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Review Article

Ustekinumab in Psoriasis Immunopathology with Emphasis on the Th17-IL23 Axis: A Primer

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Psoriasis is a chronic relapsing immunoinflammatory dermatosis that is commonly associated with systemic comorbidities. The pathogenic importance of interleukin (IL)-12 and IL-23 is beyond doubt, as well as the involvement of T helper cells (Th)1 and Th17 cells. There is upregulation of the p40 subunit shared by IL-12 and IL-23 and of the IL-23 p19 subunit, but not an increased expression of the IL-12 p35 subunit. This indicates that IL-23 appears more involved than IL-12 in the pathogenesis of psoriatic plaques. Ustekinumab is a fully human monoclonal antibody of the immunoglobulin (Ig) G1 class targeting the p40 subunit common to both IL-12 and IL-23, thus inhibiting both IL-12 and IL-23 receptor-mediated signalling. Ustekinumab is part of the recent biologic therapies active in psoriasis, autoimmune arthritides, and inflammatory bowel diseases.

1. Introduction

Disturbed immune-mediated inflammatory reactions are involved in the pathogenesis of psoriasis and its comorbidities [1]. There is evidence that the combined epidermal and microvasculature hyperplasia results from a response to the immune cell infiltrate present in the skin [2–4]. In recent years, some specific inflammatory cytokine pathways have represented promising or established therapeutic targets [1–6]. In particular, biologicals directed to tumor necrosis factor (TNF)-α, interleukin (IL)-12, IL-23, as well as CD4+ T helper (Th) 1 and Th17 effector cells fitted with the psoriasis pathobiology [7, 8].

2. The IL-12 / IL-23 Connection

IL-12 and IL-23 are structurally related cytokines that upregulate T-cell immune responses [9]. IL-12 is a heterodimeric protein consisting of the two disulfide-linked, glycosylated p35 and p40 subunits. This cytokine is secreted by dendritic antigen-presenting cells in response to inflammatory stimuli or infections. The IL-12 cytokine activates natural killer (NK) and T-cell responses, including naive CD4+ T-cell differentiation toward the CD4+ Th1 phenotype [9–11]. The heterodimeric IL23 cytokine contains the identical p40 subunit disulfide-linked to a p19 subunit [11]. Following activation by IL-6 and transforming growth factor (TGF)-β, IL-23 in concert with TNFα supports the development of Th17 cells [9–13].

The p40 subunit of both IL-12 and IL-23 binds to the IL-12 receptor-β1 (IL-12Rβ1) [14, 15]. The IL-12p35 and the IL-23p19 subunits bind to IL-12Rβ2 and IL-23R, respectively. These distinct binding processes account for the cytokine biological specificities [11, 14, 15]. Thus, despite some structural similarities between IL-12 and IL-23, they control distinct immunological pathways. IL-12 promotes the development of Th1 populations producing interferon (IFN)-γ, TNF-α, and IL-2. By contrast, IL-23 in combination with IL-21 and TGFβ drives the development of CD4+ Th17 populations producing IL-17, IL-22, TNF-α, and IL-1β [16].

3. Psoriasis Immunopathogenesis

Psoriasis apparently results from the activation of an abnormal immune response leading to excessive keratinocyte proliferation and global epidermal thickening. In particular, cytokines produced by Th1 and Th17 cell populations play a pivotal role in the development and maintenance of psoriatic lesions [13–15, 17–19]. The p40-containing cytokines are involved in the psoriasis pathogenesis [17] because there is overexpression of the IL-12p40 and the IL-23p40 in psoriasis plaques [20–22]. Gene polymorphisms encoding the shared p40 subunit or one of the components of the IL-23 receptor (IL-23R) complex are linked to psoriasis [23]. An uncommon IL-23R coding variant protecting against Crohn's disease appears to confer protection against psoriasis [24, 25]. Gene expression levels of IL-12p40, IFN-γ, and IL-23p49 are raised in psoriatic lesions [21, 23, 26]. Both IL-17 and IL-22 promote epidermal proliferation and remodelling, through activation of the keratinocyte transcription factor Stat3, and upregulate keratinocyte host defence proteins, including human β-defensin (HβD)-2 [19, 27]. IFN-γ in concert with Stat 1 activates keratinocytes to upregulate major histocompatibility complex class II, while both intracellular adhesion molecules (ICAM) and TNFα contribute to the development of psoriatic plaques [1, 18, 28, 29]. In addition, IL-23 drives monocytes to differentiate into dendritic cells [30]. This might account for the presence of many factor XIIIa+ dermal dendrocytes.

Th1 and Th17 cells are involved in the psoriasis pathobiology following secretion of a series of inflammatory cytokines, including IFN-γ, IL-17, and IL-22, that in turn activate keratinocytes to proliferate and secrete additional proinflammatory mediators [5]. The IL-12 and IL-23 cytokines produce a downstream impact on Th1 and Th17 cell activation, as well as keratinocyte triggering. Accordingly, any therapeutic agent designed to block IL-12 and IL-23 likely abates the upregulation of IFN-γ, IL-17, and IL-22 by both Th1 and Th17 cells [5].

