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Review

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Novel key cytokines in allergy: IL-17, IL-22*

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The biology of the T cell cytokines Interleukin (IL-)17 and IL-22 has been a main focus in the field of clinical immunology in the last decade. This intensive interest in both cytokines has resulted in almost 5,000 scientific publications (www.pubmed.com) dealing with the molecular structure, extra- and intracellular signaling pathways, specific transcription factors and the function of IL-17 and IL-22. This review article highlights the main findings concerning IL-17 and IL-22 in the last years.

Cellular source of IL-17 and IL-22

Although IL-17 and IL-22 have been known since 1993 [1] and 2000 [2], respectively, they did not come under scientific scrutiny until Th17 cells were discovered. In 2006, various researchers described this T-helper cell population as an independent line of T-helper cells [3, 4]. In the past two years it could be shown, however, that IL-17 and IL-22 are also secreted by other leukocytes (Table 1). Leukocytes of the innate immune system like NKT cells, certain populations of NK cells (NK22 cells) [5], as well as follicular T-helper cells [6] have been described as sources of IL-17 and/or IL-22. In 2009, we, and other study groups, could demonstrate the existence of other T-helper cells that secrete IL-22, but not IFN-g, IL-4, or IL-17. These T-helper cells were named Th22 cells in analogy to the established classification [7, 8, 9, 10]. The subject of T cell immunology is becoming more and more complex due to the increasing number of subtypes as well as the phenomenon of plasticity. T cell plasticity is the ability of T cells to change their phenotype or to exhibit characteristics of several phenotypes at the same time. This T cell plasticity is also known for IL-17+ and IL-22+ T cells; more than 10 years ago, CD4+ T cells were described that secrete IL-17 as well as IFN-g (main cytokine of Th1 cells) or IL-4 (that defines Th2 cells) [11]. Th1/IL-17 cells seem to play a key role in psoriasis and allergic contact eczema; Th2/IL-17 cells are characteristic for atopic diseases like atopic eczema [12] or bronchial asthma [13]. So, IL-17 and IL-22 are produced and secreted by a high number of leukocytes.

The role of the local microenvironment in the secretion of IL-17 and IL-22

This observation led to the development of a second research focus, namely the question of whether the cellular source of IL-17 and IL-22 is in fact relevant, or if there are specific processes in the local microenvironment that result in the release of these mediators irrespective of the cell type. Indeed, several molecules that induce the differentiation of Th17 cells from naïve progenitor cells could be identified. It was, for example, shown that certain microbial components (so-called pathogen-associated molecular patterns – PAMPS) of extracellular microorganisms like bacteria [14] and fungi [15] promote Th17 differentiation. Other, non-

Table 1. Cells described as sources of IL-17 and/or IL-22.

Cell	Cytokine	Further secreted factors	Surface markers
Th17 [45]	IL-17, IL-22	IL-21, IL-26, TNF-α, (IL-10), CCL20	CD4+ CCR4+ CCR6+CXCR3- CD161+ [46, 47] IL-23R+
Th22 [8, 9]	IL-22	TNF-α, (IL-10), FGFs	CD4+ CCR4+ CCR6+CCR10+
NKT [48]	IL-17, IL-22	IFN-γ	CD3+ CD56+
Lymphoid tissue-inducing cell [49]	(IL-17), IL-22	TNF-α, lymphotoxin	CD3- CD56- NKp44- CD117+ CD127+ CD161+
RORc+ NKp46+ cells	(IL-17), IL-22		CD3- CD56+ NKp44+ NKp46+ NKG2D+ CD117+ CD127+
NK22 [5]	IL-22	TNF-α, lymphotoxin, IL-26	CD3- CD56+ NKp44+ CD117+ CD127+ CD161+
CD8+IL-17+ [50]	IL-17		CD3+ CD8+ CD45RO+
gd T cell [51]	IL-17		Mouse: CD3+ CD4- CD8- CD27- [52] CD25+ CD122- [53]
T follicular helper cell [6]	IL-17	IL-21	CD4+ ICOS+ CXCR5+
Monocyte [54, 55] Macrophage [55]	IL-17 IL-22		CD11b+ CD68+
Neutrophil granulocyte [56]	IL-17		

