Role of Th17 cells in health and disease

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Master thesis, July 2009
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Contents

Abstract

Th17 cells are a recently discovered novel subset of helper T cells. Th17 cells differentiate along a different lineage than Th1 and Th2 cells. Already many factors which play an important role in the differentiation of Th17 cells have been discovered, like IL-6, TGF-β, IL-21, and IL-23. Also intracellular factors, like STAT3, RORγt ,and RORα, were found. Th17 cells express IL-17 and IL-22, among other cytokines. There is also increasing evidence on the function of these cells within the immune system. Th17 cells are mostly involved in the chemotaxis of neutrophils and the clearance of extracellular bacteria en fungi. Furthermore, Th17 cells have also been identified to play an important role in a broad spectrum of diseases. For instance, several autoimmune and allergic disorders have been related to Th17 cells, as well as other diseases, like inflammatory bowel disease and several forms of cancer. This master thesis gives an overview of the data discovered on the regulation, function, and relation to diseases of Th17 cells.

Introduction

The immune system is a complex organization of cells and molecules that serves to eradicate invading pathogens. It can be divided in the innate and adaptive immune system. The innate immune system functions as a fast, but non-specific defense mechanism against many pathogens. Cells of the innate immune system include macrophages, dendritic cells, neutrophils, eosinophils, basophils, natural killer cells, and mast cells. The complement system is also part of the innate immune system. In contrast to the innate immune system, the adaptive immune response is specific, but also slow. The adaptive immune system is able to induce a response against new pathogens and has 'memory', causing a faster response when the same pathogen invades the organism again. The adaptive immune system comprises B and T cells. B cells function as antibody producers when differentiated to plasma cells. Pathogen-specific antibodies can neutralize and opsonize the pathogen. T cells in turn comprise CD4+ helper T cells, CD8+ cytotoxic T cells, γδT cells, and natural killer T cells.

Th1/Th2 paradigm

Two types of helper T cells, known as Th1 and Th2, were first described by Tada *et al.* (1978) and were shown to have different characteristics in B cell assistance (Tada, Takemori et al. 1978). Th1 and Th2 cells express different cytokines. Th1 cells produce interferon-γ (IFN-γ), granulocyte macrophage colony stimulating factor (GM-CSF), interleukin-2 (IL-2), and IL-3. In contrast, Th2 cells express IL-3 and B cell stimulatory factor-1 (BSF1, also known as IL-4), among other factors (Mosmann, Cherwinski et al. 1986). The Th1/Th2 paradigm was first described by Mosmann and Coffman (1989), describing specific expression of IFN-γ and IL-2 by Th1 cells and expression of IL-4 and IL-5 by Th2 cells. Furthermore, Th1 and Th2 cells have different functions (Mosmann and Coffman 1989). Th1 cells induce a cytotoxic response, especially effective against intracellular pathogens, like viruses. In contrast, Th2 cells induce the production of antibodies, which are involved in responses against parasites and other extracellular pathogens (Mosmann and Coffman 1989; Romagnani 1997). Differentiation of naïve helper T cells to Th1 cells is known to be induced by IFN-γ. Th1 differentiation is also induced by IL-12 via signal transducer and activator of transcription 4 (STAT4) signaling, whereas differentiation to Th2 cells is induced by IL-4 via STAT6 signaling (Romagnani 1997). Besides Th1 and Th2 cells, other types of T cells are also involved in immune responses. Regulatory T cells (Tregs) function as suppressors of immune responses, inhibiting tissue damage and preventing autoimmune diseases (Sakaguchi, Yamaguchi et al. 2008). Recently, another type of helper T cells, called Th17, has been discovered. Th17 cells are named after the cytokine IL-17, which they specifically express (Harrington, Hatton et al. 2005).

IL-17

Almost 10 years before the discovery of Th17 cells, similarities between gene 13 product of the *Herpesvirus saimiri* (HVS13) and the T cell derived murine CTLA8 protein were found. HVS13 and CTLA8 both induce NF-κB activation and IL-6 expression in fibroblasts and are involved in T cell proliferation. Furthermore, HVS13 and CTLA8 both bind a newly discovered cytokine receptor. CTLA8 and HVS13 are described as IL-17 and vIL-17 respectively, whereas the new receptor is called IL-17R (Yao, Fanslow et al. 1995). IL-17 from human CD4+ T cells shares similarities with HVS13; PMA and ionomycin stimulation of CD4+ T cells in peripheral blood

induces IL-17 expression. IL-17 in turn induces IL-6, IL-8, and intracellular adhesion molecule-1 (ICAM-1) expression in fibroblasts (Yao, Painter et al. 1995). IL-17 induces IL-8 expression by gastric epithelial cells in *Helicobacter pylori* infection and these cells induce recruitment of polymorphonuclear leukocytes (Luzza, Parrello et al. 2000). IL-17 related cytokines are also discovered and until now six members of the IL-17 family, IL-17A to F, are identified. IL-17A is the founding member of the family and together with IL-17F is expressed by T cells (Kolls and Linden 2004).

Discovery of Th17 cells

IL-17 and IL-17F expression by memory T cells is induced by dendritic cell (DC) derived IL-23, whereas IL-12 is not able to induce IL-17 expression. IL-23 is also inducing GM-CSF expression and it is suggested that IL-23 induces the activation of helper T cells different from Th1 and Th2 (Aggarwal, Ghilardi et al. 2003). Furthermore, IL-23 induces IL-17, IL-17F, IL-6, and tumor necrosis factor (TNF) expression in an autoimmune-reactive CD4+ T cell population. In contrast to IL-12, IL-23 does not induce expression of IFN-γ (Langrish, Chen et al. 2005). It is shown that differentiation of naïve T cells to IL-17 producing T cells is inhibited by the Th1 and Th2 cytokines IFN-γ and IL-4 respectively. Furthermore, the induction of IL-17 producing T cells by IL-23 is independent of the Th1 and Th2 transcription factors STAT4 and STAT6 respectively. The IL-17 producing helper T cells are different from Th1 and Th2 cells in activation, regulation, and function. Therefore, the IL-17 producing helper T cells are considered a different type of helper T cells, called Th17 (Harrington, Hatton et al. 2005).

Regulation of Th17 cells

Differentiation

Since their discovery, differentiation of Th17 cells has been extensively studied. Various differences between human and mice in Th17 have been found, but some studies show conflicting results. Harrington *et al.* (2005) first described how naïve $CD4^+$ T cells differentiate into Th17 cells in the presence of interleukin-23 (IL-23) in mice, while interferon-gamma (IFN-γ) signaling is absent (Harrington, Hatton et al. 2005). In 2003, before the actual discovery of the Th17 lineage, it was already demonstrated that IL-23 is responsible for inducing IL-17 production in $CD4^+$ and $CD8^+$ T cells (Happel, Zheng et al. 2003). However, a later study showed a more prominent role for a combination of transforming growth factor beta (TGF-β) and IL-6 in Th17 cell differentiation in mice (Kimura, Naka et al. 2007). Another study showed the necessity for IL-6 receptor (IL-6R) in Th17 cell differentiation (Iwanami, Matsumoto et al. 2008). Studies on the role of IL-1 also resulted in conflicting results. IL-1β in combination with TGF-β plays no significant role in the differentiation of Th17 cells (Kimura, Naka et al. 2007), while a more recent study showed that IL-1 is necessary for early development of Th17 cells in mice. Furthermore, IL-1 works cooperatively with IL-23 and IL-6 in regulating the continuity of Th17 cytokine production. This study suggested that IL-1, IL-6, and IL-23 could induce development of Th17 cells, in both mice and humans. This process is TGF-β dependent, however only low levels of TGF-β are needed (Chung, Chang et al. 2009). Another study also shows a role for IL-1α and IL-1β in the differentiation of naïve $CD4^+$ T cells to IL-17-producing cells in humans. Furthermore, this study suggested that IL-1α and IL-1β are more important for Th17 cell differentiation in humans than IL-6 and IL-23. Stimulation of memory T cells with TGF-β results in a lower percentage of IL-17 producing T cells (Miyahara, Odunsi et al. 2008). Another cytokine that plays a role in Th17 cell differentiation is IL-21. The induction of Th17 cell differentiation by IL-21 is reported in mice (Huber, Brustle et al. 2008) and humans (Liu, Yang et al. 2009). Furthermore, IL-21-deficient mice show a lack of Th17 cell differentiation, indicating IL-21 is critical (Fina, Sarra et al. 2008).

The intracellular factors that induce Th17 cell differentiation are also beginning to be understood. Signal transducer and activator of transcription 3 (STAT3), of the JAK/STAT-pathway of cytokine signaling is required for normal Th17 differentiation in a knockout mouse-model (Liu, Lee et al. 2008). Interferon regulatory factor 4 (IRF4) is also required for Th17 cell differentiation induced by IL-21 (Huber, Brustle et al. 2008). Furthermore, Retinoic acid receptor-related orphan receptors (RORs) are involved. RORα and RORγ induce Th17 differentiation (Yang, Pappu et al. 2008).

