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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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D. F. G. Guelen (S3809579)

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Supervisors: A. Domling & M. Hadian

ABSTRACT

IL-17 and IL-6 are cytokines that are important for the homeostasis of the immune system and are affected in the pathology of plaque-type psoriasis, which is a chronic auto-immune disease that is associated with several comorbidities and currently cannot be fully cured with treatment options that are available. Thus, it is important to understand the causal biology of plaque psoriasis and investigate the roles of IL-17 and IL-6. Therefore, this review article and thesis provides a thorough and concise overview on the IL-17 and IL-6 signaling pathways specified to moderate-to-severe plaque psoriasis in respect of their clinical and pharmacological relevance and discusses the current treatment and promising developments that are in prospect. Furthermore, it provides an insight on the structural information that is available about these targets and specifies to the most common monoclonal antibody therapies that are utilized for the application of psoriasis. Moreover, this article evaluates the inextricable link between these cytokines and therefore also attempts to emphasize the axis of IL-23, which is a cytokine important in the IL-6-induced Th17 cell development and therefore also is indirectly linked to Th17-secreted IL-17, which is upregulated in psoriasis. Pharmacotherapy with antibodies targeting this signaling route are also discussed, as biologicals have realized groundbreaking innovations for the treatment of psoriasis. However, the use of antibodies might not be ideal for their cost, production processes and yield, tissue-limited bioavailability and strict storage conditions. Therefore, the shift towards a computational design of small molecules to target the pathological axes in the disease is argued with respect to newest innovations.

INTRODUCTION

Psoriasis in general

The immune system plays a role in nearly all pathologies, whether it is for conditions in which the immune system is overresponsive, such as autoimmune diseases like lupus or rheumatoid arthritis, or conditions in which the immune system is insufficient, such as cancer or AIDS. Furthermore, complete curation of patients with the abovementioned diseases is not always possible with the current treatment options. Hence, needless to say, understanding the general human immune system and immunopharmacological pathways that are involved in pathologies is of great relevance for development of pharmacotherapy. Moreover, this knowledge is required for obtaining an even more thorough perception of how certain drugs can modify the immune system. An example of such class of drugs are glucocorticosteroids which act as immunosuppressants.[1]

Another condition which is inextricably linked to the human immune system is psoriasis. Psoriasis is a chronic auto-immune disease affecting about 2% of the world population[2], which are approximately 125.000.000 people worldwide. The disease manifests itself in different ways. The most common variant is psoriasis vulgaris, or also called plaque(-type) psoriasis, of which an example is shown in figure 1.[3] In this type of pathology erythematous plaques which are sharply bordered and have scales that are silver coloured can be varyingly present on the skin of the head, torso and the extensor area of the limbs.[4] These symptoms are originating from an excessive proliferation of keratinocytes, excessive recruitment of T lymphocytes and neutrophils in the dermis and epidermis and a deficient proliferation and differentiation of the blood vessels in the skin.[5] These symptoms can be measured using an adapted quantitative evaluation model specific for psoriasis which is called the Psoriasis Area and Severity Index (PASI) score.[6] This score says something about the total body coverage and severity of the plaques and is often used to assess the efficiency of a drug in clinical trials. Often a PASI50 or PASI75 score are used as endpoint in studies, which imply that there is a reduction of 50% or 75% in the PASI score compared to the initial PASI score, respectively.[7] However, currently also often a PASI100 or PASI90 score are used as endpoints for clinical trials.[8] Moreover, the initial disease state can be classified in three categories from mild, moderate to severe, when the body is affected for less than 3%, 3 to 10% or more than 10%, respectively. This is

comparable to an initial PASI score of less than 10 for mild forms of psoriasis, while moderate and severe disease have a greater score.[9] These classifications are important to take into account when considering harsher treatment options.

However, until today no cure for psoriasis has been discovered due to the insufficient understanding of the molecular pathways involved in the pathology. Therefore, current treatment mainly focusses on alleviating and circumscribing symptoms. Nonetheless, the relevance for a cure is highlighted by the information that psoriasis can be a very painful condition which affects the quality of life of patients mentally, but also physically as acute flares can be extremely dangerous and psoriasis comes with several comorbidities.[10] Certain of these comorbidities are psoriatic arthritis, metabolic syndrome (e.g. obesity), cancer, infections or (severe) psychological problems. To illustrate, people with psoriasis are frequently obese and research has established evidence to reinforce this observation, as obesity has proven to increase the likelihood of developing psoriasis.[11] Moreover, weight reduction has demonstrated to improve the severity of psoriasis.[12] Thus, as an adequate cure is lacking, lifestyle intervention might be a considerate additive treatment option for specific cases. Another example demonstrates a clear correlation between psoriasis and infections, especially a specific type of psoriasis called guttate psoriasis, manifesting itself in acute flares of disease is often linked with *Staphylococcus aureus* infections.[13,14] Therefore, there is an unmet need to cure psoriasis.

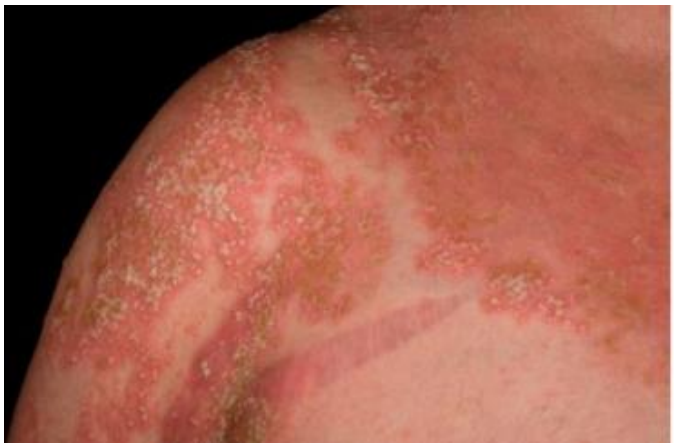

Figure 1. Example of severe plaque psoriasis with manifestations to the shoulder, chest and extensor part of the arm. This figure was taken from the research article by Rendon, A. & Schäkel, K. (2019).

Psoriasis and genetics

The genetic profile of a person is predominant in the occurrence of psoriasis and for diseases with a genetic predisposition, understanding these genetics is principal to design new agents that are suitable for pharmacotherapy. With this knowledge the causal biology can be unraveled, which has proven to be key to drug approval when molecules are still in the pipeline of drug development. For instance, AstraZeneca has released a report stating that the probability of drug development being successful was about twice as high when there was genetic information available compared to situations where there was none.[15] Therefore, it is also important to take into account what are all the genetic factors that play a role in psoriasis.

The disease can be inherited via complicated mechanisms involving 9 important loci that are called psoriasis susceptibility 1 to 9, or also PSORS1 to PSORS9.[16] Of these genetic axes, PSORS1, on chromosome 6, is most determinant for inheritance of the pathology. This loci encapsulates the HLA-C gene, which belongs to the Major Histocompatibility Complex (MHC) Class I receptors. The identification of this gene was performed by several case-control studies which indicated that there is a higher prevalence of antigen HLA-Cw6 in patients with psoriasis compared to healthy individuals.[17,18]

In addition, HLA-C has been evaluated as the most crucial genetic factor in occurrence of psoriasis in a genome wide association study in 2010.[19] In this study many genes were scored on their contribution to develop psoriasis and plotted in a Manhattan plot according to their relative prevalence. Although HLA-C currently does not have a clear drug utility[20], which might be assigned to the important function it has in immune responses and therefore cannot easily be targeted without the occurrence of adverse side effects, it still provides information on the onset of the disease and that there is a correlation with antigen presentation by T cells.

To illustrate once more the essence of understanding the causal biology, this study also identified Tyrosine Kinase 2 (TYK2) as a 'top gene' indicating it occurred frequently in patients with psoriasis. Nevertheless, TYK2 is generally recognized for its role in antiviral defenses, as for instance it is crucial in fighting off CMV infections.[21] This is interesting as TYK2 inhibitors has demonstrated to exert a beneficial effect on the PASI score of patients, being one of the most effective oral treatments that can be used for plaque psoriasis, having a beneficial effect that might be compared with that of biosimilars. In particular, the novel agent deucravacitinib, which is a specific TYK2 inhibitor, also has shown to be of great use in psoriasis. Administration of this therapeutic agent lead to a PASI 75 after 12 weeks for 67% to 75% of patients with plaque psoriasis compared to 7% for patients with a placebo, but has recently also been labelled as a proper treatment for psoriatic arthritis without having detrimental side-effects.[22] The pharmacological pathways leading to the clinical relevance of TYK2 inhibitors are mainly founded on the circumvention of IL-23 signaling, which is also mediated by this family of tyrosine kinases. IL-23 signaling is important in psoriasis and will be discussed in more detail.

