacy and loss of effect), tolerability issues, parenteral administration, and barriers to patient access, such as high cost and specialist management [7,8]. Research efforts continue in the search for oral treatment options that are safe and effective in the treatment of psoriasis and psoriatic arthritis.

2. Pathophysiology of psoriasis and dermatologic inflammation

Acute inflammatory reactions typically occur in response to infection and are coupled with the release of local factors that prevent excessive trafficking of leukocytes, allowing for resolution of inflammation. Resolution of an acute inflammatory response within the local tissues and a re-establishment of immunological homeostasis are necessary for ongoing health [10]. Skin is an important site for antigen presentation, and epidermal Langerhans cells and dermal dendritic cells play pivotal roles in T cell-mediated immune responses to antigens encountered in skin. Regulatory feedback loops help to balance pro-inflammatory signaling pathways and anti-inflammatory signaling pathways, maintaining the homeostatic functioning of the skin immune system [11].

In psoriasis and psoriatic arthritis, subsets of dendritic cells are believed to be involved in the very earliest stages of disease pathophysiology because they are the antigen-presenting cells that initiate dysregulated immune responses to antigens [12,13]. Although not fully understood, plasmacytoid dendritic cells appear to circulate in the blood of individuals with psoriasis and become activated upon interaction with antimicrobial peptides that are complexed with host DNA [12]. Activated plasmacytoid dendritic cells then produce interferon-α (IFN-α), which interacts with keratinocytes and myeloid dendritic cells to affect pro-inflammatory processes [12]. Activated dendritic cells also produce pro-inflammatory mediators, such as IL-12 and IL-23 [12]. In lesional skin from subjects with psoriasis, inflammatory myeloid dendritic cells express TNF-related apoptosis-inducing ligand (TRAIL), which is likely a direct mediator of keratinocyte inflammation [13]. The myeloid dendritic cell/T cell interaction is central to the evolution of psoriasis [12]. T cells respond to myeloid dendritic cell antigen presentation by proliferating and differentiating into type 1 helper T cells (Th1) and type 17 helper T cells (Th17), which secrete cytokines, including IL-2, IFN-γ, TNF-α, IL-17, and IL-22 [12].

In line with propagation of immune cell activation, individuals with psoriasis and psoriatic arthritis exhibit increased levels of pro-inflammatory mediators in both the target tissues and the blood. Compared with normal skin biopsies, psoriatic skin lesions have a Th1 and Th17 cytokine profile, including IL-2, IFN-γ, TNF-α, IL-17, and IL-22, without a significant component of type 2 cytokines (i.e. IL-4, IL-5, and IL-10) [14,15]. Furthermore, immunoreactivity for IL-12 and IL-23 is significantly enhanced in lesional psoriatic skin compared with non-lesional and normal skin ($P < 0.001$ for both) [16]. Significantly increased mRNA expression of IL-17A ($P = 0.0059$), IL-17C ($P = 0.0096$), and IL-17F ($P = 0.0036$) was observed in psoriatic skin compared with nonlesional skin [17]. Similarly, for subjects with psoriatic arthritis, IL-17A expression was found to be significantly higher ($P < 0.01$) in synovial fluid of subjects with psoriatic arthritis (mean 4.5% [SD 0.9]) than in subjects with osteoarthritis (mean 1.14% [SD 0.9]) [18].

Pro-inflammatory mediators seen in psoriasis and psoriatic arthritis are released by a variety of cell types, including innate immune cells, adaptive immune cells, and resident non-immune cells. Immunostaining of psoriatic lesional skin sections confirmed significantly higher expression of both subunits of IL-23 (p19 and p40) by keratinocytes in situ compared with keratinocytes in normal ($P = 0.001$) and psoriatic nonlesional ($P < 0.05$) skin [19]. CD11+ dendritic cells are a major cell type in psoriatic skin lesions. In diseased skin, these cells express two mediators of inflammation: inducible nitric oxide synthase (iNOS) and TNF-α in diseased skin [20]. Moreover, relatively high percentages of epidermal CD8 and CD4T cells isolated from psoriatic lesions are capable of producing IFN-γ, TNF-α, and IL-2, whereas few T cells express IL-4 or IL-10 [21]. IL-17(+) mast cells and neutrophils are found at higher densities than IL-17(+) T cells in psoriatic lesions and frequently release IL-17 [22].

Such chronic inflammatory signaling is believed to lead to changes in resident cells of the skin and joints. In the skin, feedback loops involving keratinocytes, fibroblasts, and endothelial cells contribute to tissue reorganization, marked by endothelial-cell proliferation and deposition of extracellular matrix [12]. Total blood vessel and lymphatic vessel areas are increased in psoriatic skin lesions compared with non-involved skin, which accounts for lesion redness [23]. Angiogenic markers, such as vascular endothelial growth factor (VEGF)-A, placental growth factor, VEGFR2, and neuropilin-1, are also increased [23]. In one study, subjects with psoriatic arthritis had higher circulating concentrations of Dikkopf-1 and macrophage-colony stimulating factor (two soluble mediators of bone remodeling) than individuals with psoriasis or healthy controls; the macrophage-colony stimulating factor concentrations positively correlated with radiographic joint erosion, joint-space narrowing, and osteolysis scores [24].

3. Role of cAMP and PDE4 in regulating inflammation

One limitation of currently available biologic agents is that they do not reach inside the cell to target intracellular signaling pathways. Instead, such agents are antibodies or compounds that selectively bind with receptors or proteins on extracellular membranes or extracellular milieu (e.g. anti-TNF), altering activity of targeted cell types, cell-to-cell interactions, and immune signaling [5]. Biologic agents tend to specifically target a single pro-inflammatory marker and interrupt the inflammatory cascade downstream from pro-inflammatory changes in gene transcription. To interrupt the inflammatory cascade at an earlier point, researchers have begun to explore modulation of intracellular signaling that controls inflammatory-mediator gene expression. Intracellular signaling and responses to environmental factors by all types of cells throughout the body, including myeloid, lymphoid, and other inflammatory cells, are regulated by key "second messengers", such as cyclic adenosine monophosphate (cAMP).

Intracellular concentrations of cAMP levels represent a balance between the activities of the various adenylylcyclases largely activated via G-protein coupled receptors and the phosphodiesterases (PDEs), of which 11 distinct families are expressed in a tissue-specific manner [25,26]. Eight PDE families are capable of hydrolyzing cAMP to AMP [27]. With four different PDE4 subtypes (A, B, C, and D) and more than 20 different isoforms defined so far, this large enzyme family manages a wide array of distinct cAMP signaling pathways that are specifically tailored to different types of cells [27]. Phosphodiesterase4 (PDE4) is one of the major cAMP-selective PDEs expressed in epithelial cells, such as those lining the airways [28]. Hematopoietic cells controlled by PDE4 include dendritic cells, T cells, macrophages, and monocytes [27,29–31]. Mesenchymal cells that express PDE4 include keratinocytes within the dermis, smooth muscle, vascular endothelium, and chondrocytes involved in the structure of the joint [27,32,33]. In the central