Regulation of T$_H$17 Cells and Associated Cytokines in Wound Healing, Tissue Regeneration, and Carcinogenesis

Leonie Brockmann $^1$, Anastasios D. Giannou $^1$, Nicola Gagliani $^{1,2,3}$ and Samuel Huber $^{1,*}$

$^1$ I. Department of Medicine, University Medical Center Hamburg-Eppendorf, 20246 Hamburg, Germany; lbrockmann@uke.de (L.B.); a.giannou@uke.de (A.D.G.); n.gagliani@uke.de (N.G.)

$^2$ Department of General, Visceral and Thoracic Surgery, University Medical Center Hamburg-Eppendorf, 20246 Hamburg, Germany

$^3$ Department of Medicine Solna (MedS), Karolinska Institute, 17177 Stockholm, Sweden

* Correspondence: s.huber@uke.de; Tel.: +49-40-7410-57273; Fax: +49-40-7410-59038

Academic Editor: Allison Cowin

Received: 30 March 2017; Accepted: 8 May 2017; Published: 11 May 2017

Abstract: Wound healing is a crucial process which protects our body against permanent damage and invasive infectious agents. Upon tissue damage, inflammation is an early event which is orchestrated by a multitude of innate and adaptive immune cell subsets including T$_H$17 cells. T$_H$17 cells and T$_H$17 cell associated cytokines can impact wound healing positively by clearing pathogens and modulating mucosal surfaces and epithelial cells. Injury of the gut mucosa can cause fast expansion of T$_H$17 cells and their induction from naïve T cells through Interleukin (IL)-6, TGF-β, and IL-1β signaling. T$_H$17 cells produce various cytokines, such as tumor necrosis factor (TNF)-α, IL-17, and IL-22, which can promote cell survival and proliferation and thus tissue regeneration in several organs including the skin, the intestine, and the liver. However, T$_H$17 cells are also potentially pathogenic if not tightly controlled. Failure of these control mechanisms can result in chronic inflammatory conditions, such as Inflammatory Bowel Disease (IBD), and can ultimately promote carcinogenesis. Therefore, there are several mechanisms which control T$_H$17 cells. One control mechanism is the regulation of T$_H$17 cells via regulatory T cells and IL-10. This mechanism is especially important in the intestine to terminate immune responses and maintain homeostasis. Furthermore, T$_H$17 cells have the potential to convert from a pro-inflammatory phenotype to an anti-inflammatory phenotype by changing their cytokine profile and acquiring IL-10 production, thereby limiting their own pathological potential. Finally, IL-22, a signature cytokine of T$_H$17 cells, can be controlled by an endogenous soluble inhibitory receptor, Interleukin 22 binding protein (IL-22BP). During tissue injury, the production of IL-22 by T$_H$17 cells is upregulated in order to promote tissue regeneration. To limit the regenerative program, which could promote carcinogenesis, IL-22BP is upregulated during the later phase of regeneration in order to terminate the effects of IL-22. This delicate balance secures the beneficial effects of IL-22 and prevents its potential pathogenicity. An important future goal is to understand the precise mechanisms underlying the regulation of T$_H$17 cells during inflammation, wound healing, and carcinogenesis in order to design targeted therapies for a variety of diseases including infections, cancer, and immune mediated inflammatory disease.

Keywords: T$_H$17 cells; cytokines; wound healing; tissue regeneration; carcinogenesis; immune regulation

1. Inflammation in Wound Healing and Carcinogenesis

In 1986, Dvorak published an essay with the vivid title: “Tumors: Wounds that do not heal”, summarizing in this one statement the relation between wound healing and carcinogenesis [1]. Wound
healing normally follows sequential but overlapping steps. The immediate reaction is hemostasis to provisionally close the wound. A fibrin clot is formed and platelets aggregate. This is followed by the inflammatory phase which is characterized by the presence of neutrophils, macrophages, and lymphocytes in the wound. These cells are attracted by chemokines, which are, for example, released by platelet cells [2]. The inflammatory phase is important for tissue regeneration due to the release of pro-inflammatory cytokines and growth factors from immune cells [3–5]. Additionally, phagocytes can ingest cell debris and invading pathogens. Therefore, the inflammatory phase is essential to prevent spreading of infections. The proliferative phase follows several days later leading to re-epithelialization, formation of new blood vessels, and fibrogenesis. During the last phase, the resolution phase, vessel regression and collagen remodeling occur [6]. Thus, occurrence of a wound has a dramatic impact on the body. Multiple cell types are necessary to secure a prompt healing process. Research elucidating this process mainly focuses on innate immunity contributing to tissue regeneration. However, adaptive immunity also plays its part during this process, even though its contribution and regulation is much less understood.