However, psoriasis is an illness with a complicated mechanism and that mechanism is different in all patients. Therefore, genetic information also serves the purpose of supporting personalized medicine. To illustrate, in cases of generalized pustular psoriasis, IL-36 is very important in the pathological picture and therefore it is also very distinct from plaque psoriasis. This is the reason why also biologicals are almost ineffective in this genetically unassociated type of psoriasis.[23]

Psoriasis and conventional to current treatment

In summary, a lot of new agents are being designed for psoriasis, but to understand what drugs are valuable to invest in, it is also important to understand the more conventional treatment for psoriasis and why this is insufficient. Many anti-psoriatic drugs focus on antagonizing inflammatory factors, since psoriasis is an inflammatory auto-immune disease. However, the inhibition of these general anti-inflammatory mediators lead to serious side effects and also often is not specific enough to yield a proper prognosis for patients with severe types of psoriasis. Initially, small molecules that non-specifically target the human immune system were dispensed to patients, such as methotrexate, which only yielded a PASI75 of about 40%. Methotrexate causes an elevated level of apoptosis of T cells upon inhibiting the dihydrofolate reductase, leading indirectly to the uncoupling of nitric oxide synthase.[24] However, methotrexate decreases the general activity of the human immune system, which is dangerous as there will be an elevated chance to develop infections and therefore is not the most suitable solution to treat psoriasis.

However, dermal treatments were also used a lot for psoriasis, such as hydroxyurea and retinoids, which can still be sufficient sometimes in mild disease manifestations. However, when it was understood that the disease is not merely topical, a shift of focus towards systemic treatments had occurred. Therefore, biologicals that target T cells, since psoriasis is mainly T cell mediated, gained more attention in respect to plaque psoriasis, as well as smaller molecules such as cyclosporine A. Cyclosporine is a calcineurin inhibitor, which therefore prevents transcription of pro-inflammatory cytokines in T cells and therefore diminishes the inflammatory response in patients with psoriasis.[25] However, when biologics appeared, the utility for cyclosporine soon declined. This started with the marketing of alefacept, which is a fusion protein that is specific for the cluster of differentiation 2

(CD2), which is a cell adhesion molecule, and via this mechanism the agent inhibits T cell activation. Moreover, it acts as a promoter for apoptosis in memory T lymphocytes.[26] Moreover, antibodies targeting TNFα, which is a pro-inflammatory mediator that also plays a role in immune responses and inflammation, were also used as first-line biological therapy. These antibodies are infliximab, adalimumab, but also etanercept was used, which is a molecule that is comprised of a ligand binding cassette attached to a human immunoglobulin G (IgG) Fragment crystallizable (Fc) region.[27] Adalimumab was brought to the market in 2005 for psoriatic arthritis and three years afterwards it was also approved for the application of psoriasis.[28] Infliximab was approved in 2006, and as well as adalimumab it neutralizes TNFα in both soluble and membrane-bound form, although infliximab has proven to have a greater outcome on patients.[29,30] However, the use of TNFα inhibitors comes with the great risk of anti-drug-antibodies, which is a serious limitation for the application of these agents.[31] Because of these reasons, the need for new therapeutic agents is large. However, there are a lot of novel developments and elaboration on the specifications of these drugs will follow in this report.

Next to the use of pharmacotherapy there are also other ways to treat psoriasis like phototherapy. This is a type of therapy where UVB or psoralen plus ultraviolet A (PUVA) radiation with specific wavelengths is emitted and absorbed by the skin of the patient to improve the intensity of the psoriatic plaques. This can be provided in combination with pharmacotherapy or as monotherapy. However, phototherapy has a lot of side effects, as it elevates the risk to develop skin cancer, it can cause skin burns, itches and dryness and also certain types of infections. Moreover, frequent therapy sessions are required in order to be effective and the immune system is not targeted systemically. Therefore phototherapy is also not considered to be the most efficient treatment.[32]

Onset and maintenance of psoriasis

As previously stated the current treatment for psoriasis has not shown great efficacy or either has serious adverse effect. Therefore, it is important to consider the traditional view on the onset and maintenance of psoriasis. The initiation occurs when the keratinocytes encounter stress and release DNA in the epidermis, which forms a complex with cathelicidin that is co-released. This complex is known to have an affinity for the toll-like receptor subtype 9 that are on specific dendritic cells called plasmacytoid dendritic cells. Subsequently, interferons, TNFα and certain interleukins, such as interleukin 6 (IL-6) are released to promote myeloid dendritic cell migration to the lymph nodes to facilitate the production of TNFα, interleukin-23 (IL-23) and other interleukins by naïve T cells. Thereupon, these cytokines stimulate the differentiation of T cells into active T helper cells of subtype 1, 17 and 22. These cells migrate to the site of inflammation and release more pro-inflammatory mediators like interferon-γ, TNFα and interleukin 17A/F.[33] This event is what leads to the excessive proliferation of the keratinocytes and effects on the blood vessels like local angiogenesis and dilatation. The keratinocytes will in turn produce inflammatory cytokines that reinforces the activation of local T lymphocytes in the dermis and is thereby maintained via a constant positive feedback mechanism. Moreover, macrophages and neutrophils are attracted to these sites of inflammation which further deteriorate the situation.[34]

Psoriasis and IL-17/IL-6

IL-17 and IL-6 are cytokines that play a role in the onset and maintenance of psoriasis as abovementioned. However, they are not only associated with and secreted by the T helper lymphocytes, but also with cytotoxic T cells, γδ T cells and also natural killer cells, in particular for IL-17A. Moreover, not merely lymphocytes are involved in IL-17 signaling, but also mast cells, macrophages, neutrophils, dendritic cells and keratinocytes.[35,36] Therefore, IL-17 and IL-6 might have a promising potential to become an adequate drug target in the treatment of psoriasis, due to their

broad spectrum of effector functions which are specific to the pathogenic pathways involved in plaque psoriasis.

Since IL-17 and IL-6 are such distinct mediators in plaque psoriasis, this review article will focus on current developments in pharmaceutical research that are merely addressing these factors and molecules that are closely related to these cytokines. Therefore, the biology of IL-17 and IL-6 signaling will be discussed in detail. Moreover, pharmaceutical agents that are currently in the pipeline for psoriasis will be examined based on their pharmacology, their latest clinical results and their side effects. Moreover, a comparison of drug development by structure based engineering versus the use of biologicals will be mentioned to find out what type of development route is most efficient and effective for psoriasis.

INTERLEUKIN-17

Pharmacological effects and intracellular downstream signaling

Interleukin 17 (IL-17) is a cytokine produced by CD4+ T helper 17 (Th17) cells and is endogenously secreted for its pro-inflammatory effects. Th17 cells are cultivated via IL-23, which is secreted by antigen presenting cells, such as dendritic cells and macrophages.[37] Th17 cells are important in immune responses and have only been discovered less than 20 years ago, when it was believed that merely Th1 and Th2 cells were the mediators of immune responses such as for patients suffering from psoriasis.[38] This outdated belief was founded on the presence of Th1-secreted cytokines, such as IL-12 and TNFα, in patients with psoriasis. Moreover, a monoclonal antibody directed against IL-12 which showed significant efficacy (ustekinumab) therefore also supported this idea. Ustekinumab, branded as STELARA®, is specific for the P40 protein subunit which both IL-12 and IL-23 contain. However, the therapeutic effect was not induced by neutralizing IL-12, as formerly believed, but upon antagonizing IL-23 and thereby undermining the activation of Th17 cells.[39] Evidence for this was established in the middle of the 2000s as IL-23 mRNA was discovered to be upregulated in human patients suffering from lesional psoriasis.[40] Moreover, as IL-23 is closely related to IL-17, the pharmacology involved in psoriasis became clearer. Importantly to notice, IL-17 has also been identified to occur as homologs in certain specific fish species, implicating it had been developed before evolution of vertebrates, whereas Th2 secreted cytokines have only been found in vertebrates and therefore only occurred later in nature. This suggests that IL-17 has a foundational role in interlocking the innate with the adaptive immune system.[41,42]

