Th22 cells in allergic disease

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Summary

During the last decade, the field of T cell immunology started to confuse the scientific community. More and more subtypes of T helper cells and their counterparts in the innate immune system are described. We are just at the beginning to understand which specific function the distinct subtypes fulfill. Th22 cells are terminally differentiated and very specialized T helper cells characterized by the secretion of their signature cytokine IL-22 and lack of IL-4, IL-17 and IFN-γ. The main function of Th22 cells is to protect epithelial barrier organs such as skin and lung, but also to modulate inflamed and injured tissue. This review summarizes our current knowledge on Th22 cells and their function in allergic disease.

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Definition of lymphocytes: a more and more confusing field

Since the eighties, our knowledge on T helper cells increased tremendously. The ongoing description of new T helper (Th) cells and innate lymphocyte populations (ILC), however, further increase the confusion in the field as commonly used classification schemes seem to be antiquated, redundant or insufficient. Therefore, it is reasonable to elaborate on the definition of T helper cells before discussing the function of Th22 cells in allergic disease.

The first classification scheme was suggested by Mosmann and Coffmann at the end of the eighties. Here, two T helper subtypes were distinguished according to their expressed signature cytokines – Th1 cells secreting interferon (IFN)-γ and Th2 secreting interleukin (IL)-4 [1]. Already at this time it was assumed that an additional population of T cells should exist that is able to limit the inflammatory effects of Th1 and Th2 cells in tissue. These cells were originally named T suppressor cells, however, only after description of the transcription factor Fox p 3 and the more attractive naming as regulatory T cells (Treg), these cells were commonly accepted.

Some years after the discovery of IL-17 in 1993 [2], and the description of Th1 and Th2 cells co-secreting IL-17 [3, 4], another T cell subtype specifically secreting IL-17 has been identified. Several studies

Abbreviations

ACD	Allergic contact dermatitis
AE	Atopic eczema
AHR	Aryl-hydrocarbon-receptor
CMC	Chronic mucocutaneous candidiasis
FGF	Fibroblast growth factor
IFN	Interferon
IL	Interleukin
ILC	Innate lymhhoid cell
Lti	Lymphoid-tissue inducer
MMP	Matrix metalloproteinase
NK	Natural killer cell
PDGF	Platelet-derived growth factor
ROR	RAR-related orphan receptor
TCR	T-cell-receptor
TGF	Transforming growth factor
Th	T helper cell
TLR	Toll-like-receptor
TNF	Tumor necrosis factor
Treg	Regulatory T cell

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elucidated that these cells represent an additional lineage in the family of T helper cells and were named according to their signature cytokine as Th17 cells [5]. Being qualified as new lineage goes along with the differentiation of naive T cells into effector T cells in presence of a specific cytokine environment (in case of Th17 cell TGF-β, IL-1β and IL-6) and the expression of a characteristic transcription factor (in case of Th17 cells RORC; ROR: "RAR-related orphan receptor"). IL-22 was described in 2000 [6] and first regarded a Th1 cytokine [5]. However, with growing knowledge on Th17 cells, IL-22 was consequently associated with this T helper subtype.

The phenomenon that some T helper cells secrete more than one signature cytokine is called plasticity. By generation of this concept, the problem in the historical grouping of T helper cells according to the expression of single cytokines was solved. Nowadays, it is widely accepted that Th1, Th2 and Th17 cells exist that co-secrete IL-22. In addition, a subgroup of T helper cells did not express the signature cytokines IFN-γ, IL-4 and IL-17, but IL-22 solely. These cells were described in 2009 for the first time of three research groups and named Th22 cells [7, 8, 9].

Meanwhile, some alternative suggestions for classification of lymphocytes appeared on the scene that take the function (e. g., follicular T helper cells) or chemokine receptor profile into account. This format of this review is not suited to discuss all the existing classification schemes. Therefore, just a summarized personal appreciation: Until now, no concept exists that classifies lymphocytes into subtypes convincingly. Furthermore, our knowledge on lymphocytes from innate immunity (ILC) – lymphocytes without a functional T cell receptor and not belonging to adaptive immunity – is steadily growing. Due to lacking and convincing concepts, also ILC are classified according to their cytokine profile [10]. But we are positive that research in the field will deliver new and reliable concepts. **Tab. 1** gives and overview on known T cell subtypes secreting IL-22.