Tissue damage, especially at barrier organs such as the intestine, the lung, and the skin, is a potential gateway for invading pathogens, therefore inflammation is an essential part of wound healing. In this regard, the involvement of T cells during wound repair has been under investigation for a long time. In 1987, the hypothesis that T lymphocytes represent the most frequent leucocyte population in skin wounds was published [7]. Several studies indicate that delayed infiltration of T cells and a lower concentration of these cells at the site of the wound are associated with impaired wound healing. Furthermore, CD4+ T cells seem to play a beneficial role during the process of wound healing and regeneration [8–10]. However, very little is known about the contribution of different T cell subsets. Furthermore, these mechanisms, which are designed to promote wound healing, also have the potential to promote chronic inflammation and carcinogenesis. Two important predisposing factors for colorectal carcinogenesis are chronic intestinal inflammation and tissue injury. This association is based on the fact that wound healing and carcinogenesis are driven by several common factors and signaling pathways. Upon tissue injury, factors promoting healing are stimulated and their action must be tightly controlled in order to avoid carcinogenesis [11]. A chronically inflamed and wounded tissue is associated with a long-lasting healing response which may lead to fibrosis, tissue dysfunction, and ultimately the development of cancer. Thus, carcinogenesis could be considered as a consequence of failing regulatory mechanisms allowing abnormal excessive healing [11].

2. CD4+ T Helper Cells

Conventional αβ CD4+ T cells are one of the main players during an adaptive immune response. Due to their great variety, CD4+ T cells can orchestrate the immune response and react to the whole spectrum of immune challenges. Two major CD4+ T helper cell subsets, Th1 and Th2, were discovered in 1989 [12]. However, the Th1/Th2 paradigm was challenged in 2005 by the description of Th17 cells, which are primarily needed for the defense against extracellular bacteria and fungi [13]. Additionally, Th17 cell associated cytokines can promote epithelial proliferation and tissue regeneration [14].

The gastrointestinal tract, like skin and lung, is constantly in contact with hundreds of different species of commensal bacteria and fungi [15]. How the commensal microbiota modulate the immune system of the host and vice versa has been an area of intensive research and is still not completely understood. Nonetheless, it is known that the induction of Th17 cells is dependent on the presence of microbiota, especially segmented filamentous bacteria (SFB) in the terminal ileum of the small intestine in mice. Hence, under physiological conditions, Th17 cells are mainly located in the small intestine [16]. Upon tissue damage, Th17 cells rapidly expand at mucosal surfaces to guarantee a quick clearance of the invading microorganisms such as commensal bacteria. To this end, Th17 cells release several chemokines and cytokines, such as IL-17A, IL-17F, and IL-22 which are the signature cytokines of Th17 cells. One major defense mechanism of Th17 cells is the attraction of inflammatory cells via chemotaxis to the site of infection, which is crucial for the fast clearance of pathogens [17,18].
Additionally, T\(H\)\(_17\) cells contribute to the crosstalk of immune cells and epithelial cells or other innate immune cells by inducing the release of anti-microbial peptides [19–22]. The signature cytokines, IL-17A and IL-17F, both binding to IL-17RA [23], and IL-22, binding to IL-22R1, mediate this effect of T\(H\)\(_17\) cells. IL-22 does not only promotes the secretion of anti-microbial peptides from the epithelium, but also exhibits tissue protective properties. An important effect of IL-22 signaling on epithelial cells is the induction of proliferation, survival, and tissue repair via induction of STAT3 [14,24,25]. Thus, T\(H\)\(_17\) cells act at different front lines during the defense of the body: (a) T\(H\)\(_17\) cells activate and attract other immune cells, mainly neutrophils, which can phagocyte pathogens. Therefore, tissue resident T\(H\)\(_17\) cells could contribute to the inflammatory phase of wound healing. (b) T\(H\)\(_17\) cells induce the release of anti-microbial peptides from non-immune cells. (c) Finally, T\(H\)\(_17\) cell associated cytokines, such as IL-22, can promote wound healing and tissue regeneration, leading to a faster closing of potential entryways of microorganisms. In the next sections, we will give an overview of how T\(H\)\(_17\) cell associated cytokines affect wound healing and carcinogenesis.