From all six various subtypes of IL-17 (i.e. A – F), IL-17A shows greatest homology with IL-17F. Both proteins can dimerize to form homodimers, but IL-17A and IL-17F can form a heterodimer as well, which is shown in figure 1, where on the left the homodimer of IL-17A is shown and on the right the heterodimer is visualized. For the IL-17A homodimer can be observed that it is very symmetrical. The dimerization of these cytokines can be facilitated upon formation of disulfide linkages when the monomers are positioned in a parallel fashion, which can also be seen in figure 2 shown as yellow sticks in the model.[43,44] Furthermore, the IL-17F protein is part of the cysteine knot protein family, thereby inherently exhibiting an uncommon design of disulfide bridges that are located also within the amino acid chain.[45] Moreover, IL-17A and IL-17F have a broad endogenous effect due to the wide extend of IL-17R expression, as stated previously. IL-17A and IL-17F are inducers of the production of CXC chemokines (such as CXC8 (IL-8)), IL-6 and specific colony-stimulating factors in order to recruit neutrophils and also cause activation. Therefore, this event is arranged by T cells which are crucial in the IL-17 signaling axis. In addition, IL-17A and IL-17F can also cooperate with other pro-inflammatory factors, such as TNFα and IL-1, as their biological effect is reinforced by co-secretion of these mediators. Contrariwise, also certain types of IL-17, IL-17B and IL-17C, can increase the production of the same pro-inflammatory mediators by IL-17RA lacking macrophages. Furthermore, IL-17E (IL-25) is important for chemokine production, in contrast to IL-17A/F, which subsequently causes eosinophil attraction, but also production of cytokines that are associated with Th2 responses. Therefore, IL-17 subtypes are both involved in certain allergic responses that are generally Th2-mediated, but also in recruitment of neutrophils via IL-17RA/F.[45] Other classes of the IL-17 family can have synergistic effects in psoriatic inflammation, such as keratinocyte-produced IL-17C that can amplify the effects of TNFα, which is shown by transgenic IL-17C mice that suffered from inflammation similar to psoriasis.[46,47]

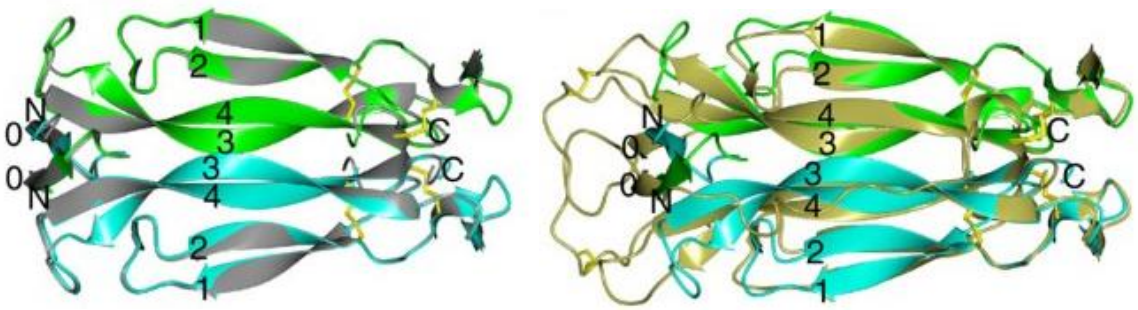

Figure 2. Simplified model of the quaternary structure of the IL-17A homodimer (left) and the IL-17A/F heterodimer (right). This image was taken from the research article by Liu, S., et al. (2013).

Both IL-17A and IL-17F bind to the IL-17 receptor (IL-17R), that are expressed in an omnipresent pattern. Moreover, they bind specifically to the IL-17R type A (IL-17RA), as shown in figure 3, where IL-17A has a significantly higher affinity for the receptor.[48] The IL-17 receptor exists in only five subclasses of transmembrane glycoproteins, from which all variants except IL-17RA has a variant which is created upon alterative splicing. This alternative splicing leads to occurrence of stop codons before the protein has been completely synthesized and therefore it is not incorporated in the membrane, which presumably leads to decoy formation. This means that there are soluble cytokine receptors can antagonize the actual receptor's ligand upon conservation of the binding domain.[48] However, the transmembrane IL-17 receptors are expressed in complexes that can change its structure due to agonist binding. Thereafter, the new conformation leads to detachment of the intracellular parts of the receptor which are suggested to cause further downstream pathways to be activated.[49] However, there is no evidence available for the IL-17R subtypes to be catalytic, which therefore gave rise to the hypothesis of a heteromeric receptor complex with a signaling domain exerting effector functions with a cascade second messengers. Thereupon, a new evaluation indicated that the IL-17RA could form a heteromeric complex with IL-17R type C (IL-17RC), which equally binds to IL-17A and Il-17F, and thus indicated that the exact mechanism from ligand binding to downstream signaling was more complicated than formerly believed.[50] However, this occurs only *in vitro*, as X-ray data revealed that asymmetric complexes of only one receptor type of the IL-17R family and a homodimer or heterodimer of IL-17A and IL-17F. Therefore, it was proposed that the cytokine is conformationally or spatially changes upon binding to one receptor and this is also induced by the receptor. Therefore, a second cytokine specific receptor, in case of spatial reorganization, cannot very easily bind to the other side of the homo-/heterodimer, in order to provide an appropriate binding site for a coreceptor that can subsequently initiate downstream signaling.[51] The coreceptor can be an IL-17R of a different type. To elaborate on this, research has established evidence for the formation of heteromeric IL-17RA and IL-17RC complexes (IL-17RA:IL-17RC), as depicted in figure 4. These complexes are built upon binding of a IL-17A/F hetero-/homodimer to the IL-17RC, which is the cytokine specific receptor and is a tall receptor. Thereupon, the complex changes to recruit an IL-17RA, which are small receptors. The change of spatial conformation drives the downstream signaling via the IL-17RA, as IL-17RA has an extended cytoplasmic region called the CBAD domain which is attached to the SEFIR domain, which is a cytoplasmic sequence segment that is involved in intracellular signaling.[52] By creating such heteromeric asymmetric complexes, the binding of homotypic multimers of IL-17RA is undermined, for it is ineffectual. Moreover, IL-17RA induces a structural change to the cytokine when it is bound, whereas IL-17RC does not, which means that an IL-17 cytokine cannot be bound to two IL-17RA, but can be bound to two IL-17RC without exerting an effect. However, there is a preferred equilibrium pending towards the formation of the heteromeric complex, as IL-17RA has a greater affinity for IL-17A, compared to IL-17RC. This may provide rationale for the difference in biological activity between IL-17A and IL-17F.[53] In this way, the ratio of IL-17RA and IL-17RC cell expression is a crucial component in determining whether the signal transduction will be mediated via the IL-17RC homomeric complex or the IL-17RA:IL-17RC complex. This is important as both cytokines IL-17A and IL-17F have previously demonstrated to have the opposite effect in inflammatory bowel disease

(IBD), where IL-17A is beneficial and IL-17F is detrimental for the intestinal health.[54] Notably, monoclonal antibodies targeting the IL-17RA specifically (brodalumab), have not been effective in treating IBD. However, now can be understood that this might be due to an inhibited heteromeric complex signaling, but a unaffected IL-17RC homomeric complex signaling pathway, which is therefore presumed to be essential in the pathology of IBD. Moreover, this is confirmed by the proven efficacy of IL-23 specific antibodies, which thus also circumvents the IL-17RC homomeric complex. Note that this is particularly true for IL-17F homodimers, due to their equal affinity for the IL-17RC subclass.[55,56] Furthermore, this hypothesis is once more fortified by the observation that IL-17A gene knockout mice showed a phenotype in which IL-17F was not able to counterbalance for the lack of IL-17A, thereby founding the principle of the heteromeric complex formation.[57] However, this might not completely be applicable to psoriasis, as brodalumab has shown to be therapeutically effective, as will be discussed in the subchapter below, but understanding these mechanisms is important for ameliorating drug design for plaque psoriasis, for which the pathology is expected to tend to an IL-17RA downstream axis as this is in accordance with the abovementioned argument.

