Pathogenesis of Atopic Dermatitis and Psoriasis

Subjects: Dermatology

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Psoriasis and atopic dermatitis fall within the category of cutaneous immune-mediated inflammatory diseases (IMIDs). The prevalence of IMIDs is increasing in industrialized societies, influenced by both environmental changes and a genetic predisposition.

Keywords: multi-omics ; psoriasis ; atopic dermatitis ; immune mediated inflammatory diseases ; genomics ; epigenomics

1. Introduction

Psoriasis and atopic dermatitis are cutaneous immune-mediated inflammatory diseases (IMIDs) and, as such, belong to a spectrum of inflammatory conditions with two pathophysiologic poles: autoinflammatory and autoimmune. Autoinflammatory diseases are caused by the activation of the innate immune system, which leads to systemic inflammation [1][2]. On the other hand, autoimmune diseases are caused by the activation of the adaptive immune system, with high levels of autoantibodies and self-reactive lymphocytes, leading to inflammation and derangement of local tissues. Some diseases can be classified as either (predominantly) autoimmune (e.g., pemphigus vulgaris) or autoinflammatory diseases (e.g., familial Mediterranean fever), but psoriasis and atopic dermatitis are considered to be mixed-pattern diseases [2][3].

The incidence of IMIDs is growing in industrial societies; environmental changes combined with a genetic background trigger the development of IMIDs [4][5][6]. Recent evidence underpins the presence of shared common pathways among IMIDs [2][6][7], but knowledge of the immune factors that drive these chronic progressive diseases is still incomplete. Treatments of IMIDs are effective in providing clinical benefits to patients, but long-term disease control is still largely unmet [6].

Multi-omics, in the context of dermatology, refers to the use of various omics technologies to comprehensively study and analyze the skin and its related conditions. “Omics” fields encompass various biological data types, and in dermatology, this may include genomics (study of genes and DNA), transcriptomics (study of gene expression), proteomics (study of proteins), metabolomics (study of small molecules and metabolites), and microbiomics (study of the skin microbiome) [8][9][10].

2. Current Knowledge in Pathogenesis of Atopic Dermatitis and Psoriasis

Atopic dermatitis (AD) is the most common chronic cutaneous IMID, with a prevalence of 10% among adults and 20% in children [11]. The underlying pathophysiological mechanisms in AD are complex, encompassing a pronounced genetic susceptibility, epidermal dysfunction, and inflammation driven by T-cells [12][13][14][15][16]. Both the innate and adaptive immune systems contribute to its etiopathogenesis [12][14]. AD was initially considered a purely Th2-mediated inflammatory disease since most patients show high counts of eosinophils and high levels of immunoglobulin E (IgE). However, the immunological pathway of AD is complex, with predominant activation of Th2/Th22 and variable activation of Th17/Th1 lymphocytes; a biphasic switch from Th2 to Th1 responses has been reported in both acute and chronic cutaneous lesions of patients with AD [12][13][14]. The main cytokines related to AD etiopathogenesis are IL-4 and IL-13 [17][18]. They play a crucial role in the differentiation of Th2 cells and the production of IgE. Acute AD skin shows increased expression of Th2 cytokines, like IL-4, IL-5, and IL-13 [18]. In addition, IL-4 and IL-13 cause a disruption in epidermal barrier integrity by decreasing the number of main terminal differentiation proteins, such as filaggrin, loricrin, and involucrin. Levels of IL-13 correlate with the disease severity of AD [19][20][21].

Psoriasis is a chronic skin IMID with a prevalence of 1–3% in Western populations. The pathogenesis of psoriasis is characterized by an interaction of keratinocytes with the innate and adaptive immune systems [22][23][24]. Multiple theories have been put forth attempting to explain the pathogenesis of psoriasis [24][25][26]. The most accepted contemplates an initiation phase followed by a chronic inflammatory phase that is sustained by a feed-forward mechanism based on