infectious molecules that promote Th17 differentiation are, for instance, bleomycin [16] and uric acid [17], both activating the inflammasome in immune cells which results in the release of the Th17-induced cytokine IL-1β. In contrast to Th17 differentiation it is, however, widely unknown under which circumstances differentiated Th17 cells actually release IL-17. What could be clearly shown is that the ability of leukocytes to produce IL-17 is linked to the transcription factor RORC (in the murine system: RORgT) [18]. Furthermore, it is probable that strong stimuli are necessary for the secretion of IL-17. Such strong stimuli can, for example, be bacterial superantigens like SEB that stem from *Staphylococcus aureus* [12].

SEB does not only induce IL-17 but also the secretion of IL-22 [19]. In addition, the transcription factor aryl hydrocarbon receptor (AHR) was identified to be essential for the secretion of IL-22. Exogenous agonists like dioxins [8, 20] or endogenous agonists like degradation products of the amino acid tryptophan [21] induce the secretion of IL-22. This suggests that IL-22 is an important cytokine at the interface between toxicology and immunology.

The functions of IL-17 and IL-22

IL-17 and IL-22 belong to a new class of cytokines that mainly, or exclusively, affect tissue cells (so-called tissue signaling cytokines) [22]. This pattern is explained by the distribution of specific receptors for IL-17 and IL-22. IL-17 binds as a dimer to the IL-17 receptor A, expressed on almost all epithelial cells of the body and also on immune cells, and/or to the IL-17 receptor C, that is exclusively found on epithelial cells [23]. IL-22 binds, also as a dimer, to a receptor complex composed of the ubiquitously expressed IL-10 receptor B and the IL-22 receptor that is only expressed on epithelial cells [24].

The essential function of both cytokines is the induction of an innate immune defense in the peripheral tissue, particularly in the skin and the mucosa. The first hints of this

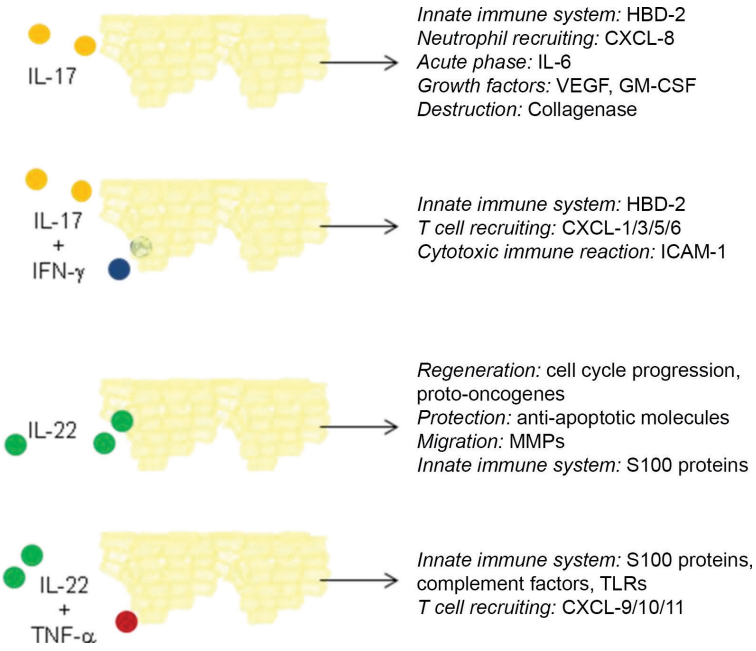

Figure 1. Effects of IL-17 and IL-22 alone and in combination with pro-inflammatory cytokines on epithelial cells. Modified from: Eyerich et al., Trends Immunol. 2010.

important function were seen when, in 2006, it was discovered that IL-17 and IL-22 syntergistically induce the secretion of the antimicrobial peptide HBD-2 in keratinocytes [25]. Further important information on the primary function of IL-17 and IL-22 was provided by two rare human diseases associated with a loss of both cytokines: autosomal dominant hyper-IgE syndrome [26] and chronic mucocutaneous candidiasis [27]. In both diseases, patients characteristically suffer from chronically relapsing infections of the skin and mucosa with extracellular microorganisms like the fungus *Candida albicans*, while not suffering from systemic infections. The impact of IL-17 and IL-22 on numerous infectious diseases of the skin and mucosa have been described [28].