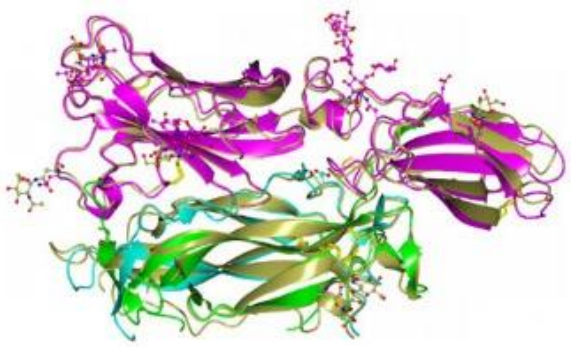

Figure 3. Simplified model of the protein-protein interaction between the IL-17RA (in purple) with the IL-17A/F heterodimer (in green/gold/blue, as in figure 2). This figure was taken by the research article by Liu, S., et al. (2013).

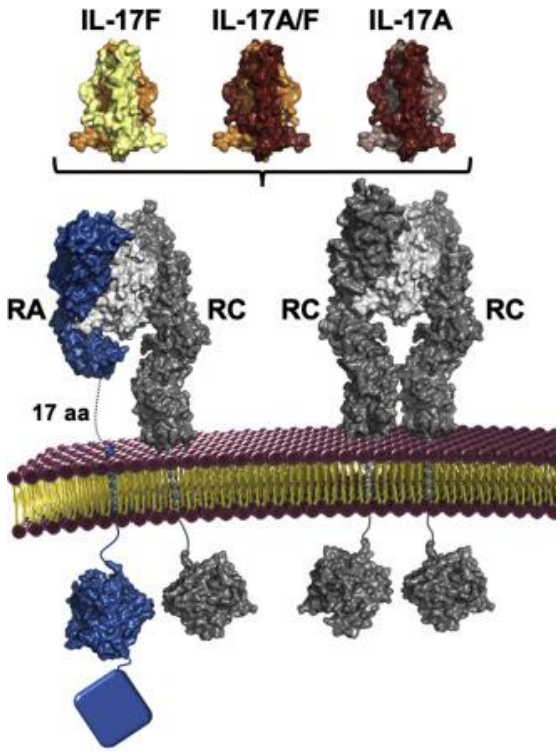

Figure 4. Model of the interactions with IL-17A, IL-17F and IL-17A/F with the IL-17RA and IL-17RC heteromeric complex or the IL-17RC homomeric complex. IL-17RA is depicted in blue, whereas IL-17RC is depicted in grey. The SEFIR-domain is depicted in the intracellular part at the bottom of the figure and the extended SEFIR domain, the CBAD domain is shown as blue square underneath the SEFIR domain of the IL-17RA. This picture was taken from the research article by Goepfert, A., et al. (2019).

Therefore, it is important to take into account the exact signal pathways that lead to inflammation in the disease (Figure 5). The extended SEFIR domain of IL-17RA is able to have molecular interactions with Act1, which is an adaptor molecule that shows binding with TNF receptor associated factor 6 (TRAF6) and thereby it leads to activation of the NF-κB or mitogen activated protein kinase (MAPK) pathways.[58] Therefore, the downstream effects of IL-17 signaling is mainly postulated to be via the route of either NF-κB or MAPK. The exact pathway to activation of NF-κB is explained by a specific domain that occurs in the protein structure of Act1, for which also heat shock protein 90 (Hsp90) is necessary to induce proper protein folding. Act1 contains a U-box domain that is analogous to a part of the E3-ubiquitin ligase protein structure. This means that Act1 can couple activated ubiquitin that is carried by the ubiquitin conjugating enzyme (E2) to other proteins. Ubiquitin attachment can be done to label proteins for degradation by the proteasome, but it can also facilitate certain protein-protein interactions when it is coupled to specific lysine residues (the 48th and 63rd residues). In the case of TRAF6, it is ubiquitinated at Lys63, which is thus caused by the U-box domain of Act1, which is required for NF-κB activation. Moreover, Act1 has two domains that can bind TRAF, but also a domain that can interact with IKK, which is an IkB kinase. IkB is a protein that endogenously binds NF-κB in the cytoplasm and inhibits its downstream pathway. However, IKK can phosphorylate IkB in order to detach NF-κB. Furthermore, TRAF6 undergoes interactions with another protein called TAK1, when it is bound to Act1, which causes activation of the IKK in order to initiate the signal cascade. TAK1, which is an abbreviation for TGFβ activated kinase 1, ultimately leads to the activation of IKK and thereupon indirectly to NF-κB upregulation.[58]

For the abovementioned reasons Act1 is an important mediator in psoriasis and also in other inflammatory auto-immune diseases. Experimental models of induced auto-immune diseases, such as experimental autoimmune encephalomyelitis (EAE), are circumvented when Act1 is lacking.[59] Paradoxally, research has demonstrated that a complete deficiency or a mutation of Act1 also can induce the establishment of auto-immune diseases.[58,60,61] Therefore, the protective or adverse effect

that Act1 can have is mainly determined by the cell type that is involved. Act1 is mainly involved in IL-17 signaling in macrophages, epithelial cells, endothelial cells and also fibroblasts. Therefore, antagonizing this would have a positive effect on the course of inflammation in psoriasis. However, in B cells, that also express IL-17RA and IL-17RC,[62] Act1 has been described as an important mediator in regulating the total cell population and in preventing auto-antibody synthesis and other immunopathologies.[63] Therefore, it can be of importance to consider the pleiotropic functions of Act1 during the development of agents that target the IL-17 signaling axis.

The NF-κB pathway is a route that can be initiated by several stimuli, of which IL-17signaling is an important one in the case of psoriasis. This is an example of the canonical pathway, in which stimuli cause the release of NF-κB from IkB upon activation of IKK.[64] The IkB family can bind to all five NF-κB subclasses: NF-κB1 (p50), NF-κB2 (p52), RelA (p65), RelB and c-Rel. These subclasses can form various dimers with each other to promote binding to specific sites on the DNA called kB enhancers and therefore promote pro-inflammatory gene transcription.[65] These genes are often encoding for pro-inflammatory cytokines or chemoattractants that play an important role of recruitment of neutrophils, macrophages, eosinophils and their activation as well as the activation of other immune cells that contribute to the inflammation. However, the exact genes that are transcribed will be discussed in more detail in the section about Th17 development and IL-17 effectors.

Moreover, the MAPK pathway also is activated upon IL-17 stimulation in keratinocytes. The MAPK pathway plays an important role in especially B cell migration towards the site of inflammation in accordance to production of Th17 cytokines. The p38 subunit of MAPK is mainly responsible for the downstream signals that lead to the attraction of B cells, as this was experimentally discovered by Rabih Halwani and colleagues who found that inhibition of this subunit lead to a diminished B cell migration in asthma .[66] However, B cells might also play an important role in psoriasis, as they have shown to also express the IL-17RA.[67] Furthermore, activation of MAPK also leads to several other effects, such as the production of cytokines. Moreover, in the MAPK pathway, p53, extracellular signal regulated kinase (ERK) and JUN N-terminal kinase (JNK) play a role, which can be observed from figure 5. This is initiated with the phosphorylation of p105 by IKK that leads to the detachment of TLP2 from p105. Via the classical route, the MAPK pathway leads to phosphorylation of a specific tyrosine containing motif in the ERK, JNK or p38 kinase that activate the AP-1 protein, which is a transcriptional activator using 12-O-tetradecanoylphorbol-13-acetate, which is a phorbol ester tumor promotor.[68] This therefore leads to the production of pro-inflammatory mediators. However, the MAPK pathway that is promoted in case of IL-17R stimulation, also has different transcription factors that are additional to AP-1, which are the CCAAT/enhancer-binding protein (C/EBP) factors (C/EBPβ and C/EBPδ), for which also binding sites are expressed in large quantities on target genes for IL-17. Some cytokines need the additional C/EBPβ or C/EBPδ transcriptional factors for synthesis, such as IL-6.[69,70] Furthermore, there are other mechanisms that lead to an amplified functioning of IL-17, such as the cooperative effect with TNF-α upon inducing mRNA stabilization.[71]

Moreover, the p38MAPK/NF-κB pathways in psoriatic inflammation, that inherently leads to elevated IL-17A production, have demonstrated to also increase several inflammatory inflammation in the brain and caused depression-like symptoms in mice.[72] This therefore corresponds to the observed psychological effects in patients with moderate-to-severe psoriasis and emphasizes the clinical relevance of targeting these pathways.