Th17 cells play a central role in the development of psoriasis [2, 31]. IL-23 represents the major regulator of Th17 cells. These cells conduct immunosurveillance in the epidermis and secrete IL-17A, IL-17F, and IL-22 [32]. In psoriatic lesions, the proinflammatory IL-17 leads to the production of other cytokines and angiogenic factors, committing naive T cells to the Th17 lineage and creating a positive feedback loop for Th17 inflammation. IL-22 acts on keratinocytes through the IL-22 and IL-10 receptors, resulting in hyperproliferation and altered keratinocyte maturation leading to the typical acanthosis of psoriatic lesions [33, 34]. IL-17 and IL-22 produce a synergist stimulation of keratinocytes to be resistant to microbial infection through the expression of antimicrobial peptides. Some Th17 cells produce IL-17 only, while Th22 cells solely produce IL-22 [35, 36].

Both IL-12 and IL-23 are overexpressed in lesional psoriatic skin. However, the p40 subunit was used as a surrogate for assessing IL-12 expression. Thus, no differentiation was possible between the presence of IL-12 and IL-23 [37–40]. A pivotal study showed RNA upregulation of the p40 subunit shared by IL-12 and IL-23 and of the IL-23p19 subunit, but not an increased expression of the IL-12p35 subunit [38]. Such finding suggested that IL-23 was more involved in the maintenance of psoriatic lesions than IL-12. Additionally, IL-23 is a more potent activator of keratinocyte proliferation than IL-12 [39, 40].

4. Ustekinumab

The psoriasis immunopathogenesis has provided new therapeutic options in recent years [7]. Among recent breakthroughs, ustekinumab (Stelara, Janssen Pharmaceutica, Beerse, Belgium) is a fully human monoclonal antibody of the IgG1 class. It is directed to the shared p40 subunit of both IL-12 and IL-23 [41–43]. Thus, the drug neutralizes the bioactivities of both cytokines by blocking interaction with the IL-12R β1 cell surface receptor. The pharmacological characteristics and both the clinical efficacy and tolerability of ustekinumab are clearly proven in patients with chronic moderate to severe plaque psoriasis, including subjects with psoriatic onychopathy and psoriatic arthritis [8, 43–46].

IL-23 expression is significantly increased in the psoriatic epidermis [5, 38]. IL-23 messenger RNA expression is significantly higher in lesional skin of psoriatic patients as compared with healthy skin in the same patients [5, 38]. IL-23 secretion by monocytes and mature dendritic cells derived from patients with psoriasis is unusually high [38]. This cytokine promotes survival and proliferation of Th17 cells [47–51]. As a result, Th17 cytokines, such as IL-17, stimulate keratinocyte proliferation enabling further stimulation of keratinocyte proliferation in psoriatic lesions [6, 29].

The therapeutic efficacy of ustekinumab is obtained after IL-12 and IL-23 inhibition leading to the abated expression of cell surface markers associated with skin homing (CLA), activation of anti-inflammatory cytokines including IL-5, and inhibition of the secretion of the proinflammatory cytokines IFNγ, IL-2, IL-8, IL-10, IL-17A, and TNFα. A reduction in CD4+ Th cells and NK cells was reported after a single dose of ustekinumab. However, changes varied across time and did not appear to be dose dependent. Ustekinumab pharmacokinetics is notably affected by body weight. This aspect is particularly important to consider in case of metabolic syndrome comorbidity.

5. Beyond Psoriasis

Recent clinical trials conducted in humans emphasized the crucial role of Th17 cells boosted by IL-23 in the immunopathogenesis of several other inflammatory skin diseases, including allergic contact dermatitis, systemic scleroderma, and sarcoidosis [52–58]. In addition, the IL-23/Th17 axis appears to play a prominent role in the development of other diseases with possible cutaneous involvement. These include systemic lupus erythematosus [59, 60], rheumatoid arthritis [61], inflammatory bowel disease [62], and Behçet disease [63]. Considering the major role of IL-23-dependent Th17 cells in several skin diseases, future indications for IL-23 pathway inhibitors will probably emerge in a field much more broader than currently documented.

At present, the advent of biological therapies has already revolutionized the treatment of autoimmune diseases beyond psoriasis, including autoimmune arthritides, and inflammatory bowel diseases.

6. Conclusion

Psoriasis is a frequent chronic relapsing immunoinflammatory dermatitis particularly triggered by the Th17/IL-23 axis. The long-term limitations of conventional systemic psoriasis therapies because of the potential for severe renal, hepatic, and pulmonary adverse events have led to the development of biotherapies. An increased understanding of the immunopathogenesis of psoriasis helped focusing on specific targets. These agents alter specific immunologic pathways involved in the development of the disease, including some cytokine productions. At present, it appears that IL-23 is more involved than IL-12 in the pathogenesis of psoriasis.

Ustekinumab is a monoclonal antibody to the common p40 subunit shared by IL-12 and IL-23. It represents a masterpiece in the treatment of plaque psoriasis. Other conditions including psoriatic arthritis, Crohn's disease, and some other autoimmune diseases are expected to become recognized indications for the drug.

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