Starting with this pessimistic attitude, it is questionable if Th22 cells can be really defined as separate lineage. Two reasons argue for it: Th22 cells represent the extreme of a spectrum of IL-22 secreting cells and, importantly, Th22 cells are characterized by a combination of cytokines that in their totality have essential function in tissue. This function will be elucidated in more detail in the next section.

Definition and phenotype of Th22 cells

Th22 cells differentiate, like other T helper cells, from naive precursor cells. The specific microenvironment for generation of Th22 is composed of tumornecrosis factor (TNF)-β and IL-6 [8] (**Fig. 1**). Also skin dendritic cells have been shown to play an essential role in this differentiation process [8, 11]. Once differentiated, the phenotype of Th22 cells remains stable over many weeks in culture and is not skewable into another phenotype [7]. This argues for Th22 cells being terminally differentiated effector cells. The aryl-hydrocarbon-receptor (AHR) was suggested as transcription factor [9], however, it is not exclusively expressed in Th22 cells and does not explain all pattern of the Th22 phenotype. Th22 cells are characterized by expression of the chemokine receptors CCR4 and CCR4 and more characteristic CCR10 [8]. Chemokines that bind to these receptors are strongly expressed in the skin. This explains the abundance of Th22 cells in tissue and their low numbers in circulation. In the skin, Th22 cells are guided into the upper parts of the epidermis due to production of the CCR10 ligand CCL27 by keratinocytes [7, 12].

To evaluate the function of a T helper cell in tissue with a special focus on allergic disease, some more parameters next to migratory capacity or homing have to be defined: the expression of functional surface proteins, secreted mediators and the mechanisms of activation with respect to their antigen-specificity.

Next to the above mentioned chemokine receptors, Th22 cells express all typical markers for T helper cells such as CD3 and CD4 [7]. More characteristic is the high expression of platelet-derived growth factor (PDGF) receptors [7]. The functional relevance of this receptor is not known, yet. Molecules involved in induction of apoptosis such as Fas and TRAIL are weakly expressed in Th22 cells [13] and consequently, the closely related CD8+ T22 cells (Tc22 cells) have a lower capacity to induce apoptosis compared to their IL-22 negative counterparts [14, 15].

As already mentioned, Th22 cells do not secrete signature cytokines of Th2-, Th2-, or Th17 cells. However, Th22 cells co-secrete little amounts of IL-13 and TNF-β [7]. On gene expression level, Th22 have been shown to express a bunch of fibroblast growth factors (FGF) [7]. Until now, it has not been investigated if FGF are secreted in functionally relevant amounts.

