



PSORIASIS AND INTERLEUKIN-MEDIATED CHRONIC INFLAMMATION:

Unraveling the essence and dynamics of targeting interleukin-6, interleukin-17
and interleukin-23 signaling in moderate-to-severe plaque psoriasis

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INTRODUCTION

Psoriasis is a chronic inflammatory auto-immune disease, affecting approximately 125.000.000 people worldwide and is characterized by erythematous plaques bordered by silver scales that are present on various body parts
Psoriasis is associated with comorbidities, like psychological conditions, cancer, infections, metabolic disorders and psoriatic arthritis
There is still no cure for psoriasis, thus the relevance for further research is emphasized



Figure 1. Psoriatic plaques on the skin of a severe plaque psoriasis patient

Genetic profiles of patients with psoriasis indicated interleukin-17 (IL-17), interleukin-23 (IL-23) and interleukin-6 (IL-6) are major mediators in chronic inflammation inherent to the pathology



INTERLEUKIN-17

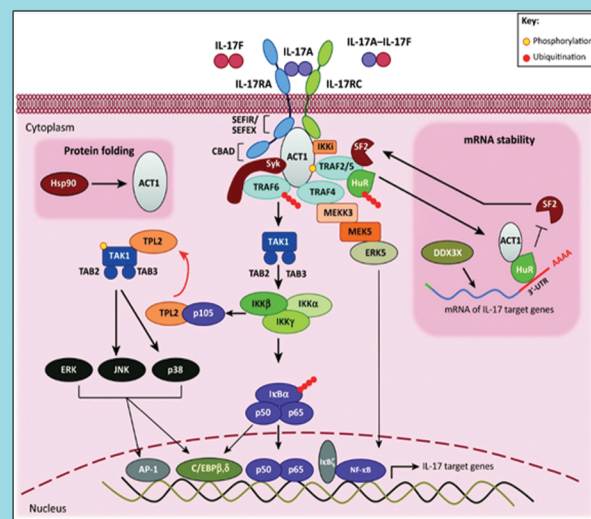


Figure 2. Simplified model of downstream signaling of IL-17RA receptor after activation via IL-17A, IL-17F or IL-17A/F. Downstream signaling occurs via the NF-κB or MAPK pathway

INTERLEUKIN-23

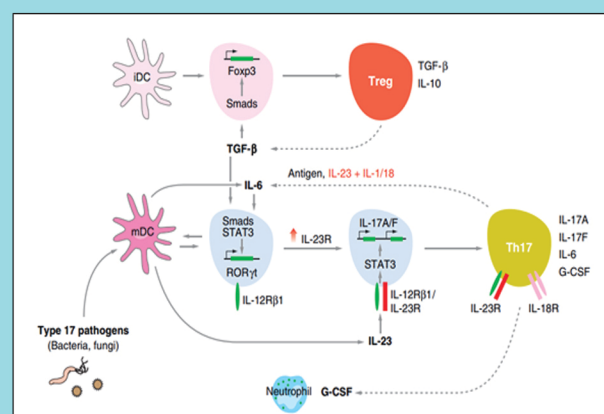


Figure 3. Simplified model of IL-23-mediated Th17 cell commitment during the development of IL-17 producing cells from naive T cells. IL-6 induces the expression of RORγt and IL-23R and prevents Treg differentiation

INTERLEUKIN-6

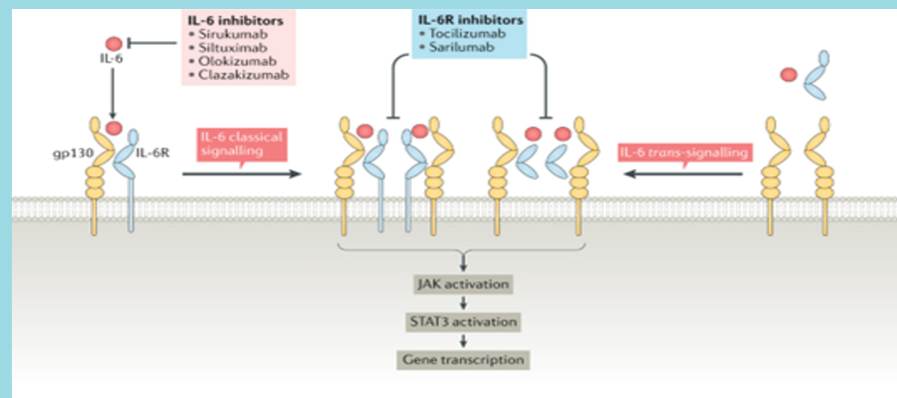


Figure 4. Simplified model of IL-6 signaling via IL-6R that forms a hexameric complex leading to downstream signaling to induce gene transcription of IL-6 effectors via upregulation of STAT3

IL-6 is important for the expression of RORγt and IL-23R in the differentiation of Th17 cells and therefore decreases Treg count, as shown in figure 3
IL-6 acts via the IL-6R and gp130 in a hexameric complex that can induce downstream signaling via the classical, transmembrane receptor-mediated, pathway or via the trans-signaling pathway, which is mediated by soluble IL-6R
Downstream signaling of IL-6 leads to STAT3 activation and thereupon target gene transcription (Figure 4)
IL-6 is associated with increased angiogenesis, which is a symptom of psoriasis leading to red plaques on the dermis

DISCUSSION

IL-6 axis targeting antibodies, such as tocilizumab, showed no efficacy in patients suffering from psoriasis
IL-17 axis targeting antibodies showed to be effective, such as brodalumab (IL-17RA specific), but demonstrated severe side effects such as suicidal thoughts and depression
This implies these targets might not be appropriate to inhibit in order to treat moderate-to-severe plaque psoriasis
Guselkumab, an IL-23(p19) specific antibody showed great efficacy, which is mostly explained by the upstream occurrence of IL-23 in the excessive IL-17 production in psoriasis
However, whether this will be effective on the long term still requires additional data
Moreover, research also evaluates the drug utility of computationally designed small molecules to overcome the disadvantages of biologicals, such as limited uptake, high costs, low production yield and very specific storage conditions
The urgency for further research is highlighted

