

# PSORIASIS AND INTERLEUKIN-MEDIATED CHRONIC INFLAMMATION:

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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 autoimmune 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 Figure 1. Psoriatic plaques on the skin of a severe arthritis

There is still no cure for psoriais, thus the relevance for further research is emphasized





plaque psoriasis patient

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

## **INTERLEUKIN-17**

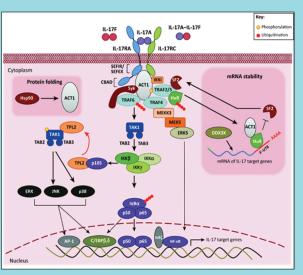
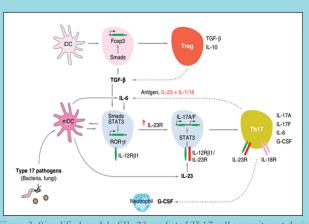


Figure 2. Simplified model of downstream signaling of IL-17RA receptor after activation via IL-17A, IL-17F or IL-17A/F.

IL-17 is a cytokine produced by Th17 cells to and occurs in dimer formation of subclasses A and F: IL-17A, IL-17F and IL-17A/F IL-17 binds to IL-17 receptor (IL-17R) type C which induces the spatial organization for correct IL-17 to bind to IL-17RA IL-17RA signals via its intracellular domains to initiate the NF-κB or MAPK pathway, which leads to IL-17-target cell DNA transcription of pro-inflammatory molecules, cytokines (IL-6) and chemokines for the attraction of macrophages and neutrohpils (Figure 2)

## **INTERLEUKIN-23**



the development of IL-17 producing cells from naive T cells. IL-6 induces the expression of RORyt and IL-23R and prevents Treg differentiation

IL-23 is involved in the cell commitment during Th17 cell differentation from naive T cells (Figure 3)

This process is mediated by the expression

However, also IL-6 can be produced by IL-17 effector cells in a positive feedback mechanism to aid in the cultivation of Th17

IL-23 is upstream for IL-17 signaling and inhibiting this target might block both the IL-17RA and IL-17RC axis

IL-6 inhibits Treg differentation, as together Figure 3. Simplified model of IL-23-mediated Th17 cell commitment during with TGF-β, it leads to the cell development into an IL-17-secreting phenotype

### **INTERLEUKIN-6**

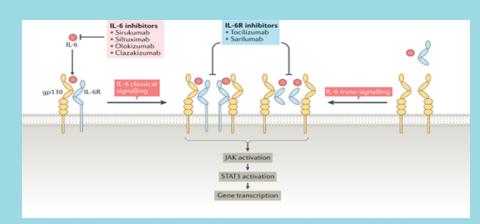


Figure 4. Simplified model of IL-6 signaling via IL-6R that forms a hexameric complex leading to downstream signaling to induce gene transcription of IL-6 effectors via upregulation of STAT3

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 angiogensis, which is a symptom of psoriasis leading to red plaques on the dermis

# DISCUSSION

IL-6 axis targeting antibodies, such as tocilizumab, showed no IL-17 axis targeting antibodies showed to be effective, such as efficacy in patients suffering from psoriasis 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 ustream occurence of IL-23 in the excessive IL-17 production in psoriasis However, whether this will be effective on the long term still

Moreover, research also evaluates the drug utility of computationally designed small molecules to overcome the disadvanrequires additional data tages of biologicals, such as limited uptake, high costs, low production yield and very specific storage conditions The urgency for further research is highlighted





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