IL-22: a many-sided cytokine

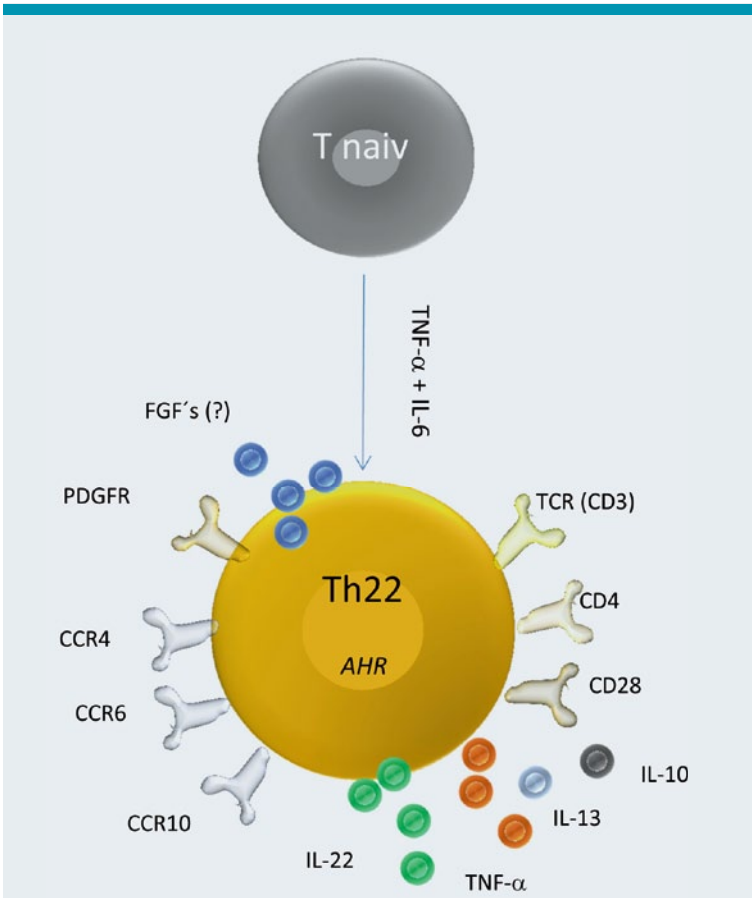
The overall phenotype of Th22 cells points to a per se protective role in tissue, in particular the skin. This is represented especially by the function of IL-22 itself (**Fig. 2**). IL-22 binds to a heterodimeric receptor consisting of the IL-10Rβ and the IL-22RA chain. While the IL-22 receptor (IL-22R) is strongly and abundantly expressed on epithelial cells, immune cells lack IL-22R [16]. Therefore, Th22 cells form

Tab. 1: Cellular source of IL-22* (modified according to [5] and [63])

cell	additional secreted factors	development	transcription factor	surface marker
adaptive immunity				
Th17 [44]	IL-17 IL-21 IL-26 TNF-α (IL-10) CCL20	differentiation: naive T cell plus TGF-β/IL-1β/IL-6 [45, 46]; amplification: IL-21 [47]; stability: IL-23 [48]	RORC	CD4+ CCR4+ CCR6+ CXCR3- CD161+ IL-23R+ [49, 50]
Th22 [9, 51]	TNF-α IL-13 (IL-10) FGF(?)	naive T cell plus TNF-α/IL-6	AHR(?)	CD4+ CCR4+ CCR6+ CCR10+ PDGFR+
Th1/IL-22	IFN-γ TNF-α (IL-10)	unknown		
Th2/IL-22	IL-4 IL-5 IL-13 IL-22 (IL-10)	unknown		
CD8+ T cell [52]		*murine:* CD8+ T cell plus TGF-β/IL-6 [53]/ IL-1β/IL-23 [54]	*murine*: RORγt	CD3+ CD8+ CD45RO+
T follicular helper cell [55]	IL-21	naive T cell plus + IL-21 + IL-6 + ICOSL [56]	unknown (BCL6? [57])	CD4+ ICOS+ CXCR5+
innate immunity				
ILC1	IFN-γ	ID2+ precursor cell (?)	Tbet	LIN-CD56+NKp46+NKp30+NKp44+IL-7Rα *murine*: LIN-Thy1+SCA1+
ILC1 - NK	IFN-γ, TNF	ID2+ precursor cell (?)	Tbet, Eomes	CD122+NKG2D+CD161+KIR+ *murine*: NKp46+NK1.1+CD122+NKG2D+ CD161+CD16+CD11b+
ILC2	IL-5, IL-9, IL-13, IL-4	ID2+ precursor cell (?)	GATA3	LIN-IL-7Rα+CD45hiCD161+CRTH2 *murine*: LIN-ICOS+SCA1+IL-7Rα+
ILC3 [10]	IFN-γ, TNF	ID-2+ precursor cell (?)	ID-2 (?)	LIN−CD56+NKp46+NKp30+NKp44+ IL-7Rα+murine: LIN-NKp46+
Lti (to ILC3) [59]	IL-5, IL-9, IL-13, IL-4	unknown (NK cell?)	RORC, AHR	LIN-IL-7RαhiCD45int *murine*: NKp46-
NKT [58]	IL-17, IL-22 LT-α, LT-β	lymphoid precursor cell	ROR	CD3+ CD56+ CD161+ CD16+
γδT-cell [60]	IL-17 IFN-γ	naive T cell		CD3+CD4+γδTCR+ *murine*: CD3+ CD4-CD8- CD27- [61] CD25+ CD122- [62]