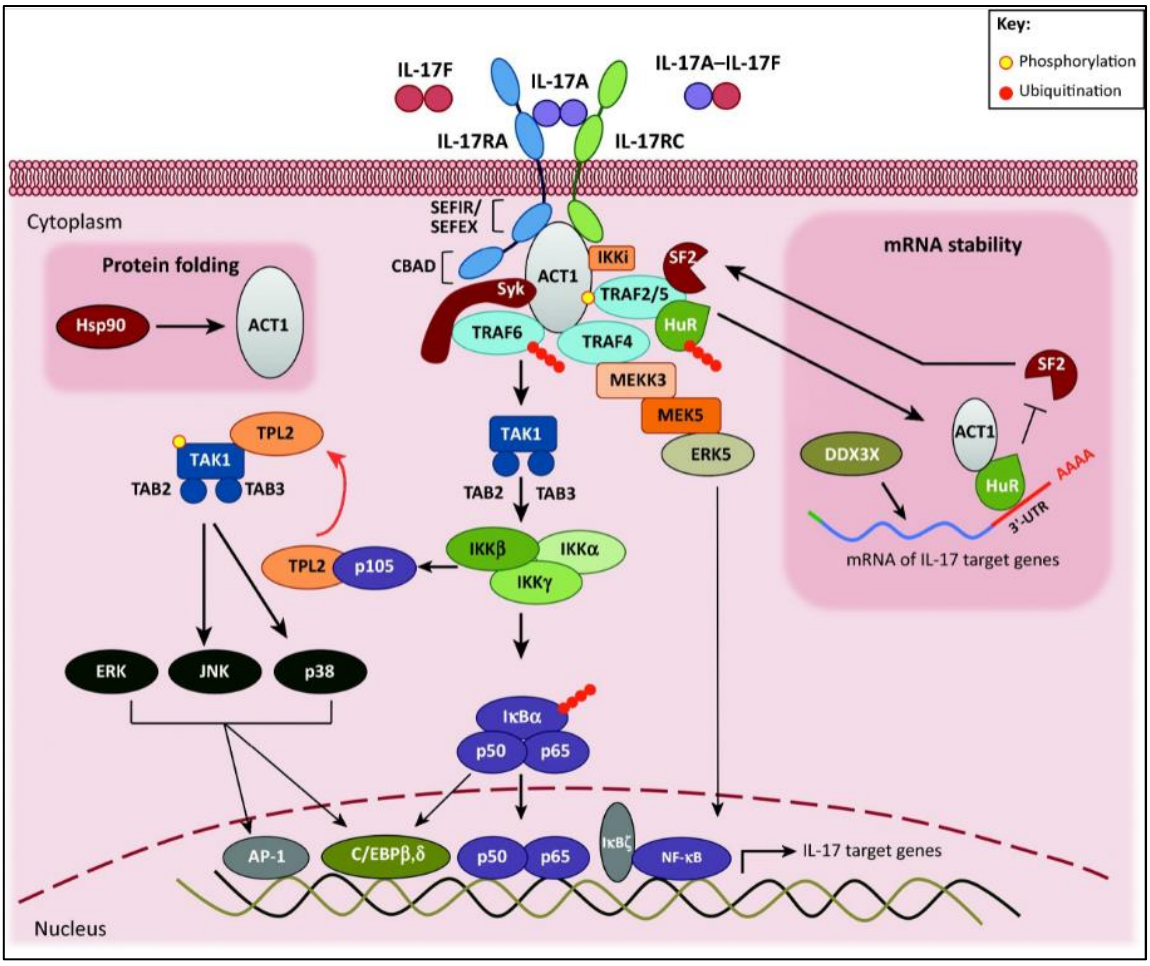

Figure 5. Schematic representation of immune cell downstream signaling routes involved in IL-17-induced transcription of pro-inflammatory target genes via the NF-κB and MAPK pathway. p50 = NF-κB1, p65 = RelA (part of NF-κB family). This figure was taken from the research article by Amatya, N., et al. (2017).

Biologicals for psoriasis targeting the IL-17 axis

Currently the emphasis on biologicals for the treatment of various pathologies is exponentially growing. The cause of this observation may be granted to the high specificity, clinical efficacy and possible dose optimization that is inherent to therapy with most biologicals.[73] Therefore also monoclonal antibodies have been designed in order to ameliorate conditions relating to IL-17A signaling. Two of these are ixekizumab (TALZ®) and secukinumab (COSENTYX®), which were approved by the U.S. Food and Drug Administration (FDA) in 2016 and 2015, respectively.[74] Both medicines target IL-17A and IL-17A homodimers, of which the dimer conformation is also recognized for its biological effect exerted via the IL-17RA.[75] Treatment with ixekizumab has also formerly demonstrated to yield greater benefit in patients with moderate to severe psoriasis compared to etanercept[76], which is a TNFα blocker that is used in clinical applications to treat plaque psoriasis.[77] This was an important new view on therapy for psoriasis, as TNFα inhibitors (TNFIs) previously had developed into first-line treatment for moderate to severe psoriasis, but it has proven not to be appropriate for several reasons. These reasons are that a substantial group of patients remains unresponsive to TNFI treatment, TNFI treatment causes immunosuppression with possible dangerous side effects, it can reactivate latent tuberculosis and it can induce a specific type of TNFα inhibitor-induced psoriasis.[78,79]

Nevertheless, both ixekizumab secukinumab did not prove to neutralize the heterodimer of IL-17A and IL-17F, which binds to the same receptor as the homodimer of IL-17A.[80] However, the

heterodimer also plays an important not to be neglected role in endogenous IL-17RA downstream signaling upon having the same effector functions. Therefore, also a monoclonal antibody was designed which targets both IL-17A and IL-17F. This IgG1 antibody is called bimekizumab and is planned for release at the end of this year.[81]

However, targeting the IL-17RA might seem like a more promising approach in treating psoriasis as thereby all the subclasses of IL-17 that can interact with the IL-17RA are prevented to exert their biological downstream effect. This was the reason why also a human monoclonal antibody called Brodalumab (SILIQ®) was developed and the FDA approved this agent in 2017 to treat plaque psoriasis.[82] Brodalumab showed efficacy as after 12 weeks only it showed a PASI75 of 83 to 86% during the phase three trials.[83] However, as it has a relatively non-specific effect by neutralizing IL-17RA, it also demonstrated to have more side effects, especially causing depression and suicidal thoughts. This was the reason to set up a specific program to inform all health professionals involved in dispensing and prescribing the drug as well as the patient about the risks that are inherent to therapy with Brodalumab, which is called the Siliq REMS Program.[84] Moreover, superficial candida infections were also more prevalent in patients who received this IL-17RA inhibitor, which is most probably explained by the important function IL-17 signaling has in human defense against fungal infections. However, this was indicated in the use of all agents targeting IL-17 and is commonly easy to treat.[85]

INTERLEUKIN-23 IN COOPERATION WITH TH17

Pharmacological effects of IL-23 and development of Th17 cells including IL-17 effectors

IL-23 plays an important role in the development of Th17 cells, and thereby indirectly enhances the pro-inflammatory response mediated by IL-17. This was experimentally demonstrated, due to the increased pathological response in murine CD4+ Th17 lymphocytes that were cultivated by IL-23 compared to murine Th1 cells cultivated by IL-12, as the first cell type showed severe development of EAE. Therefore, it was again confirmed that IL-17 is a key messenger in inflammatory auto-immune reactions. However, upon polarizing cells with Il-12, like the Th1 type, more expression of molecules associated with cytotoxicity could be observed, such as IFNγ and Fas Ligand (FasL), whereas for polarized Th17 cells, these molecules were mainly involved in chronic inflammatory responses, such as TNFα and the cytokine family of IL-17.[86] Moreover, the development of Th17 cells from naïve CD4+ T cells takes place independently from Th1 cells. Th1-produced IFNγ even causes inhibition of Th17 development. The same is true for the Th2-secreted IL-4 that inhibits differentiation of naive lymphocytes into Th17 cells, whereas IL-23 has no influence on the cultivation of Th1 or Th2. This implies that functioning of Th1 and Th2 cells also has a major influence on the development of Th17 cells, and therefore overexpression of IL-4 or IFNγ can also lead to a decreased production of IL-17.[87]