cytokine-mediated keratinocyte activation and proliferation [27][28]. Genetically predisposed patients become exposed to a trigger (trauma, infection, drugs) that will induce keratinocytes to undergo apoptosis or necrosis, releasing nucleic acids (DNA or RNA) that may induce a type I interferon-mediated autoinflammatory response, and potential autoantigens such as cathelicidin (LL37), ADAMTSL-5, and phospholipase A2 (PLA2G4D). LL37 interacts and forms complexes with self-DNA or -RNA that will trigger the innate immune system via Toll-like receptors (TLR) [29][30]. The activation of TLR7 and TLR8 leads to the production of interferon (IFN)-α and IFN-β by keratinocytes and plasmacytoid dendritic cells (pDCs), and interleukin (IL)-6 and tumor necrosis factor (TNF) by myeloid dendritic cells (mDCs). IL-6 induces differentiation of CD4+ naive T-cells into T helper (Th)-17 cells [31][32], whereas type I IFNs and TNF promote the secretion of IL-12 and IL-23 by mDCs [33][34]. IL-12 and IL-23 are clue cytokines in the immune chain reaction causing psoriasis. CD4+ naïve T-cells differentiate into Th1 cells upon exposure to IL-12, along with tumor growth factor (TGF)-β and IL-6 [35][36][37][38][39]. IL-23 leads to Th17 cell development and activates αβT-cells [35][36][37][38][39]. Th1-activated cells exhibit a distinctive cytokine secretion profile, including IFN-γ and TNF. Meanwhile, Th17-activated cells release IL-17, IL-22, and TNF [40]. Together, these cytokines induce keratinocyte proliferation, differentiation, and inflammatory activation, although IL-17A constitutes the main effector cytokine driving psoriasis pathogenesis and is essential for the development and maintenance of psoriasis plaques [40]. Inflammatory cytokines such as IL-1, IL-6, and TNF, chemokines (including CXCL1, CXCL2, and CXCL3), and AMPs (including S100A7/8/9, human-defensin 2, and LL-37) are produced by stimulated keratinocytes, which attract and activate immune cells and exacerbate psoriatic inflammation [38][41][42]. S100A8/A9 is overexpressed in keratinocytes and innate immune cells, and their transcripts are significantly overexpressed in psoriasis lesions compared to non-lesional psoriasis or atopic dermatitis (AD) skin [43]. Furthermore, psoriasis treatment has been shown to reduce S100A8/A9 levels. Christmann et al. identified the induction of S100-alarmins in an imiquimod-induced murine model of psoriasis-like skin inflammation, which was associated with increased expression of IL-1*α*, IL-6, IL-17A, or TNF [44]. However, recent evidence has observed that lower epidermal levels of S100A9 in mice lead to more severe psoriasis skin lesions [45].

The maintenance phase of psoriatic inflammation is driven by this positive feedback loop between keratinocytes and T lymphocytes, enhancing further epidermal hyperplasia and a sustained inflammatory response.

Psoriasis encompasses multiple clinical variants, such as pustular psoriasis, guttate psoriasis, and nail psoriasis, among others. Guttate psoriasis was previously thought to be closer to contact dermatitis than psoriasis; however, novel insights by using gene expression profiling and gene set enrichment scores have been observed that are more similar to chronic psoriasis [46]. Regarding pustular psoriasis, in contrast to psoriasis vulgaris, where the IL-23/17 axis plays a pivotal role, pustular psoriasis shows hyperactivation of innate immunity, prominently involving the IL-36 axis [47]. Analysis of gene expression in skin biopsy specimens obtained from individuals affected with either generalized pustular psoriasis (GPP) or plaque psoriasis has unveiled discernible patterns. Specifically, GPP lesions manifest increased expression of IL-1 and IL-36, coupled with diminished levels of IL-17A and interferon-c, when juxtaposed with lesions characteristic of plaque psoriasis [47]. The pathomechanisms of ungual psoriasis remain elusive; however, a variant in IL1RN has been identified in patients with nail psoriasis. IL1RN functions to regulate the proinflammatory activity of IL-1A. The latter has been demonstrated to induce nail changes, suggesting a potential association with nail involvement in patients affected by psoriasis [48][49].

The clinical manifestations and course of both psoriasis and AD are highly variable; most patients achieve satisfactory responses with currently available treatments, but clinical and therapeutic challenges can be vexing in some cases.

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