Several factors are involved in inhibiting the differentiation of Th17 cells. It was early shown by Harrington *et al.* (2005) that IFN-γ inhibits Th17 cell differentiation. Furthermore, IL-4 and STAT1 reduce the development of Th17 cells (Harrington, Hatton et al. 2005). Kimura *et al.* (2007) showed that IL-27 and IFN-γ inhibit Th17 cell differentiation induced by IL-6 and TGF-β (Kimura, Naka et al. 2007) and that IL-27, IL-12, and Tumor necrosis factor α (TNF-α) reduce IL-17-producing T cells (Miyahara, Odunsi et al. 2008). It was later shown in humans that IL-27 regulates the inhibition of Th17 cell differentiation by inhibiting RORγt. This process depends on STAT1 and suggests that IL-27 induces STAT1 to inhibit RORγt (Diveu, McGeachy et al. 2009).

The differentiation of naïve T cells into Th17 cells is influenced by the other lineages, Th1, Th2, and regulatory T (Treg) cells. The Th1 related transcription factor T-box expressed in T cells (T-bet) negatively regulates Th17 cells (Guo, Cobb et al.

2009). Th1 and Th2 related cytokines (IFN-γ and IL-4 respectively) also inhibit Th17 cell development (Harrington, Hatton et al. 2005; Komiyama, Nakae et al. 2006; Kimura, Naka et al. 2007). These cytokines do not affect IL-17 production by mature Th17 cells *in vitro*. Mature Th1 and Th2 cells also do not influence IL-23 production (Harrington, Hatton et al. 2005). This suggests that the Th1, Th2, and Th17 lineages only influence each other in the developmental stage of these effector cells. Treg cells however, are transformed into Th17 cells via IL-1 signaling (Chung, Chang et al. 2009). The number of IL-17+ T cells and Foxp3+ Treg cells is negatively correlated in the joints of Juvenile idiopathic arthritis (JIA) patients (Nistala, Moncrieffe et al. 2008). Furthermore, stimulation of naïve T cells with only TGF-β results in the expression of the Treg related transcription factor Foxp3, while stimulation of naïve T cells with TGF-β in combination with IL-6 results in reduced expression of Foxp3, leading to Th17 cell differentiation in mice (Kimura, Naka et al. 2007; Korn, Mitsdoerffer et al. 2008; Leppkes, Becker et al. 2009) and humans (Miyahara, Odunsi et al. 2008). However, IL-6 is dispensable for RORγt induction, while TGF-β alone is sufficient (Ichiyama, Yoshida et al. 2008), indicating that IL-6 is needed for Foxp3 inhibition. RORγ does not play a role in the inhibition of Foxp3 by IL-6 (Leppkes, Becker et al. 2009), but conversely, Foxp3 inhibits RORα (Du, Huang et al. 2008) and RORγt (Ichiyama, Yoshida et al. 2008) function.

Taken together, Th17 differentiation is induced by several factors, including the cytokines TGF-β, IL-6, IL-23 and IL-21 (as shown in Figure 1). Several cytokines induce the activation of the transcription factors STAT3 and RORγt, while others, like IL-6, also inhibit the development of other lineages. Factors that induce the development of Th1 and Th2 cells can be involved in the inhibition of Th17 differentiation. IL-12, IFN-γ, STAT1 and T-bet, required for Th1 development, and IL-4, required for Th2 development, inhibit the differentiation of Th17 cells. Furthermore, the Treg related transcription factor Foxp3 inhibits RORα and RORγt.

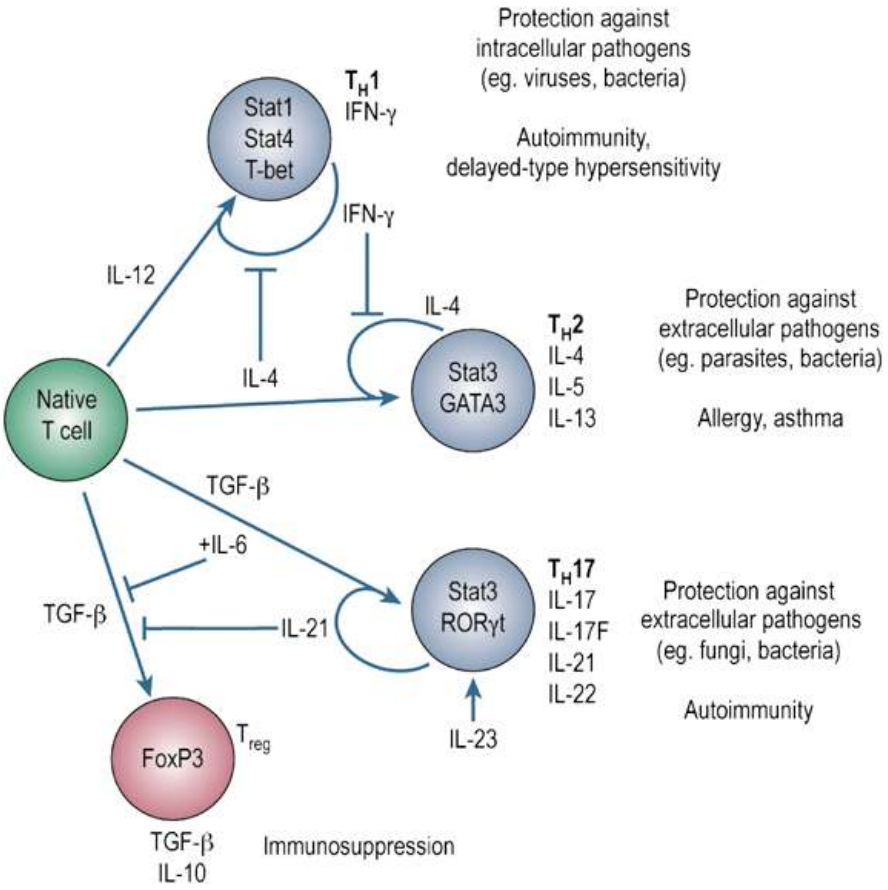

Fig. 1 Differentiation of T-helper cells.
The differentiation of native T cells to T-helper 17 cells is mediated by TGF-β, IL-6, IL-21, and IL-23. Furthermore, IL-6 and IL-21 inhibit the differentiation of native T cells to regulatory T cells. Adapted from (Deenick and Tangye 2007).

Cytokines and chemokines

The role of many cytokines and chemokines on the development of Th17 cells has been extensively studied. The exact function of the most important cytokines, involved in the induction of the Th17 cell lineage, is described here. Known inducers of the Th17 fenotype are IL-6, IL-23, IL-1, and IL-21. Inhibitors of Th17 development are IL-27 and IFN-γ.

IL-6
IL-6 deficient mice lack Th17 cells (Ivanov, McKenzie et al. 2006). Furthermore, IL-6 and TGF-β stimulation induces RORγt in mice (Ivanov, McKenzie et al. 2006; Kimura, Naka et al. 2007) and humans (Diveu, McGeachy et al. 2009). IL-6 and TGF-β induce STAT3 activation in mice (Kimura, Naka et al. 2007) and IL-6 induces expression of the Interleukin-receptors IL-1R (Chung, Chang et al. 2009) and IL23R (Yang, Panopoulos et al. 2007).

IL-23
IL-23 was shown to induce expression of IL-17A, IL-17F, IL-6, and TNF in CD4+ T cells. Furthermore, IL-23 induces the expression of its own receptor, IL-23R. IL-23 also induces the expression of several chemokines, among which CCL7, CCL17,

CCL20, CCL22 and the chemokine receptor CCR1 (Langrish, Chen et al. 2005). Mice that are deficient of IL-23 have reduced levels of IL-17, IL-6, keratinocyte-derived chemokine (KC or CXCL1), and matrix metalloproteinase-9 (MMP-9). IL-23 deficient mice also have diminished bronchoalveolar lavage neutrophil infiltration and reduced airway inflammation in a mouse model of *Pseudomonas aeruginosa* infection (Dubin and Kolls 2007). In myelin oligodendrocyte glycopeptides (MOG) immunized mice to induce experimental autoimmune encephalomyelitis (EAE), a mouse model for multiple-sclerosis, knockout of the IL-23 subunit p19 reduces expression of IL-17A, TNF, and IFN-γ (Thakker, Leach et al. 2007).

IL-1

Chung *et al.* (2009) showed that IL-1 signaling, together with IL-6 and IL-23, is important for the development of Th17 cells and Th17 cytokine expression. IRF4 and RORγt are induced in naïve T cells by IL-1 and IL-6 stimulation. Furthermore, IL-6 induces expression of the IL-1 receptor IL-1R1 and this receptor is required on T cells for the production of IL-17A, IL-17F, IL-21, and IL-22. Deficiency of the IL-1R1 on dendritic cells (DCs) does not affect production of these cytokines (Chung, Chang et al. 2009).

IL-21

Like IL-6 and IL-1, also IL-21 is involved in the induction of RORγt. IL-21 induces RORγt and IL-17A expression in CD4+ T cells, indicating differentiation to the Th17 phenotype (Liu, Yang et al. 2009). Furthermore, IL-21 regulates RORγt and RORα via the induction of STAT3. This results in IL-17A, IL-17F, and IL-23R production (Huber, Brustle et al. 2008).