In addition to infectious diseases, IL-17 and IL-22 also seem to play an important role in autoimmune diseases. It could be shown that Th17 cells are essential in the pathogenesis of experimental autoimmune encephalitis [29] and rheumatoid arthritis [30]. Interestingly, the assumption that these effects of Th17 cells can be traced back to IL-17 and/or IL-22 is not necessarily supported by newer findings. Although for both autoimmune diseases, pathogenic effects of IL-17 could be shown, these were by far weaker than those of Th17 cells [31]. IL-22, on the other hand, showed no pathologic characteristics in several disease models and even had protective effects in experimental myocarditis [32]. Similar observations were made for experimental uveitis [33]. Thus, it seams clear that Th17 cells have to produce further factors that, at least in the murine model, cause several autoimmune diseases; IL-17 is only partially responsible while IL-22 is not responsible for this effect.

IL-22 has pronounced regenerative and tissue-protective features. This was first described for the liver where IL-22 has protective effects against toxic hepatits [34]. This is due to the induction of anti-apopotitic molecules in hepatocytes [34, 35]. In the lung, IL-22 increases the transepithelial resistance and protects against cellular damage [36]. In the skin, IL-22 induces the proliferation and migration of keratinocytes and inhibits their differentiation; all these effects are essential for wound healing [37].

Important information on the function of IL-17 and IL-22 was gained by cell culture models that studied the isolated effect of IL-17 or IL-22 on epithelial cells. Numerous recent studies, however, show that both cytokines interact with other mediators on a functional level. For IL-17, for example, an interaction with the pro-inflammatory IFN-g has been shown. Both cytokines synergistically induce the adhesion molecule ICAM-1 on keratinocytes. This results in an increased binding of T cells to keratinocytes and thus in their unspecific apoptosis [38]. This means that IL-17 enhances an unspecific T cell-mediatiated cytotoxic immune reaction in the skin which seems to be of particular importance in the context of allergic contact dermatitis. IL-22 also interacts with pro-inflammatory cytokines. For example, it enhances the TNF-α-induced secretion of pro-inflammatory chemokines and molecules of the innate immune defense in keratinocytes [39, 40].

The role of IL-17 and IL-22 in allergy

In allergic inflammation tissue-damaging as well as tissue-repairing processes take place so that IL-17 and IL-22 play an ambivalent role. In this context, it is interesting to note that the Th17-promoting IL-23 also supports the differentiation of Th2 cells [41]. In asthma, IL-17 levels are increased in the lung and this induces IL-6 and IL-11 in fibroblasts [42]. These pro-inflammatory effects of IL-17 seem to be of particular importance in steroid-resistant bronchial asthma [43].

The role of IL-22 in allergic inflammation is not yet completely understood. It could be shown that the neutralization of IL-22 inhibits the infiltration of eosinophil but not of neutrophil granulocytes in the lung [44]. In humans, it seems to be clear that IL-22-producing T cells infiltrate into lesions from allergic skin diseases [39] as well as into lung tissue damaged by asthma [unpublished data]. Further investigation has to show whether IL-17 and IL-22 could be an interesting target for to controlling changes of tissue, in particular in chronic allergic reaction.

Conclusion

In general, the effects of IL-17 and IL-22 can be protective – as in the case of extracellular infections – as well as pathogenic – as in psoriasis, allergies, and other inflammatory diseases of the tissue. How both cytokines act in the tissue depends on their concentration as well as on the local microenvironment and on other key cytokines that interact with IL-17 and/or IL-22 in multiple ways.

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