Moreover, the development of Th17 does not merely require IL-23 stimulation (Figure1). It requires initially the stimulation of naive CD4+ T cells by TGF-β, which is also the same for the development of regulatory T cells (Treg) from naive T cells. Thereupon, the second step in the initiation is the antigen presentation by either immature dendritic cells or mature dendritic cells for regulatory T cells or Th17 cells, respectively. This antigen presentation triggers the production of IL-6 by innate immune cells and together with TGF-β this leads to the expression of the nuclear receptor that is referred to as retinoic orphan receptor (ROR) γt in these lymphocytes and an increased transcription of IL-23 receptors (IL-23R). Moreover, for regulatory T cell development, this antigen presentation triggers the transcription of Forkhead Box P3 (Foxp3) and therefore ultimately the maturation of the Treg.[88] However, for development of Th17 cells, more steps are required. After elevated RORγt and IL-23R expression, IL-23 signaling is of relevance to the amplification after the commitment of Th17 cells, and therefore plays a role somewhat later in the developmental stages. Moreover, production of Th17 cytokines can thereupon occur and mediators such as IL-17A, IL-17F are secreted, but also G-CSF and IL-6, of which the first is an important chemokine for attraction of neutrophils and the latter is responsible for a positive feedback loop of Th17 cell development.[89] Moreover, the production of IL-17 by stimulation of IL-23 by itself is relatively low, as there is a system which is T cell receptor (TCR) independent that leads to an increased cytokine production upon co-stimulation with the factors IL-18 and IL-1β after the T cells have been committed upon TGF-β and IL-6 stimulation, which is also shown in figure 6. In other words, IL-23 acts as a mediator for final differentiation of the Th17 cells, which effectors can be amplified utilizing co-stimulation that is not dependent on TCR interaction, but which is important for the completeness of Th17 functioning and in summary this is facilitated by the interaction IL-23 has with immune cells that do not belong to the class of T lymphocytes.

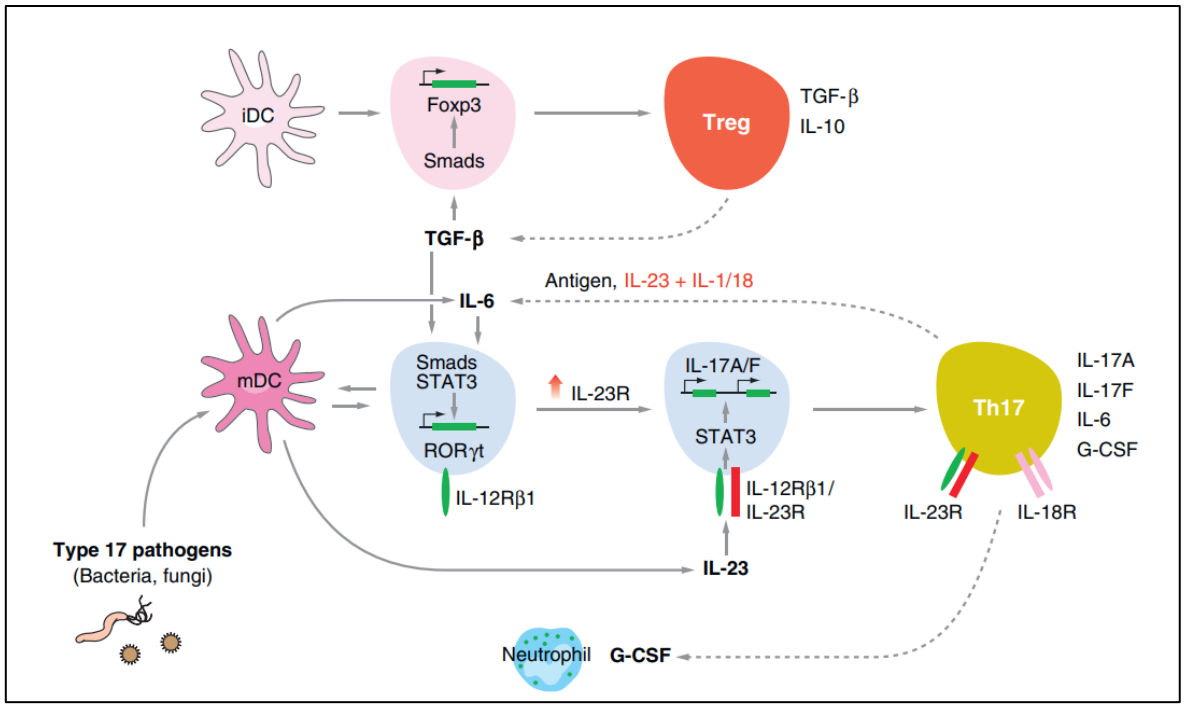

Figure 6. Schematic representation of the signaling pathways involved in Th17 cell development and Treg development. This figure was taken from the research article by Weaver, C. T., et al. (2007).

Biologicals for psoriasis targeting the IL-23 axis

The first biological that was specifically designed for its application in psoriasis was Ustekinumab, whereas other monoclonal antibodies were often first approved for other inflammatory diseases, such as rheumatoid arthritis or Crohn's disease. Ustekinumab was approved in 2009[90] and is an IL-12 antagonist as well as an IL-23 antagonist, due to its selectivity for the p40 subunit that is homologous between the two cytokines. Therefore, it also has a lot of side effects, such as an increased prevalence of different types of infections amongst patients who are administered with this drug.

Furthermore, the development of biologicals is currently still ongoing. Only in the last three years, two antibodies were approved that target the IL-23 p19 subunit: tildrakizumab (ILUMYA®, FDA approved 2018)[91] and risankizumab (SKYRIZI®, FDA approved 2019)[92]. Therefore, they do not interfere with the p40 subunit that is present on both IL-23 and IL-12 and this feature makes these antibodies more specific than the formerly used IL-23 antibody ustekinumab. Therefore, there is no altered Th1 cell signaling which causes less side effects, while being also more effective in the case of risankizumab.[93] Moreover, the first antibody targeted against the p19 subunit was released to the market in 2017, which was guselkumab (TREMFYA®)[94], and this already showed great efficacy in comparison with TNFα inhibitor treatment. Where adalimumab sowed a PASI90 at 16 weeks of 46.8% to 49.7%, guselkumab showed a score of 70% to 73.3% (versus approximately 3% for placebo).[95,96] Moreover, blocking the p19 subunit from IL-23 revealed to be a better treatment in CNS inflammation mediated by Th17 cells in comparison to blocking IL-17A.[97] This might be explained by the not yet fully understood axis of IL-17F that is untouched or additional effects of IL-23, but as IL-23 is a broad spectrum mediator, it remains unsure whether its blockade could possibly lead to an increased susceptibility to infections or to dysregulation of the appropriate immune response against pathogens.