IL-27

The cytokine IL-27 is known to be an inhibitor of the Th17 lineage. It has been reported that IL-27 results in the reduction of IL-17 production by T cells (Fitzgerald, Ciric et al. 2007). IL-27 induces STAT1 (Kimura, Naka et al. 2007) and STAT1 is required for the IL-27 mediated inhibition of RORγt, thereby resulting in the reduction of IL-17A, IL-17F, and IL23R. IL-27 also induces the Treg cell polarizing cytokine IL-10. This induction is not inhibited by IL-23 (Diveu, McGeachy et al. 2009). It has also been reported that IL-27, together with IL-4 and IFN-γ produced by monocytes, is inhibiting the production of IL-17 by CD4+ T cells (Zhang, Jin et al. 2008).

IFN-γ

Like IL-27, also IFN-γ is a known inhibitor of the Th17 lineage. IFN-γ inhibits the production of IL-17 (Jain, Tartar et al. 2008). Furthermore, the expression of IL-23R is inhibited by IFN-γ (Harrington, Hatton et al. 2005). IFN-γ also increases the secretion of the IL-27 subunit p28 by astrocytes (Fitzgerald, Ciric et al. 2007), indicating a Th17 suppressing function of IFN-γ within the central nervous system. Furthermore, Komiyama *et al.* (2006) showed an increase in IL-17 producing T cells in IFN-γ knockout mice (Komiyama, Nakae et al. 2006). However, Kryczek *et al.* (2008) showed several Th17 lineage stimulating functions of IFN-γ. IFN-γ is stimulating antigen-presenting cells (APCs) to produce IL-1, IL-23, and CCL20, which is a Th17 attracting chemokine. IL-1 and IL-23 in turn, are inducing IL-17 producing T cells. IFN-γ stimulation, together with IL-17, induces the production of human defensin β2 by keratinocytes (Kryczek, Bruce et al. 2008).

Chemokines

CC chemokine receptor 6 (CCR6) is expressed by Th17 cells in an animal model of rheumatoid arthritis (Hirota, Yoshitomi et al. 2007) and in tissue-infiltrating Th17 cells of patients with psoriasis, rheumatoid arthritis, Crohn's disease, or asthma (Pene, Chevalier et al. 2008). Also expression of CCR4 on Th17 cells was indicated

(Miyahara, Odunsi et al. 2008; Nistala, Moncrieffe et al. 2008). Furthermore, Th17 cells produce the CCR6 ligand CCL20 (Hirota, Yoshitomi et al. 2007) and IL-17+ CD4+ T cells are attracted to CCL20 (Nistala, Moncrieffe et al. 2008). CCR4, CCR6, and the CCR6 ligand CCL20 are important factors in the chemo-attraction of Th17 cells.

Intracellular signaling

As described, development and function of Th17 cells is regulated by several cytokines and chemokines. Cytokines determine gene expression by regulating the activity of transcription factors. Most cytokines signal through the JAK-STAT pathway by binding to their respective cytokine-receptor, which activates the coupled Janus kinase (JAK). JAK subsequently phosphorylates Signal Transducer and Activator of Transcription (STAT). The activated STAT dimerizes and then induces gene transcription of other specific transcription factors in the nucleus.

STAT3 is involved in IL-6 and IL-23 signaling and is critical for the differentiation of inflammatory T helper cells. Furthermore, STAT3 induces the Th17 specific transcription factor RORγt and STAT3 deficiency results in decreased expression of RORγt and increased expression of the Th1 specific transcription factor T-bet and Treg specific Foxp3 (Yang, Panopoulos et al. 2007). Another study also described increased Foxp3 expression in STAT3 deficient T cells, together with increased expression of Treg lineage specific IL-10. Expression of Th1 lineage specific IFN-γ and Th2 lineage specific IL-4 is increased in STAT3 deficient T cells (Liu, Lee et al. 2008). An increase of Suppressor of Cytokine Secretion (SOCS) 3, an inhibitor of the JAK-STAT pathway, diminishes IL-6 and IL-23 expression in multiple sclerosis patients (Zhang, Jin et al. 2008).

Interferon regulatory factor 4 (IRF4) is needed for Th17 differentiation, induced by IL-21. IRF4 is thought to play a role in the inhibition of Foxp3 and the induction of RORα and RORγ. Furthermore, it is suggested that the regulation of Th17 phenotype by IRF4 is independent of STAT3 activity (Huber, Brustle et al. 2008).

Retinoic acid receptor-related orphan receptors (RORs) are nuclear receptors and known to regulate gene transcription. RORα and RORγt are reported as Th17 lineage specific transcription factors (Yang, Pappu et al. 2008). RORγt deficient mice lack Th17 cells. Furthermore, RORγt is involved in IL-6 and TGF-β induced IL-17A and IL-17F production by naïve CD4+ T cells (Ivanov, McKenzie et al. 2006). RORγ is involved in the regulation of IL-17A and IL-17F expression (Leppkes, Becker et al. 2009) and Ichiyama and colleagues (2008) found that RORγt induces activation of the IL-17A promoter by binding to the ROR-responsive elements (RORE)-1 and -2 (Ichiyama, Yoshida et al. 2008). RORγt induces IL-17 and CCR6 expression in naïve T cells (Hirota, Yoshitomi et al. 2007) and RORγ deficiency results in a reduction of IL-17, IL-6, IFN-γ, and granulocyte/macrophage-colony stimulating factor (GM-CSF) expression by T cells (Leppkes, Becker et al. 2009). Kimura *et al.* (2007) found that RORγt is induced by IL-6 and TGF-β and suggested that RORγt is required for IL-17 expression in naïve T cells, but since IL-27 and IFN-γ inhibit the development of Th17 cells, while RORγt was only partially inhibited, RORγt alone may not be sufficient to induce Th17 phenotype and IL-17 expression (Kimura, Naka et al. 2007). This was confirmed when overexpression of RORα and RORγt failed to fully recover the Th17 phenotype in IRF4 knockout mice (Huber, Brustle et al. 2008). RORα is induced by IL-6 and TGF-β and signaling is dependent on STAT3 (Yang, Pappu et al. 2008) and RORα induces the production of IL-17, IL-22, and CXCR3 (Du, Huang et al. 2008). RORα and RORγt are both directly inhibited by Foxp3. Both RORs interact

with the exon 2 region of Foxp3 (Du, Huang et al. 2008; Ichiyama, Yoshida et al. 2008). The inhibition of RORγt mediated IL-17A expression is dependent on the forkhead domain of Foxp3 (Ichiyama, Yoshida et al. 2008). In contrast, forkhead domain of Foxp3 is not involved in the inhibition of RORα mediated gene expression (Du, Huang et al. 2008).

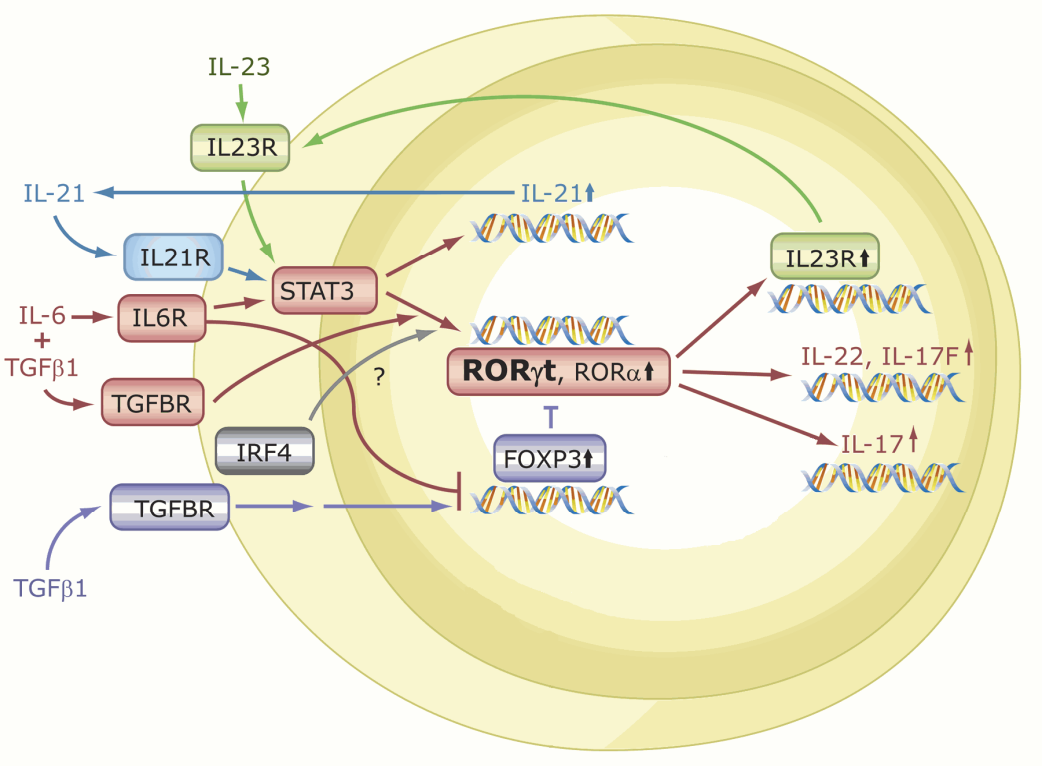

Fig. 2 Intracellular factors involved in the Th17 phenotype
STAT3 and RORs are induced via several cytokine receptors resulting in gene transcription of IL-17 and IL-22, among others. Adapted from (Jetten 2009).