3. Effects of T\(H\)\(_17\) Cell Associated Cytokines on Wound Healing and Carcinogenesis

3.1. Effects of IL-17 on Wound Healing

Interleukin-17 (IL-17), also known as IL-17A, is the main member of the IL-17 family, which consists of six members: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (also named IL-25), and IL-17F. This mediator is not only secreted by T\(H\)\(_17\) cells alone, but also by other immune cell types such as natural killer (NK), natural killer T (NKT), lymphoid tissue inducer (LTi), and LTi-like cells. Apart from immune cells, IL-17A can also be produced by Paneth cells which are epithelial cells located in the small intestine. To conduct its biological functions, IL-17 binds to a heteromeric receptor complex consisting of IL-17RA and IL-17RC. Along with three additional variants, namely IL-17RB, IL-17RD and IL-17RE, IL-17RA and IL-17RC, they comprise the IL-17 receptor family [26]. IL-17 is a pro-inflammatory cytokine, which is commonly found at high levels in inflamed sites. Recent studies have identified a link between the IL-23 induced expansion of T\(H\)\(_17\) cells followed by IL-17 secretion and the pathogenesis of IBD [27]. T\(H\)\(_17\) cells are mainly responsible for IL-17 production, which is elevated in IBD. Controversially, a role of IL-17 in IBD-related mucosal healing was recently found. Song et al. showed that following epithelial barrier damage, FGF2 is highly expressed and cooperates with IL-17 in order to enhance tissue repair. Specifically, upon barrier destruction, dysregulated microbiota cause an upregulation of TGF-\(\beta\) which subsequently stimulates FGF2 production by regulatory T cells. Then, FGF2 together with IL-17 upregulates genes associated with epithelial healing and boosts epithelial cell proliferation [28].

Recent studies focusing on skin wound healing have concluded that IL-17 plays a role in the early inflammatory stage of the wound and could act as an inhibitor to normal wound repair. As seen in psoriasis, IL-17 has several functions in the skin. The expression of IL-17 receptor on keratinocytes, fibroblasts, and inflammatory cells reveals that IL-17 can affect numerous cell types in the skin. In skin lesions, it is macrophages and not T cells which are the main cellular source of IL-17. To elucidate the role of IL-17 in skin wound healing, Rodero et al. used \(II17\)\(^{-/-}\) mice and showed that absence of IL-17 enhances and accelerates skin tissue repair. Blocking IL-17 with specific antibodies during the early steps of healing also resulted in wound closure promotion [29]. On the other hand, a beneficial role of IL-17 in sensory nerve regeneration has been recently revealed. In a mouse model of corneal abrasion, an IL-17 dependent signaling pathway involving IL-17, neutrophils, platelets, and vascular endothelial growth factor (VEGF)-A was found to promote corneal repair and nerve regeneration [30].

In conclusion, IL-17 seems to have dual functions during wound healing. It may have beneficial functions in the intestine and for nerve regeneration [31]. However, in the skin, especially in psoriasis, it seems to be mainly pathogenic. Environmental factors may play a crucial role determining the part IL-17 has in wound healing, but further studies are needed to clarify this point.

Likewise, the role of IL-17 during carcinogenesis is still not completely understood. T\(H\)\(_17\)-related events and specifically the role of IL-17 were first thought to promote tumor growth and invasion and
to enhance angiogenesis [32]. However, other studies identified a protective role in tumor immune
surveillance together with an inhibition of cancer cell proliferation and metastasis [33–35]. Using
spontaneous intestinal carcinogenesis models, the role of IL-17A in colorectal cancer development
was further elucidated. Recent studies showed that blocked or genetically-induced absence
of IL-17A resulted in significantly attenuated tumor burden in ApcMin/+ mice infected with
enterotoxigenic Bacteroides fragilis and in the standard ApcMin/+ model [36,37]. In the dextran
sulfate sodium/azoxymethane (DSS/AOM) carcinogenesis model, Il17a−/− mice displayed reduced
tumorigenesis, which could be attributed to lower levels of intestinal TNF-α, interferon (IFN)-γ, IL-6,
and STAT3 activity [38]. Interestingly, a highly expressed Th17 cell related mRNA pattern correlates
with poor prognosis in human colorectal cancer [39,40]. This observation is likely associated with the
fact that Th17 cells are the main IL-17A producers in the tumor. However, other immune cell subsets
such as CD8+ CTLs (Tc17 cells), γδ T cells (γδT17 cells), and innate lymphoid cells (ILCs) also produce
IL-17A [41–43]. Notably, upon dendritic cell (DC)-mediated stimulation, γδT17 cells produce IL-17 and
enhance the recruitment and expansion of myeloid-derived suppressor cells. This finding suggests that
IL-17A is likely to be associated with immune silencing in colorectal cancer. Due to the well-described
implication of IL-17A in colorectal cancer, targeting of IL-17A may serve as a promising therapeutic
approach. Interestingly, a recent study showed that blocking of IL-17A in an adenomatous polyposis
coli (APC)-mediated colon carcinogenesis model enhanced tumor sensitivity to the anticancer agent
5-fluorouracil [44]. Similarly, antiangiogenic therapies might fail due to the IL-17A-driven emergence
of resistant tumor stromal cells [45].