**If not marked explicitly as "murine", the table summarizes human data.*

AHR, aryl-hydrocarbon-receptor; IFN, interferon; IL, interleukin; ILC, innate lymhhoid cells; Lti, lymphoid-tissue inducer; PDGF, platelet-derived growth factor; ROR, RAR-related orphan receptors; TGF, transforming growth factor; Th, T helper cell; TNF, tumor necrosis factor



AHR, aryl-hydrocarbon-receptor ; FGF, fibroblast growth factor; IL, interleukin; MMP, matrix metalloproteinase; PDGF, platelet-derived growth factor; TNF, tumor necrosis factor; TCR, T-cell-receptor

Fig. 1: Phenotype of Th22 cells. Shown is differentiation from naive T cells under influence of TNF-β and IL-6, the putative transcription factor Ahr, the surface profile and secreted cytokines.

an important link between adaptive immunity and barrier organs leading to their functional attribute being "tissue signaling leukocytes" [5]. By binding to its receptor, IL-22 induces proliferation and migration of the target cell and simultaneously inhibits differentiation and reactivity to apoptosis [17, 18, 19]. A combination of these effects builds the basis for efficient wound healing reactions. Indeed, it could have been shown that Th22 cells are important players in wound healing reactions [7, 20]. This per se positive attribute can turn pathologic if regulatory mechanisms are missing. Too much of IL-22 effects can lead to a psoriatic phenotype with over activated metabolism in keratinocytes resulting in acanthosis and hyperkeratosis [21]. In addition, under some circumstances it might be not useful to protect an epithelial cell from apoptosis, especially in case of (pre)-malignancies and intracellular infections. In line with this, it has been reported that Th22 cells have negative effects on gastrointestinal tumors [22, 23]. In tumors, the protective function of IL-22 is additionally reinforced through a direct antagonism with IFN-γ, a known inducer of apoptosis and tumor senescence [14, 24]. Therefore exact regulation of IL-22 is of outermost importance and happens mainly via a soluble antagonist, the IL-22 binding protein (IL-22BP) [25].

Besides its protective effects on epithelial cells, IL-22 plays an important role in the induction of innate immune responses at barrier organs. A binding of IL-22 to the IL-22R weakly induces the expression of anti-microbial peptides such as S100 proteins and defensins (e.g. HBD-2) [7, 16]. More impressive, however, is the amplifying impact on cytokines that induce innate immunity in epithelial cells. Here, IL-22 clearly synergizes with IL-17 [26] and TNF-α [27] with functional relevance in the defense against pathogens for instance *Candida albicans*. Patients suffering from the rare disease chronic mucocutaneous candidiasis (CMC) represent a dramatic example. Due to different reasons, CMC patients are not able to express IL-17 and IL-22 leading to severe and persistent infections of skin and mucosa with *Candida* species [28, 29].

One recommendation at the end of the section. It is not possible to judge on the overall function of Th22 cells without careful consideration of the local microenvironment.

Th22 cells in context of allergic diseases

According to the exclusive expression of the IL-22R in tissue, Th22 cells do interact directly with epithelial cells but do not influence the memory of adaptive immunity in response to allergens. Another essential argument against a direct contribution of Th22 cells to allergic disease is the observation that neither Th17 nor Th22 cells show an allergen reactivity in cell culture models of atopic eczema (AE) or allergic contact dermatitis (ACD) for the relevant allergen or hapten [13, 30]. In fact, both T helper subtypes specifically recognize extracellular microorganisms such as *Staphylococci* and *Candida* species or auto-antigens that are presented via CD1 molecules [31, 32, 33]. Fitting to this fact, IL-17 and IL-22 are induced in T cells by enterotoxins of staphylococci [30, 34].