Function of Th17 cells

As newly discovered subtype of helper T cells, Th17 cells play an important role in the clearance of extracellular bacteria en fungi. By secreting IL-17A and IL-17F, among other cytokines, Th17 cells recruit and activate other immune cells, especially neutrophils and macrophages. Also epithelial cells are affected by Th17 cells. IL-17A and F are known to induce the production of defensin β (Ishigame, Kakuta et al. 2009). IL-17 also induces production of granulocyte-colony stimulating factor (G-CSF), macrophage inflammatory protein 2 (MIP-2), TNF-α (Ye, Garvey et al. 2001), and TNF-receptor 2 (Zrioual, Ecochard et al. 2009). Furthermore, production of granulocyte/macrophage-colony stimulating factor (GM-CSF), IL-8 (CXCL8), CXCL10, and TNF-α by keratinocytes is induced by IL-17 (Koga, Kabashima et al. 2008). Together with TNF-α, IL-17 induces the production of CXCL8, CXCL1, and CCL20 (Lee, Wang et al. 2008). IL-17 also increases intercellular adhesion molecule 1 (ICAM-1) expression on keratinocytes after IFN-γ induction (Albanesi, Scarponi et al. 2000). The induction of G-CSF, GM-CSF, CXCL8, CXCL1, MIP-2 and ICAM-1 especially results in the recruitment of neutrophils (Ye, Garvey et al. 2001; Lee, Wang et al. 2008).

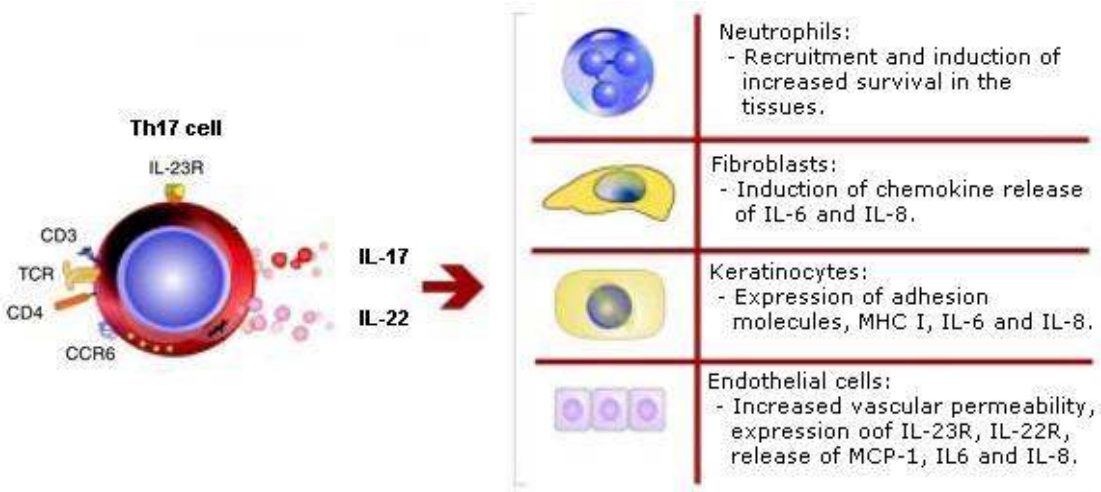

Fig. 3 Effect of Th17 cells on several cell types
Production of IL-17 and IL-22 influences neutrophils, fibroblasts, keratinocytes, and endothelial cells, among other cell types. IL-17 causes inflammation and recruitment of neutrophils. Adapted from (Mesquita, Cruvinel et al. 2009).

Role of Th17 cells in the defense against bacterial infections

Klebsiella pneumoniae
Mice deficient of IL-17R are severely affected by *Klebsiella pneumoniae* infection. Migration of neutrophils to the inflamed tissue is impaired and lower levels of G-CSF, stem cell factor (SCF) and macrophage inflammatory protein 1 (MIP1) and MIP2 are found in IL-17R knockout mice (Ye, Rodriguez et al. 2001). *K. pneumoniae* infection causes IL-17 production by CD4+ T cells in wild-type mice. Overexpression of IL-17 results in an increased immune response against *K. pneumoniae*. Adenovirus mediated upregulation of IL-17 in the lungs causes an increase in IL-1β, TNF-α, G-CSF, and MIP2. Furthermore, infiltration of neutrophils and bacterial clearance are increased. However, overexpression of IL-17 is only protective against *K. pneumoniae* when overexpression via adenovirus treatment is induced before bacterial challenge (Ye, Garvey et al. 2001). IL-17 and IL-22 induce defensin β2,

S100A7, S100A12, and other antimicrobial proteins. Furthermore, IL-17 and IL-22 are enhanced in *K. pneumoniae* infected mice, as well as the CCR4 and CCR6 ligands CCL17 and CCL20. IL-17 and IL-22 are critical for *K. pneumoniae* clearance and IL-23 is required for IL-22 expression (Aujla, Chan et al. 2008). Earlier, it was shown that Toll-like receptor 4 (TLR4) plays a critical role in IL-23 expression by DCs after *K. pneumoniae* challenge. Supernatant of DCs that are challenged with *K. pneumoniae* can induce IL-17 expression by CD4+ and CD8+ T cells and this is induced by IL-23 (Happel, Zheng et al. 2003). IL-12/23 p40 subunit deficient mice are severely affected by *K. pneumoniae* infection, due to the lack of IL-17A and F and IFN-γ production. IL-23 p19 subunit deficient mice show normal IFN-γ expression, but lack IL-17A and F and *K. pneumoniae* is inefficiently cleared. IL-17 treatment of p19 deficient mice enhances the defense against the bacteria and partially in p40 deficient mice, indicating that IL-12 and IL-23 play an important role in the clearance of *K. pneumoniae* via the induction of IFN-γ and IL-17 (Happel, Dubin et al. 2005). Furthermore, oral consumption of ethanol by mice for two weeks before *K. pneumoniae* challenge causes a reduction in IL-17 expression. The decrease in IL-17 causes a reduction of neutrophil infiltration and increased mortality of mice challenged with *K. pneumoniae* (Shellito, quan Zheng et al. 2001). These data indicate that Th17 cells, and especially IL-17 and IL-17R, are required for neutrophil infiltration and efficient clearance of *K. pneumoniae*.

Pseudomonas aeruginosa

IL-17A, IL-17F, and IL-23 are enhanced in cystic fibrosis patients who are infected with *Pseudomonas aeruginosa*. Also other cytokines are enhanced, including IL-6, IL-1β, G-CSF, GM-CSF, TNF-α, and IL-8. Antibiotic treatment of these patients reduces the level of IL-17A, IL-17F, IL-23, and also the other cytokines. IL-17A, IL-17F, and IL-23 play a major role in the induction of proinflammatory cytokine production by human bronchial epithelial cells (McAllister, Henry et al. 2005). Furthermore, IL-17 expression by T cells is enhanced when mice are immunized with a live-attenuated vaccine of *P. aeruginosa*. Neutrophils of immunized mice are migrating more efficiently to the lungs after challenge with *P. aeruginosa* and lethal pneumonia is inhibited. Anti IL-17 antibody treatment or IL-17R deficiency abolishes the inhibition of lethal pneumonia (Priebe, Walsh et al. 2008). It was also shown that IL-23 deficiency in mice results in decreased expression of IL-17, IL-6, keratinocyte-derived chemokine (KC), MIP1-α, IP-10 (CXCL10) and matrix metalloproteinase-9 in the lungs. Furthermore, infiltration of neutrophils to the lungs is reduced (Dubin and Kolls 2007). IL-23 is therefore likely to regulate Th17-dependent recruitment of neutrophils via the induction of IL-17 production, among other proinflammatory cytokines, in *P. aeruginosa* infection.

Mycobacterium tuberculosis

Challenge of IFN-γ deficient mice with *Mycobacterium bovis* results in an increase of IL-17 producing T cells, suggesting a role for IFN-γ in reducing the IL-17 response after *M. bovis* infection (Cruz, Khader et al. 2006). It was reported that γδT cells play a major role in the expression of IL-17 after *M. tuberculosis* infection and the expression is induced by IL-23, which is secreted by DCs that are infected with *M. tuberculosis* (Lockhart, Green et al. 2006). IL-23 is also involved in IFN-γ expression by T cells. However, IL-23 is not required for *M. tuberculosis* clearance (Wozniak, Ryan et al. 2006). IL-23 induces IL-17 expression in CD4+ T cells after *M. tuberculosis* vaccination and challenge. IL-17 induces expression of CXCL9, 10, and 11 in the lungs and is involved in the infiltration of IFN-γ expressing CD4+ T cells to the lungs after *M. tuberculosis* challenge. IL-23 is required for the induction of memory Th17 cells (Khader, Bell et al. 2007). IL-17 involvement in *Mycobacteria* infection was also shown in humans. IL-17 and IL-22 are expressed by CD4+ T cells in the peripheral blood of vaccinated individuals, exposed to *Mycobacteria*. However,

IL-17 and IL-22 are not expressed together by CD4+ T cells. IL-17 and IL-22 producing CD4+ T cells show characteristics of memory cells, whereas IFN-γ producing cells are most likely effector cells. IL-22 is also expressed in the lungs of pulmonary tuberculosis patients, but not IL-17. IFN-γ inhibits expression of IL-17 by CD4+ T cells (Scriba, Kalsdorf et al. 2008). These studies suggest that *M. tuberculosis* clearance is likely to be mediated by Th17 and Th1, in which Th17 memory cells induce recruitment of Th1 effector cells.