INTERLEUKIN-6

Pharmacological effects and intracellular downstream signaling

For over three decades has been known that the pro-inflammatory cytokine IL-6 plays a large role in psoriasis, as this cytokine production by keratinocytes was found to be upregulated in the pathology and showing a clear correlation with keratinocyte proliferation that is inherent to psoriasis.[98] To elaborate on this, IL-6 is important for the homeostasis of IL-17 and Treg.[99] Moreover, IL-6 expression is induced by IL-17A[100], but it is also required for amplification of the Th17-mediated cytokine production, as discussed previously. Furthermore, IL-6 is secreted upon innate immune cells that have been activated due to pathogens via toll like receptors (TLR), causes the activation of naive CD4+ T cells into a pro-inflammatory phenotype of Th17 cells, which establishes a linkage of the innate with the adaptive immune system.[100] Next to keratinocytes and immune cells like macrophages, dendritic cells and Th17 cells, IL-6 is also produced by endothelial cells and fibroblasts. General effects of the cytokine are the proliferation of Th17 cells, as discussed previously, expression of adhesion molecules on endothelial cells, stimulation of cytokine and chemokine production and facilitating differentiation of neutrophils.[101] Moreover, the importance of IL-6 in the onset of psoriatic inflammation was experimentally demonstrated by a delayed onset of inflammation in IL-17C transgenic, IL-6 knockout mice compared to the same mice that expressed IL-6.[102] Additionally, as IL-6 facilitates Th17 cell commitment, but inhibits the Treg differentiation that is mediated by TGF-β (Figure 6 & 7), IL-6 overexpression is clearly correlated with a more prevalent induction of auto-immune diseases, such as multiple sclerosis and rheumatoid arthritis.[103] Furthermore, IL-6 has several other biological effects, such as upregulating RANK ligand (RANKL), that thereupon leads to resorption of bone matrix and this can have detrimental consequences, like causing osteoporosis. Moreover, IL-6 production leads to an increased synthesis of vascular endothelial growth factor (VEGF), which causes upregulation of angiogenesis and vascular permeability, which is in line with the visible symptoms of the disease, as redness of the skin is commonly caused by vasodilation in psoriatic patients.[104]

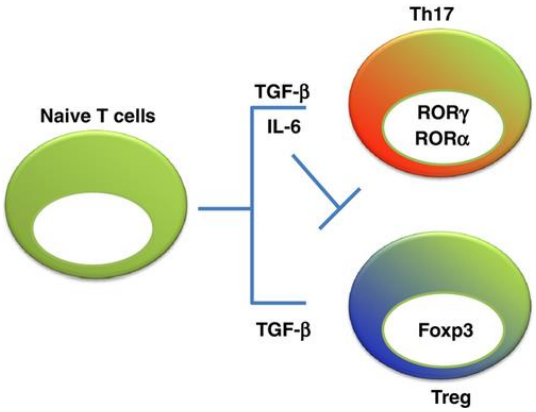

Figure 7. Simplified illustration of Th17 and Treg differentiation from naive T cells. This figure was taken from the research article by: Kimura, A. & Kishimoto, T. (2010).

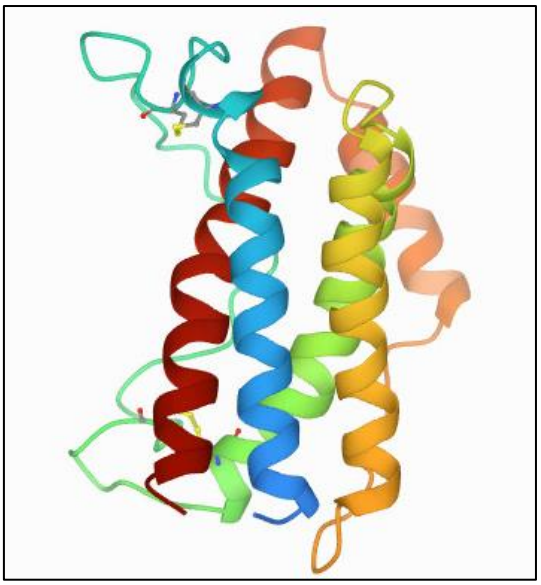

Figure 8. Schematic model of the tertiary protein structure of IL-6. This figure was taken from the research article by: Xu, G. Y., et al. (1997).

IL-6 (structure shown in figure 8)[105] is mostly secreted by dendritic cells and endothelial cells in the psoriatic lesions and can bind to the IL-6 receptor which is can be expressed as a soluble or transmembrane form. Therefore, IL-6 signaling can occur via the classical pathway via transmembrane receptors or via trans-signaling in case of the soluble receptors. Moreover, soluble and transmembrane receptors of the IL-6R class, together with IL-6 and glycoprotein130 are appreciated to from hexameric complexes (Figure 9). Because of the formation of such high affinity complexes, the synthesis of a small molecule targeting the IL-6 axis has been commonly perceived to be difficult.[106] Upon binding, the protein-protein interaction facilitates downstream signaling via the receptor subunit glycoprotein 130 (gp130), which has interactions with Janus kinases (JAK). These kinases are phosphorylated upon ligand binding to IL-6R and thereupon activate a family downstream signaling factors called the signal transducer and activator of transcription (STAT) class. In the case of IL-6R signaling, specifically STAT1 and STAT3 are activated, of which the latter leads to increased RORγt and RORα expression and therefore leads to commitment of Th17 cells. However, STAT1 normally inhibits this biological effect, that is shown by IL-27 and IFNγ that inhibit differentiation of Th17 cells via STAT1.[107,108] Nevertheless, the effect of STAT1 is blocked *in vivo* during IL-6 downstream signaling. Additionally, pathogenic IL-6-mediated signaling in psoriasis is hypothesized to be mainly via trans-signaling of the soluble IL-6R (sIL-6R) via the activation of STAT3. This was also demonstrated by the induction of psoriatic-like disease in mice after sIL-6R administration, but conversely the psoriatic symptoms were diminished upon administration of soluble glycoprotein 130 fusion protein (sgp130Fc) which is a selective antagonist for the IL-6 trans-signaling, proving the importance of the soluble IL-6 receptors in psoriasis.[109]

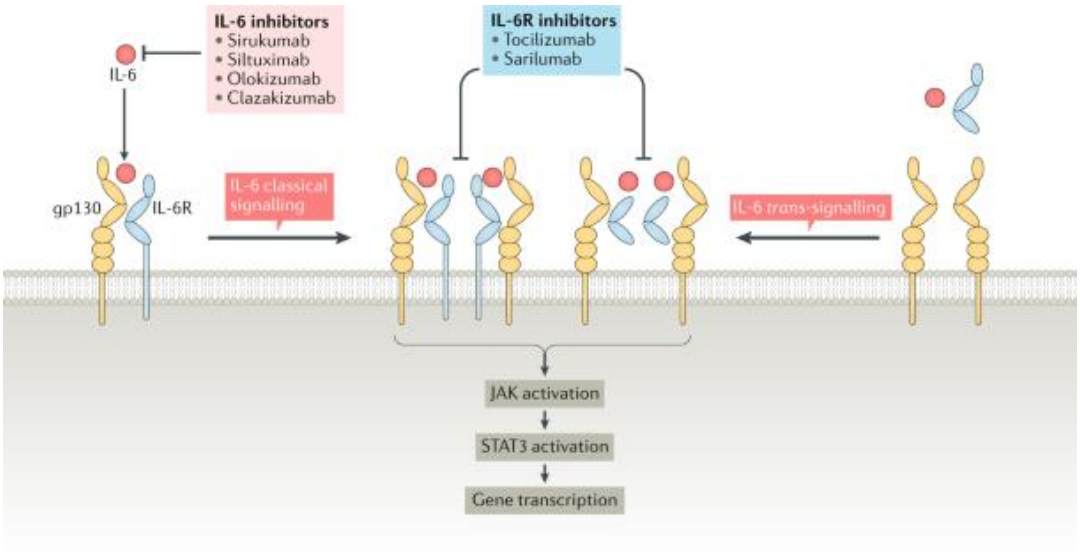

Figure 9. Simplified overview of IL-6 signaling pathway via the IL-6R upon activation via the classical route involving transmembrane receptors or via the trans-signaling route that involved the soluble receptor type. IL-6R receptor signaling takes place via hexameric complexes of IL-6, IL-6R and gp130. This figure was taken from the research article by: Choy, E. H., et al. (2020).