Even if Th22 do not primarily induce immune reactions against allergens or haptens, they are relevant for allergic reactions in the skin in an indirect way. Most patients with AE are colonized permanently with *Staphylococcus aureus* [35, 36]. The number of IL22 producing cells in AE skin is quite high, also in comparison with other inflammatory skin diseases such as psoriasis. Although many more IL-22 producing Th17 cells are present in pso-

riasis lesions, the number of IL-22 secreting cells in total is the same in both diseases [37, 38]. This is due to a considerably elevated proportion of Th22 cells in AE [39]. Th22 or Tc22 seem to be of relevance in the chronic state of AE [40]. Actually, for Tc22 a correlation with severity of AE was shown [39]. Therefore, it is likely that Th22 cells act as allergen-independent modulators in inflamed tissue and are involved in remodeling processes during chronification. Similar results have been obtained in models of asthma bronchiale. Here, IL-22 is mediating remodeling in tissue and contributes to transition of disease from active into the chronic state [14, 41]. However, in the early phase of asthmatic inflammation, Th22 seem to have rather positive and tissue-protective effects [14, 42].

Data on a potential role of Th22 cells in allergic Typ-1 reactions such as anaphylaxis, mastocytosis or urticaria do hardly exist. Interestingly, it is speculated about an interaction of IL-22+ cells and mast cells in tissue and that this close proximity of both cell types leads to induction of Th22 cells via mast cells [43]. In conclusion, the demand on motivated allergy researchers in the field of Th22 cells is not covered, yet!

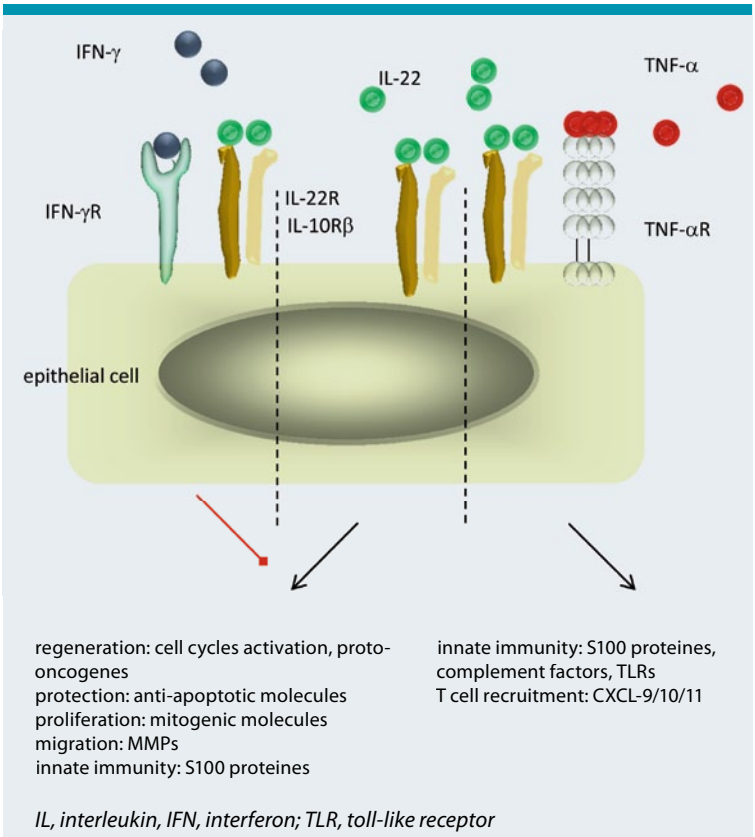


Fig. 2: Function of IL-22 in dependence of the local microenvironment. Per se IL-22 induces proliferation and migration in epithelial cells and inhibits differentiation and reactivity to apoptosis (middle); these effect are inhibited by IFN-γ (left). Together with TNF-β and IL-17 strong innate immune reactions in epithelial cells are induced (right).

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Conflict of interest
The authors declare no conflict of interest.

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