Salmonella enterica

Infection of mice with *Salmonella enterica* serovar Enteritidis induces IL-17A expression. IL-17A is expressed by CD4+ Th17 cells and γδ T cells. Mice deficient of IL-17A show reduced infiltration of neutrophils to the spleen and some reduction in *S. enteritidis* clearance. IL-17A deficiency does not affect the expression levels of IL-6, TNF-α, IFN-γ, IL-12, and inducible nitric oxide synthase, indicating IL-17A is not required for a Th1 response against *S. enteritidis* (Schulz, Kohler et al. 2008). *Salmonella enterica* serovar Typhimurium infection of the ileum of rhesus macaques induces IL-17, IL-22, IL-26, and IFN-γ expression. Also the expression of inducible nitric oxide synthase, lipocalin-2, IL-8, CXCL10, and CCL20 is increased. Simian immunodeficiency virus (SIV) infected macaques show a reduced number of CD4+ T cells, lower expression of IL-17, IL-22, lipocalin-2, IL-8, CXCL10, and CCL20 and reduced *S. typhimurium* clearance. The reduced number of CD4+ T cells and lower expression of IL-17 are directly related to each other (Raffatellu, Santos et al. 2008), indicating Th17 cells could be the source of IL-17 in *S. typhimurium* infection. Decreased clearance of *S. typhimurium* is also shown in IL-17R deficient mice (Raffatellu, Santos et al. 2008) and *S. typhimurium* activation of murine DCs results in IL-17 and IFN-γ induction (Perona-Wright, Jenkins et al. 2009). These data indicate that IL-17 and IL-17R, among other factors, are involved in the induction of neutrophil-mediated *Salmonella* clearance. The source of IL-17 in *Salmonella* infection is not exactly clear, but Th17 cells are likely to be involved.

Escherichia coli

An increase in IL-17 and IL-23 p19 subunit expression is found in mice after intraperitoneal (i.p.) *Escherichia coli* infection. The peak of expression is reached first by IL-23 p19 subunit, with the peak of IL-17 expression closely following. Neutrophil infiltration is also enhanced after *E. coli* infection, with the peak approximately 18 hours later than the peak of IL-17 expression. Furthermore, anti IL-17 antibody pretreatment of the mice results in diminished neutrophil infiltration and bacterial clearance after *E. coli* infection. γδT cells play a major role in IL-17 expression and neutrophil infiltration. IL-17 production by γδT cells is induced by IL-23 and dependent on TLR4 (Shibata, Yamada et al. 2007). IL-17 expression, neutrophil infiltration, and *E. coli* clearance are also dependent on Tyrosine kinase 2, which is involved in IL-23 signaling (Nakamura, Shibata et al. 2008). However, mice deficient of γδT cells do not show total blockage of IL-17 production (Shibata, Yamada et al. 2007), indicating a possible role for Th17 cells in *E. coli* clearance. Intranasal challenge of mice with *E. coli* lipopolysaccharide (LPS, endotoxin) results in enhanced IL-17 production by T cells in the lungs. Also infiltration of neutrophils, macrophages, and lymphocytes to the lungs is increased after LPS challenge (Prause, Bossios et al. 2009).

Taken together, Th17 cells are involved in the clearance of a variety of bacteria. Th17 cells are most likely induced to produce IL-17 via DC-derived IL-23. IL-17 in turn, induces neutrophil recruitment and bacterial clearance. Therefore, Th17 cells act as a link between DCs and neutrophils. Th17 cells also act as memory cells and in some cases cooperate with Th1 effector cells.

Fungal clearance

Candida albicans

Th17 cells are involved in the clearance of *Candida albicans*. Memory T cells, specific for *C. albicans*, express IL-17, CCR6, and CCR4, indicating these memory T cells are Th17 cells. Furthermore, hyphal *C. albicans* induces IL-23 expression by DCs and IL-17 production by CD4+ T cells (Acosta-Rodriguez, Rivino et al. 2007). Requirement for IL-17A and IL-17R in the clearance of systemic *C. albicans* is earlier described. IL-17R deficient mice show decreased recruitment of neutrophils, an increase of *C. albicans* colonies, and decreased survival (Huang, Na et al. 2004). IL-17 and IL-22 expression by peripheral blood mononuclear cells is decreased in chronic mucocutaneous cadidiasis patients and the number of IL-17 producing T cells, coexpressing CCR6, is lower (Eyerich, Foerster et al. 2008). IL-23 p19 subunit deficient mice, orally challenged with *C. albicans,* show decreased infiltration of neutrophils to the tongue, compared to IL-12 p35 subunit deficient mice. Furthermore, epithelial damage is more severe in IL-23 deficient mice, compared to IL-12 deficient mice. Deficiency of IL-17R also results in a decrease of neutrophil infiltration and increase of epithelial damage. This indicates that a Th17, instead of a Th1, response is required for *C. albicans* clearance. Furthermore, Th17 related cytokines, including IL-6, IL-22, and CCL20 are expressed in the tongue of *C. albicans* infected mice. Also host defense proteins, including lipocalin-2, defensin β3, S100A8, and S100A9 are expressed (Conti, Shen et al. 2009). Antigen presenting cells are required for the induction of IL-17 expression by memory CD4+ T cells by *C. albicans*. Furthermore, the macrophage mannose receptor is required to induce IL-17 expression, indicating a role for *C. albicans* mannan in inducing a Th17 response (van de Veerdonk, Marijnissen et al. 2009). However, is has also been reported that the Th17 response against gastrointestinal *C. albicans* inhibits clearance and induces inflammation and tissue damage (Zelante, De Luca et al. 2007). From these data we can conclude that Th17 cells are involved in *C. albicans* infection. *C. albicans* induces IL-23 production by DCs, in which *C. albicans* mannan may play an important role. IL-23 causes the activation of IL-17 production by CD4+ T cells. This induces inflammation and infiltration of neutrophils, which could result in the clearance of *C. albicans*.

Cryptococcus neoformans

IL-12/IL-23 p40 subunit deficient mice infected with *Cryptococcus neoformans* show reduced survival, compared to mice deficient of IL-12 subunit p35. IL-23 treatment of p40 deficient mice results in increased survival, comparable with survival in IL-12 p35 deficient mice. Survival is slightly reduced in IL-23 subunit p19 deficient mice. However, survival is longer than in IL-12 p35 deficient mice. IL-23 p19 deficiency in mice reduces the expression of IL-17. IFN-γ expression is normal, compared to wild-type mice. IL-23 p19 deficient mice also show a reduction in granuloma formation in the liver, decreased leukocyte infiltration and microglial cell activation in the brain, and lower IL-6, IL-1β, and CCL2 (MCP-1) expression, compared to wild-type mice. Therefore, it has been suggested that IL-23 is involved in the clearance of *C. neoformans*, however IL-12 is more important (Kleinschek, Muller et al. 2006). IL-17A expression is reduced in mice susceptible to *C. neoformans* infection and expression of IL-17A is enhanced in IL-13 deficient mice. These IL-13 deficient mice are resistant to *C. neoformans* infection, indicating a role for IL-17 in fungal clearance (Muller, Stenzel et al. 2007). Resistance to *C. neoformans* infection is also seen in IL-4Rα deficient mice. IL-4Rα functions as a receptor for IL-4 and IL-13. IL-17 expression is enhanced in IL-4Rα deficient mice, compared to IL-4Rα positive mice. In contrast, the Th2 cytokine IL-5 is decreased in IL-4Rα deficient mice (Muller,

Stenzel et al. 2008). Recently, it was shown that IL-17, IFN-γ and TNF-α enhances phagocytosis of *C. neoformans* and *C. gattii* by macrophages. Proliferation of both *Cryptococci* within macrophages is inhibited by these three cytokines, whereas IL-4 and IL-13 results in increased proliferation (Voelz, Lammas et al. 2009). These studies indicate a protective role for Th17 and Th1 cells, not Th2 cells, in *C. neoformans* infection. However, Th1 cells may be more important in *C. neoformans* clearance than Th17 cells.

Parasitic and viral clearance

The role of Th17 cells in the clearance of parasites and viruses has also been studied. However, till now there is not much clear evidence. Several studies show a protective role, while others report a negative role for Th17 cells in viral or parasitic diseases. Some studies report a role for Th17 cells in HIV or SIV (Maek, Buranapraditkun et al. 2007; Cecchinato, Trindade et al. 2008), Hepatitis B (Ge, Wang et al. 2009), Hepatitis C (Rowan, Fletcher et al. 2008) and influenza virus (McKinstry, Strutt et al. 2009) infection. It has also been suggested that IL-17 inhibits clearance of viruses via the induction of anti-apoptotic factors, which cause survival of infected cells in a Theiler's murine encephalomyelitis virus mouse model for multiple sclerosis (Hou, Kang et al. 2009). Conflicting results on the role of Th17 cells are also found in *Toxoplasma gondii* infection.