Biologicals for psoriasis targeting the IL-6 axis

Just over eleven years ago, tocilizumab (ACTEMRA®) was approved by the FDA, which is a monoclonal antibody targeting the IL-6 receptor (IL-6R).[110] The idea to design an IL-6R specific antibody was derived from the experimental evidence that IL-6 gene knockout mice were resistant to recombinant IL-23-induced psoriasis-like disease.[111] However, in patients with moderate-to-severe rheumatoid arthritis, for whom the drug was initially approved, psoriasis-like symptoms developed. Moreover, reportedly, the drug also demonstrated a very limited effect in psoriatic arthritis. This is particularly true for plaque psoriasis, which sometimes could even worsen upon utilizing anti-IL-6 drugs.[112,113] The latter may be dedicated to the pleiotropic effect of IL-6, which implies that IL-6 is necessary for various immune functions. Therefore, IL-6 imbalance is detrimental to adequate immune responses and inflammation. This is also demonstrated by the negative effect of clazakizumab, which is an IL-6 specific antibody that had been studied in 2016 to investigate its utility for psoriatic arthritis.[114] However, this antibody did not serve the purpose of treating patients with psoriasis and showed no effects of ameliorating plaque-type psoriasis, whereas several antibodies targeting the IL-6 axis did show to be effective in rheumatoid arthritis.[115] Moreover, tocilizumab also showed to decrease cytokine storm that is commonly caused by immunotherapy in cancer patients, which can be a life-threatening cascade of immune responses activated by the elevated activation of T cells.[116]

Thus, suggesting from all the data, it would be of greater importance to investigate the psoriasis-specific downstream effectors of IL-6 in order to discover utile drug targets. However, whereas IL-6 targeting antibodies might not be efficacious for psoriasis, it might have drug utility for viral infections, such as SARS-CoV-2 infections. Research has established that elevated IL-6 levels lead to a more severe pathology and COVID-19 prognosis.[117]

FROM SMALL MOLECULES TO BIOLOGICALS BACK TO SMALL MOLECULES

Therapy with biologicals has shown great clinical results in patients suffering from psoriasis, rheumatic arthritis and many other chronic inflammatory diseases. However, biologicals have several disadvantages which makes their application for psoriasis more challenging. These disadvantages are that biologicals are very costly medicines, their production process is difficult and can only yield small quantities, they can cause adverse immunogenicity (e.g. chimeric or non-human antibodies), their uptake in certain tissues is limited and they require very specific storage conditions as a consequence of their biological sensitivity.[118] Furthermore, using small molecules to inhibit certain pathogenic targets in psoriasis, the inhibitory effect can be maintained in a dose-dependent and time-dependent manner in order to keep levels of targets within healthy endogenous amounts, whereas biologicals most commonly neutralize the target, which thereupon required *de novo* transcription in order to exert its biological effect again. Therefore, the urgency of developing small molecules to treat moderate-to-severe psoriasis is emphasized. In correspondence with this information, research strays from using biological immunotherapies for applications of chronic inflammation due to auto-immune disease and also investigates the utility of computationally designed smaller molecules, as for example the use of macrocycles. Macrocycles were found potently inhibits the IL-17RA binding sites that are necessary for interaction with IL-17.[119] However, their clinical relevance still has to be evaluated and is to be established based on additional data. Moreover, there is still limited post marketing surveillance data available about targeting the IL-17 axis utilizing biologicals. Therefore, it remains equivocal to ascertain the significance of this segment of immunopharmacotherapy.

SUMMARY AND DISCUSSION

Psoriasis is a chronic auto-immune disease that is developed differentially amongst patients, of which the most common variant, plaque psoriasis, manifests itself in the occurrence of red plaques on the skin, clearly bordered by silver scales on various body parts. The pathology is associated with several comorbidities, such as psoriatic arthritis, severe psychological conditions, metabolic disorders, infections and cancer. Nevertheless, the disease is not yet fully curable and therefore development of new pharmaceutical agents in the application of plaque psoriasis urgently requires notice.

Treatment initially started with topical agents or phototherapy, but as soon as was discovered that the disease was not only a dermal condition, but was associated with the complete immune system, the focus has shifted towards systemic treatments merely.

Moreover, psoriasis can have different causes of which genetics play the largest role. In a genome wide association study by Strange, A. and colleagues from 2010[19] showed that HLA-C was the biggest determinant in the development of psoriasis, which encodes for an MHC class I type receptor and therefore this enabled the association with T cell antigen presentation dysfunctioning. However, due to the important role of T cell presentation in immunity and the versatility of this target, a drug utility is lacking. Nonetheless, genetic profiles also showed an altered transcription and translation of interleukins, of which in particular IL-17, IL-23 and IL-6. Mainly in plaque-type psoriasis these cytokines are of great importance.

IL-17 occurs in dimer formation, as a homodimer of subclass A, IL-17A, as a homodimer of subclass F, IL-17F, or as a combination of these two, IL-17A/F. IL-17 is secreted by mainly T helper cells, while there are also many other immune cells that are a source of IL-17. The biological effect of this cytokine is exerted via IL-17RA, the IL-17 receptor class A. However, IL-17 initially binds to IL-17RC, which is the cytokine specific coreceptor that is important for the spatial organization of IL-17 and thereby facilitates effectual binding to IL-17A via the formation of a heteromeric complex. Downstream signaling cascades are activated via the extended intracellular SEFIR domain of IL-17RA, the CBAD domain. This can trigger NF-κB or MAP kinase signaling pathways in IL-17 effector cells. Thereupon, this leads to DNA transcription of more pro-inflammatory molecules, cytokines (such as IL-6) and chemokines for the attraction of mainly neutrophils and macrophages.

In the treatment of psoriasis, brodalumab, an IL-17RA specific antibody, showed greatest efficacy of all antibodies targeting the IL-17 signaling axis, as it showed a PASI75 score of 83 to 86% in a patient cohort after 12 weeks.[83] However, there were serious side effects by blocking this axis fully, such as depression and suicidal thoughts, which led to the construction of a specific program: the Siliq REMS Program, to help inform patients an health professionals about these great adverse effects. In addition, candida infections were more prevalent with IL-17-targeting agents, but could easily be prevented or treated, and is a common side effect of IL-17 therapy, due to the important role of IL-17 in host defense. Furthermore, in B cells Act1 is inhibited upon IL-17R inhibition by specific antibodies, such as brodalumab. However, Act1 is important for preventing hyper B cell responses and is also important for the migration of B cells, and thus antagonizing this target could lead to a novel phenotype that displays autoimmunity. Therefore, the IL-17 signaling pathway might still need to be investigated more thoroughly to become an appropriate drug target.

IL-6 is a cytokine that is produced by immune cells, such as mature dendritic cells, that can thereupon help for the expression of certain crucial receptors on naive T cells that are important for cell commitment in the development of Th17 cells. These receptors are RORγt and IL-23R. Moreover, IL-6 can be produced by Th17-target cells, in a positive feedback loop to aid in the cultivation of Th17 cells. However, also IL-17 effectors can help amplify the function of IL-6. Since IL-6 is interlinked with excessive IL-17 production and the increased angiogenesis that are both inherently associated with the common symptoms of plaque psoriasis, IL-6-targeting antibodies were also created. The most important example is tocilizumab, which is an IL-6R specific antibody, which showed efficacy in inflammatory conditions like rheumatoid arthritis, but showed however not to be effective in plaque-type psoriasis and could sometimes even deteriorate the condition. This clearly demonstrated the

pleiotropic character of IL-6 and it would thus be more beneficial to look further downstream in the specific signal cascade leading to excessive inflammation.

However, psoriasis is also highly associated with altered IL-23 signaling. IL-23 is a cytokine that is involved in the development of Th17 cells and therefore by blocking this target the excessive IL-17 production could indirectly be regulated, rather than neutralizing all cytokines or receptors of the IL-17, or IL-6 family. Guselkumab is the most important antibody in the IL-23 axis, which blocks the p19 subunit of IL-23 and showed a PASI90 of up to 73.3% in patients after 16 weeks. This great efficacy is in all likelihood assigned to the fact that IL-23 is upstream to IL-27 signaling, and therefore it does not only inhibit IL-17RA, but also IL-17RC signaling. This is apparently beneficial in psoriasis, but not in other inflammatory auto-immune disease, such as IBD, in which IL-17RC is also pathogenic, but IL-17RA signaling is beneficial to a good prognosis. However, it is currently unclear whether blockade of IL-23 could lead to increased risk of infections or dysregulation of appropriate immune responses, due to the important function of IL-17 in protection against pathogens.

Nonetheless, the use of biologicals might not serve the full purpose of ameliorating psoriasis, as there are several disadvantages: they are costly medicines, their production is difficult and yields small quantities, they can cause adverse immunogenicity and they require special storage conditions. Therefore, current research shifts to the computational design of small molecules that can potently inhibit these interleukin signaling cascades. This might provide a more promising view on the interleukin targeting axis, as interleukin homeostasis is important for the balance of the human immune system and via this route, the beneficial effects of such agents can be monitored, compared to biologicals where this is not always the case. However, whether this will be effective to treat psoriasis still has to be discovered, as clinical data is required to evaluate these agents and there is still limited long-term information about biologicals targeting these axes specifically. Therefore, the urgency to promote further research is emphasized.

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