Toxoplasma gondii

Oral infection with *Toxoplasma gondii* induces almost total mortality in IL-17R knockout mice, whereas wild-type mice all survive. When *T. gondii* dose is doubled, all mice die, including wild-type mice, however surviving time is longer in wild-type mice, compared to IL-17R knockout mice. Also parasite distribution in brain, spleen, gut, and liver is increased in IL-17R knockout mice and infiltration of neutrophils to liver and gut tissue and into the peritoneal cavity is reduced in IL-17R knockout mice. Furthermore, expression of MIP-2 in the serum of IL-17R knockout mice is lower, compared to wild-type mice (Kelly, Kolls et al. 2005). These results could indicate a possible role for Th17 cells in *T. gondii* infection. However, it has also been suggested that an increased Th17 response in *T. gondii* infection can cause lethal inflammation in the brain and IL-27 is shown to regulate this Th17 response by inhibiting IL-17 production in TGF-β and IL-6 induced CD4+ and CD8+ T cells (Stumhofer, Laurence et al. 2006). This indicates that a tightly regulated Th17 response can be protective in *T. gondii* infection.

The role of Th17 cells in infections

In conclusion, Th17 cells play an important role in the clearance of extracellular bacteria and several fungi. IL-17 production by Th17 cells is mainly induced by IL-23, which can be produced by activated DCs. IL-17 induces the expression of chemokines, adhesion molecules and antimicrobial factors by endothelial cells, fibroblasts, and keratinocytes. This causes the infiltration of neutrophils and clearance of the pathogen. Th17 cells have also been implicated in viral and parasitic infections, although not much evidence is found yet.

Th17 cells in autoimmune disorders

Th17 cells have been implicated in several autoimmune disorders. In this part the role of Th17 cells in rheumatoid arthritis, psoriasis, multiple sclerosis, and type I diabetes will be described.

Rheumatoid arthritis

IL-17 and Th17 cells play a role in rheumatoid arthritis (RA). IL-17A and F are expressed in the synovium of RA patients (Zrioual, Ecochard et al. 2009). Furthermore, IL-17 producing T cells were found in inflamed tissue of RA patients. These T cells were expressing RORγ (Pene, Chevalier et al. 2008). IL-17+ T cells were also present in joints of Juvenile idiopathic arthritis (JIA) patients (Nistala, Moncrieffe et al. 2008) and another study showed the presence of Th17 cells in the synovial fluid and tissue of RA patients. The latter study also showed that IL-17 and TNF-α treatment of synovial fibroblasts, isolated from RA patients, increased the survival of co-cultured neutrophils (Parsonage, Filer et al. 2008). A role for IL-17 in RA was already earlier described when Rohn and colleagues (2006) discovered in mice that collagen induced arthritis (CIA), a model for RA, could be ameliorated by immunizing the mice against IL-17 (Rohn, Jennings et al. 2006). Reduction of arthritis was also seen with anti-IL-17 antibody treatment in glucose-6-phosphate isomerase (GPI)-induced arthritis in mice (Iwanami, Matsumoto et al. 2008). It has been suggested that only IL-17A and not IL-17F has an important role in CIA (Ishigame, Kakuta et al. 2009). Hirota *et al.* (2007) found in mice that arthritis was inhibited by IL-17 or IL-6 deficiency and discovered that self-reactive T cells from the thymus, when activated in the periphery, were able to induce IL-6 production by antigen-presenting cells (APCs). IL-6 from T cells and APCs induced the differentiation of naïve self-reactive T cells to Th17 cells, causing arthritis (Hirota, Hashimoto et al. 2007). Th17 cell number was increased in CIA (Fujimoto, Serada et al. 2008). Furthermore, blockage of the IL-6 receptor with an anti-IL6R antibody reduced CIA and this was related to diminished Th17 development (Fujimoto, Serada et al. 2008). However, in GPI-induced arthritis, only early anti-IL6R treatment was effective against arthritis. Anti-IL6R antibodies administered within three days after immunization caused protection against arthritis, whereas administration after 8 days only caused reduction of arthritis. When anti-IL6R antibodies were administered 14 days after immunization, no reduction of arthritis was seen (Iwanami, Matsumoto et al. 2008). IFN-γ deficiency in mice caused enhanced differentiation of CD4+ T cells to Th17 cells and arthritis was increased (Hirota, Hashimoto et al. 2007). This was confirmed in GPI-induced arthritis, were anti-IFN-γ antibody treatment resulted in enhanced arthritis development (Iwanami, Matsumoto et al. 2008). This indicates that IFN-γ has a suppressive role on the development of arthritis. IL-22 is also involved in arthritis. Geboes *et al.* (2009) showed increased amounts of IL-22 in sera and IL-22 receptor 1 in lymphoid tissue in CIA and IL-22 knockout mice showed reduced arthritis in CIA. Furtheremore, IL-22 induced osteoclastogenesis (Geboes, Dumoutier et al. 2009). The amount of IL-23 in the joints correlated with the severity of RA and also a high level of CCL20 was present in the synovial fluid of RA patients (Melis, Vandooren et al. 2009). Furthermore, IL-17, IL-1β, or TNF-α stimulation of arthritic synoviocytes induced CCL20 production and IL-17 and CCL20 levels correlated in joints of RA patients. CCL20 production was inhibited by IL-4 or IFN-γ (Hirota, Yoshitomi et al. 2007). In short, IL-6 from self-reactive T cells can induce IL-6 production by APCs, which induces differentiation of Th17 cells and expression of IL-17 and IL-22. Stimulation of synovial fibroblasts and arthritic synoviocytes by IL-17 and other pro-inflammatory cytokines causes the expression of cytokines and chemokines that stimulate the recruitment of more Th17 cells and increased survival

of neutrophils. This ultimately results in arthritis. IFN-γ inhibits Th17 cells and the formation of arthritis.

Psoriasis

IL-17 producing T cells, expressing RORγ, which were found in RA patients, were also found in inflamed tissue of psoriasis patients (Pene, Chevalier et al. 2008) and IL-17A and IL-22 producing cells were present in psoriatic skin lesions (Harper, Guo et al. 2009). Other studies also confirmed a higher expression of IL-17A or IL-17A mRNA in psoriasis (Li, Chen et al. 2007; Guttman-Yassky, Lowes et al. 2008; Lowes, Kikuchi et al. 2008; Johansen, Usher et al. 2009), as well as a higher mRNA or cytokine level of IL-17C (Johansen, Usher et al. 2009), IL-17F (Guttman-Yassky, Lowes et al. 2008; Johansen, Usher et al. 2009), IL-23 (Li, Chen et al. 2007; Guttman-Yassky, Lowes et al. 2008), IL-23R (Guttman-Yassky, Lowes et al. 2008), and IL-6 (Li, Chen et al. 2007). IL-23, IL-17A, and IL-17F expression levels were elevated in a mouse-model of psoriasis. IL-23 and IL-17R deficiency prevents the development of the disease. Furthermore, an increase in Th17 cells in the spleen was found in this mouse-model (van der Fits, Mourits et al. 2009). In another mouse-model, increased expression of IL-17, IL-1β, IL-6, and IL-22 in the inflamed ear skin was revealed and also IL-12 and TNF-α expression was enhanced (Hvid, Teige et al. 2008). Anti-IL-22 antibody treatment reduces Th17 cytokine expression, infiltration of inflammatory cells, and disease progression and injection of IL-22 in mouse ear skin induces expression of inflammatory proteins, including S100A8 and 9, and defensin β1 (Ma, Liang et al. 2008). In another study, IL-17 was shown to induce the production of CCL20, IL-23 subunit p19, S100A7, A9 and A12, human defensin β2, and lipocalin 2 in keratinocytes. IL-22 was not inducing the production of any of these proteins (Guttman-Yassky, Lowes et al. 2008). Furthermore, Th17 cells were discovered in the dermis of skin lesions of psoriasis patients (Lowes, Kikuchi et al. 2008) and psoriatic dermal dendritic cells (DCs) induced T cells to differentiate to Th1 and Th17 cells. Furthermore, these DCs induce a specific T cell population that produces both IL-17 and IFN-γ (Zaba, Fuentes-Duculan et al. 2009). Lowes *et al.* (2008) also suggested a combined influence of Th1 and Th17 cells in psoriasis (Lowes, Kikuchi et al. 2008). Psoriatic DCs produce IL-23 and TNF-α (Guttman-Yassky, Lowes et al. 2008) and anti-TNF treatment in psoriasis patients with Etanercept inhibited IL-23 production by DCs and also reduced the expression of IL-17, IL-22, IL-23, CCL20, and defensin β4 in psoriatic skin (Zaba, Cardinale et al. 2007). It has also been reported that myeloid APCs could induce IL-17+ T cells in psoriasis and IL-1, IL-23, and CCL20 production by these APCs was induced by IFN-γ (Kryczek, Bruce et al. 2008). Furthermore, CCL20 and CCR6 expression and T cell infiltration in the skin of mice is induced by IL-17A, IL-22, and TNF-α. It has been suggested that the production of CCL20, due to Th17 cytokines, was resulting in the maintenance of CCR6+ Th17 cells in psoriasis (Harper, Guo et al. 2009). These data suggest that psoriatic dermal DCs induce differentiation of Th1 and Th17 cells via IL-23 and TNF-α expression. Production of IL-17, IL-22 and IFN-γ by these cells then leads to expression of inflammatory and antimicrobial proteins in the skin, for example by keratinocytes. This results in the infiltration of leukocytes and tissue damage.

Multiple-sclerosis

IL-17 producing T cells were more efficient in inducing experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple-sclerosis (MS), compared to IFN-γ producing T cells and anti IFN-γ antibodies were exacerbating EAE (Langrish, Chen et al. 2005). Soon after the discovery of Th17 cells, it was demonstrated that

EAE was less severe in IL-17 knockout mice (Komiyama, Nakae et al. 2006). Immunization against IL-17 resulted in amelioration of EAE (Rohn, Jennings et al. 2006) and IL-17A was more important in the development of EAE, compared to IL-17F (Ishigame, Kakuta et al. 2009). Astrocytes induce IL-17 and IFN-γ expression by T cells (Miljkovic, Momcilovic et al. 2007). Furthermore, IL-17+ T cells were increased in lesions of MS patients (Tzartos, Friese et al. 2008) and IL-17 and IL-22 receptors were expressed on endothelial cells of the blood-brain barrier (BBB) in lesions of MS patients. IL-17 reduces tight junctions on endothelial cells of the BBB. IL-17 and IL-22 increased the permeability and allowed CD4+ T cells to migrate across the BBB. IL-17 and IL-22 expressing Th17 cells that were migrating across endothelial cells of the BBB, were also expressing granzyme B and were shown to kill human fetal neurons (Kebir, Kreymborg et al. 2007). Th17 cells induce expression of CXCL1 and CXCL2 in murine spinal cords and deficiency of CXCR2, the receptor for these chemokines, resulted in diminished BBB permeabilization and infiltration of leukocytes and inhibited the development of EAE (Carlson, Kroenke et al. 2008). More cytokines were shown to be involved in MS. IL-6 knockout mice showed no development of EAE (Korn, Mitsdoerffer et al. 2008) and EAE was also inhibited by anti-IL6R antibody treatment (Serada, Fujimoto et al. 2008). IL-23 and IL-10 expression is enhanced in MS (Krakauer, Sorensen et al. 2008) and astrocytes express IL-23 subunits p19 and p40 (Miljkovic, Momcilovic et al. 2007). Development of EAE is totally blocked in mice deficient of IL-23 subunit p19 (Langrish, Chen et al. 2005), but Thakker *et al.* (2007) showed that transfer of reactive T cells to p19 deficient mice caused EAE, suggesting that IL-23 was only necessary for the induction and not the progression of EAE (Thakker, Leach et al. 2007). Development of EAE is prevented in IL-1R1 knockout mice, which showed impaired differentiation of Th17 cells. Expression of IL-1R1 by Th17 cells is mediated by STAT3, RORγt, and RORα and IL-1R1 activation induces IRF4 and RORγt (Chung, Chang et al. 2009). Furthermore, EAE is reduced in mice deficient of RORγt (Ivanov, McKenzie et al. 2006) and deficiency of both RORy and RORα totally blocks the development of EAE (Yang, Pappu et al. 2008). Also mice with STAT3 deficient CD4+ T cells are protected against the development of EAE (Liu, Lee et al. 2008). The cytokine IL-27 inhibits EAE (Diveu, McGeachy et al. 2009) and reduces the number of Th17 cells (Fitzgerald, Ciric et al. 2007). EAE is increased in mice deficient of the IL-27 subunit p28 (Diveu, McGeachy et al. 2009). Taken together, Th17 cells could be activated by astrocyte-derived IL-23 to produce IL-17 and IL-22, resulting in the loss of tight junctions on endothelial cells of the BBB, causing an increased permeability. This allows reactive Th17 cells, and maybe other immune cells, to migrate across the BBB. Th17 cells could then produce granzyme B and destroy neuronal cells. IL-1, IL-6, and their receptors also contribute to this whole process, however, exact mechanisms are still unclear. IFN-γ and IL-27 reduce the effects of Th17 cells.

Type I diabetes

Induction of IFN-γ in non-obese diabetic (NOD) mice by glutamic acid decarboxylase 2 (GAD2) peptide treatment results in reduced IL-17 production. GAD2 treatment also decreased infiltration of the pancreatic islets of Langerhans by leukocytes and the number of insulin producing β-cells of the pancreas was increased. Furthermore, the blood glucose level of hyperglycemic mice was reduced to normal levels with GAD2 treatment. It was suggested that blood glucose level was normalized by the inhibition of IL-17 production, due to IFN-γ induction (Jain, Tartar et al. 2008). IL-17A and IL-17F are expressed in the pancreas of NOD mice and this is related to infiltration of leukocytes to the islets of Langerhans and the development of diabetes. Anti-IL-17 antibody treatment reduces infiltration of leukocytes and it was suggested that Th17 cells were involved in the infiltration of macrophages to the islets of

Langerhans (Martin-Orozco, Chung et al. 2009). Another study also showed a reduction in T cell infiltration with anti-IL-17 antibody treatment in NOD mice, as well as with IL-25 (IL-17E) treatment, suggesting a role for Th17 cells in the development of diabetes. Furthermore, the number of Treg cells is increased in lymph nodes of the pancreas after both treatments (Emamaullee, Davis et al. 2009). Although IL-17 is involved in the infiltration of leukocytes to the islets of Langerhans, IFN-γ is required for the destruction of the islets and the induction of diabetes (Martin-Orozco, Chung et al. 2009). IL-21 is also involved in the development of diabetes. The forming of diabetes was almost totally blocked in IL-21 receptor knockout mice and the amount of IL-17 and IL-17 producing cells in the spleen and lymph nodes of the pancreas was reduced. Also expression of the Regenerating (Reg) gene family of regenerating β-cells in the pancreas is enhanced in IL-21R knockout mice (Spolski, Kashyap et al. 2008). The development of diabetes is also inhibited by bone marrow stromal cells (BMSCs), which secrete TGF-β. BMSCs reduce the glucose level in the blood and co-culturing with CD4+ T cells induces the development of Treg cells. TGF-β blockage results in the development of Th17 cells (Zhao, Wang et al. 2008). In short, the production of IL-17 by Th17 cells leads to infiltration of leukocytes in the islets of Langerhans, causing destruction of β-cells, reducing the insulin production and ultimately increasing the blood glucose level. IL-21 plays an important role in this process, since IL-21R knockout causes almost total inhibition of diabetes. IL-25 inhibits the infiltration of T cells. The exact role of IFN-γ is unclear, but it was shown to be required for the destruction of the islets.

The role of Th17 cells in autoimmune disorders

Taken together, Th17 cells seem to facilitate permeability and infiltration of leukocytes. In some cases, e.g. multiple-sclerosis, Th17 cells were found to destroy cells. However, often Th17 cells induce other cells to produce tissue damaging factors.

Th17 cells in allergic disorders

The role of Th17 cells in allergic disorders has been studied extensively, but is less clear compared to their role in autoimmune disorders. The role of Th17 cells in asthma, contact hypersensitivity, and atopic dermatitis is described here.

Asthma

IL-17 is involved in asthma. IL-17 producing T cells that express RORγ, are present in inflamed tissue of allergic asthma patients (Pene, Chevalier et al. 2008). Furthermore, the mRNA level of IL-17A is enhanced in the sputum of asthma patients, as well as the mRNA level of IL-8. The mRNA level of IL-17A and IL-8 is related to the number of neutrophils in the sputum of asthma patients (Bullens, Truyen et al. 2006). Airway hypersensitivity is inhibited in IL-17 deficient mice (Nakae, Komiyama et al. 2002). Th17 cells and IL-23 induce neutrophil infiltration and inflammation of the airways, as well as induction of Th2-mediated infiltration of eosinophils (Wakashin, Hirose et al. 2008). This suggests that asthma is a Th17 and Th2 mediated disease. Furthermore, both Th17 and Th2 cells induce airway inflammation, but Th17 induced inflammation is resistant to steroid therapy (McKinley, Alcorn et al. 2008). Airway hyperresponsiveness is mediated by myeloid dendritic cells. These myeloid DCs express IL-6 and IL-23, indicating a role for Th17 cells (Lewkowich, Lajoie et al. 2008). IL-17 is enhanced in bronchoalveolar lavage (BAL) fluid of asthma patients. However, it has been suggested that production of IL-17 was mostly carried out by macrophages instead of Th17 cells, because IL-17 positive macrophages were found in a mouse model of asthma related inflammation and macrophage deficiency resulted in inhibition of inflammation (Song, Luo et al. 2008). Th17 cells could play an important role in asthma, but more research is needed in order to reveal the exact mechanisms.

Contact hypersensitivity

A role for IL-17 in contact hypersensitivity (CHS) was described by several studies. CHS is inhibited in IL-17 deficient mice (Nakae, Komiyama et al. 2002) and especially IL-17A, not IL-17F, plays an important role in CHS (Ishigame, Kakuta et al. 2009). IL-17 is secreted by CD4+ T cells in the inflamed skin and peripheral blood of CHS patients (Albanesi, Scarponi et al. 2000). Furthermore, expression of IL-17, IL-22, and IL-22R was found in skin lesions of CHS patients after nickel stimulation and CD4+ T cells were expressing CCR6. Also infiltration of neutrophils was found and keratinocytes were secreting IL-23 after stimulation with nickel (Larsen, Bonefeld et al. 2009).

Atopic dermatitis

IL-17 is expressed in the skin after ovalbumin injection in a murine model of atopic dermatitis (AD). Also IL-17 positive T cells were found in the draining lymph nodes and spleen of these mice and IL-17 was enhanced in the serum (He, Oyoshi et al. 2007). Another study reports an increase in Th17 cells in the inflamed skin and peripheral blood of AD patients (Koga, Kabashima et al. 2008). A small increase of IL-23, IL-17 A and F was shown in inflamed skin of AD patients (Guttman-Yassky, Lowes et al. 2008).

Th17 cells in other diseases

Inflammatory bowel disease

Several studies report a relation between Th17 cells and inflammatory bowel disease (IBD). Th17 cells are present in inflamed tissue of Crohn's disease patients. These cells express CCR6, CD161, IL-17, IL-22, and IL-23R. Stimulation with IL-23 induces IL-17 and IFN-γ production by these Th17 cells and T cell supernatant, together with CCL20, induces IL-6 and TNF-α production by intestinal cells, indicating tissue inflammation (Kleinschek, Boniface et al. 2009). Expression of the IL-23R was found in Crohn's disease and ulcerative colitis and IL-23 induced IL-17 expression in ulcerative colitis (Kobayashi, Okamoto et al. 2008). Another study reported that IBD was related to IL-17 production and Th17 differentiation, due to IL-23 production by DCs (Sheibanie, Yen et al. 2007). Th17 cells are present in mice with colitis after transfer of reactive CD4+ T cells to severe combined immunodeficiency (SCID) mice. Th17 cells cause inflammation and anti IL-23 p19 subunit antibody treatment results in apoptosis of Th17 cells, reduction of inflammatory cytokines, and inhibition of colitis (Elson, Cong et al. 2007). A relation between Th17 cells and colitis was also found when T cells were transferred to recombination activation gene 1 (RAG1) knockout mice. T cells deficient of IL-17A, IL-17F, or IL-22 cause colitis, whereas RORγ deficient T cells do not cause colitis. RORγ deficient T cells show a decreased production of IL-6, IL-17A, IL-17F, GM-CSF, and IFN-γ. Interestingly, anti IL-17A antibody treatment of mice with IL-17F deficient T cells inhibited colitis and IL-17A treatment of mice with RORγ deficient T cells induced colitis (Leppkes, Becker et al. 2009). This suggests that down regulation of IL-17A or F alone in T cells is not sufficient to inhibit colitis, whereas a deficiency of the downstream regulator RORγ is sufficient. RORγ expression is enhanced in Crohn's disease and ulcerative colitis (Kobayashi, Okamoto et al. 2008). IL-17 expression is enhanced in Crohn's disease (Fina, Sarra et al. 2008) and the mRNA level of IL-17 is increased in ulcerative colitis (Kobayashi, Okamoto et al. 2008). The mRNA level of IL-17F is enhanced in Crohn's disease (Seiderer, Elben et al. 2008) and also other cytokines were found to be related to IBD. IL-21 expression is enhanced in Crohn's disease, compared to healthy controls (Fina, Sarra et al. 2008). IL-21R expression is enhanced in IBD and IL-21 induces T- and NK cells to produce IFN-γ and TNF. Also CD4+ T cells are induced by IL-21 to express RORγt and IL-17A, indicating a Th17 phenotype (Liu, Yang et al. 2009). Colitis is prevented in IL-21 deficient mice, due to a lack of Th17 differentiation. Also IL-17 production by T cells in the lamina propria of IBD patients is inhibited by anti IL-21 antibody treatment (Fina, Sarra et al. 2008). IL-22, expressed by CD4+ T cells and NK cells, inhibits IBD in mice (Zenewicz, Yancopoulos et al. 2008). From these data, we can conclude that Th17 cells can be induced by IL-23 and IL-21 to produce IL-17 and IFN-γ. This leads to IL-6 and TNF-α production by intestinal cells, an increased level of inflammatory cytokines, and ultimately to inflammatory bowel diseases. IL-22 is also playing a role in this process, although the exact mechanism is unknown.

Periodontal disease

Th17 cells are found in the gingival tissue of periodontitis patients. Also expression of IL-1β, IL-6, IL-23, and TGF-β is enhanced in periodontitis. Furthermore, IL-17 and receptor activator for nuclear factor κ B ligand (RANKL) are expressed in periodontitis. RANKL is a bone destruction factor and was found in the alveolar bone (Cardoso, Garlet et al. 2009). Another study showed that IL-17 and RANKL were positively correlated to each other and to RORγt in inflamed tissue of periodontitis

patients (Dutzan, Gamonal et al. 2009). The expression levels of IL-17A and IL-12 p35 subunit are enhanced in periodontitis, compared to gingivitis. CCR4 and CCR6 seems to be increased and the CCR6 ligand CCL20 is enhanced in periodontitis, compared to gingivitis (Honda, Aoki et al. 2008). This suggests that Th17 cells may be involved in the progression of gingivitis to periodontitis and the subsequent bone destruction, however also inhibition of IL-17 production by IL-12 may occur.

Cancer

Th17 cells have been implicated to play a role in various forms of cancer. Th17 cells are present in ovarian tumors. The ovarian tumor cells and antigen presenting cells (APCs) express IL-6, TGF-β, and IL-1β. These cytokines are known to induce Th17 cells. Also TNF-α is expressed by the tumor cells and APCs in ovarian cancer. Ovarian tumor cells and APCs are able to induce Th17 cell differentiation in a population of CD4+ T cells and IL-1 is critical in this process (Miyahara, Odunsi et al. 2008). Th17 cells were also found in peripheral blood of patients with gastric tumors and the number of Th17 cells is increased when disease status is more severe. The expression of RORγ, IL-17, and IL-23 p19 subunit is enhanced in severe gastric tumors. Furthermore, the expression levels of IL-17 and IL-23 are higher in the serum of patients (Zhang, Rong et al. 2008). IL-17 positive T cells are found in mice with melanomas, prostate tumors, head and neck tumors, and fibrosarcomas and in human patients with ovarian tumors, pancreas tumors, and renal cell carcinoma. IL-2 treatment results in a decreased number of IL-17 positive T cells and an increase of Treg cells in the tumors (Kryczek, Wei et al. 2007). Th17 cells are increased in patients with myeloma. Furthermore, phagocytosis of apoptotic myeloma cells by DCs results in the induction of a higher number of Th17 cells (Dhodapkar, Barbuto et al. 2008). Th17 cells are more efficient in killing melanoma cells, compared to Th1 cells. However, IFN-γ expression by these Th17 cells plays a major role in melanoma rejection, in contrast to the expression of IL-17 and IL-23, which was hardly affecting tumor rejection (Muranski, Boni et al. 2008). Tumor rejection by IL-17 producing T cells was found in prostate cancer. CD4+ and CD8+ T cells, activated by IL-6 released by prostate tissue after heat shock protein 70 (hsp70) induction, produce IL-17 and are able to reject prostate tumors (Kottke, Sanchez-Perez et al. 2007). IL-23 treatment induces tumor rejection in a mouse model of fibrosarcoma and CD4+ and CD8+ T cells and NK cells are involved in the rejection of the tumor (Kaiga, Sato et al. 2007). Taken together, Th17 cells are present in various tumors. Weather they are protective or not is in many cases unknown. In gastric tumors, the severity of the tumor is related to the amount of Th17 cells and Th17-related cytokines. Th17 cells are able to eliminate melanoma cells, however, IFN-γ expression is more important than IL-17 and IL-23 expression. IL-17 producing T-cells are able to destroy prostate tumor cells after stimulation with IL-6. Furthermore, CD4+ and CD8+ T-cells and NK cells play a role in the rejection of fibrosarcoma cells. It seems that, in some cases, Th17 cells can play a protective role in the elimination of tumor cells.

Concluding remarks

The exact differentiation process of Th17 cells remains vague, but many important factors have already been identified, for example IL-6, TGF-β, IL-21, and IL-23. Cytokine signaling induces gene transcription via the intracellular factors STAT3, RORγt, and RORα, which leads to IL-17 production and Th17 phenotype. Also inhibitors of Th17 differentiation, like IL-27 and IFN-γ, have been found. The natural function of Th17 cells is still not completely understood, however, it is shown by many studies that Th17 cells are able to induce neutrophils and macrophages to eradicate extracellular bacteria and fungi. Furthermore, Th17 cells stimulate endothelial cells, fibroblasts and keratinocytes to produce inflammatory cytokines and antimicrobial factors. The understanding of Th17 cell differentiation and function are important subjects for further research since Th17 cells are also involved in several autoimmune diseases, allergic diseases, and several forms of cancer. Better knowledge on these processes may lead to the discovery of targets for treating these diseases.

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