Apart from IL-17A, another member of the IL-17 superfamily and ligand of IL-17RE, IL-17C, was
shown to be expressed in intestinal epithelial cells during early stages of colon carcinogenesis. In both
the ApcMin/+ and the DSS/AOM-induced carcinogenesis models, mice lacking IL-17RE displayed a
decreased tumor burden together with a lower expression of the anti-apoptotic proteins BCL-2 and
BCLXL. Interestingly, IL-17C can be associated with the human condition, since it is overexpressed in
human colon cancers [46]. IL-17F, which also belongs to the IL-17 family, resembles IL-17A and acts
via the same receptor, and may play an opposite role in colon carcinogenesis. In contrast to IL-17A and
C, IL-17F is significantly downregulated in human colorectal cancer. Notably, it reduces carcinogenesis
in the DSS/AOM carcinogenesis model by inhibiting angiogenesis [47].

3.2. Effects of IL-22 on Wound Healing

Interleukin-22 (IL-22), a member of the IL-10 cytokine family, participates in the signaling between
the immune system and the peripheral tissues. IL-22 can be produced by several other cell types
such as Th22, T cell receptor (TCR)-γδ, NK, NKT, ILCs, and LTi cells, with the notable exception
of Th17 cells. IL-22 acts via binding to the heterodimer IL-10R2/IL-22R1 complex [48]. IL-22R1 is
expressed on non-hematopoietic cells, such as intestinal epithelial cells, hepatocytes, and fibroblasts
in the skin. After binding of IL-22 to the receptor complex, STAT3, STAT1, and STAT5, as well as
the Janus kinase (JNK) and mitogen-activated protein kinases are activated. The translocation of
activated STAT dimers into the nucleus leads to the activation of several genes linked to proliferation
and cell survival. IL-22 is known to play a key role in tissue regeneration and wound healing [3].
In a mouse model of acute skin injury, an upregulation of Il22 mRNA expression was observed
during the inflammatory stage and IL-22 was identified as a critical mediator for normal fibroblast
function, extracellular matrix protein production, and myofibroblast differentiation during skin wound
healing [49]. IL-22 was found to facilitate the crosstalk between immune cells and fibroblasts during
skin wound healing. It has also been shown to promote keratinocyte proliferation and migration
while acting as an inhibitor for keratinocyte differentiation [3,50–52]. IL-22 is unlikely to play a major
role in the early stages of skin wound healing such as immune cell accumulation and angiogenesis.
Similarly, loss of IL-22 does not affect keratinocyte function during skin wound healing. However,
upon wound healing, fibroblast function was shown to be IL-22-dependent. Specifically, absence of
IL-22 leads to impaired granulation, tissue formation, production of extracellular matrix components
(ECM), and wound contraction. Primary dermal fibroblasts are directly affected by IL-22, since they express IL-22R1, whose IL-22-triggered activation can lead to STAT3 phosphorylation. IL-22 stimulates ECM production by inducing ECM gene expression in fibroblasts and by promoting myofibroblast differentiation. A decreased number of myofibroblasts in the wound may lead to defective wound contraction and impaired ECM formation, as seen in Il22−/− mice. IL-22 may induce the expression of ECM genes, mainly via STAT3 activation. IL-22-mediated STAT3 phosphorylation leads to activation of the promoters of fibronectin and collagen.

Interestingly, IL-22 is also essential for intestinal healing and the maintenance of the mucosal barrier. In studies using the DSS-induced acute intestinal injury in Il22−/− mice, IL-22 was shown to enhance intestinal wound healing, specifically via STAT3 activation, which in turn regulates signaling pathways commonly associated with tissue repair and gut homeostasis. Mice lacking IL-22 exhibited an impaired and delayed recovery from DSS-caused intestinal injury [14]. Similarly, targeting of IL-22 with specific neutralizing antibodies led to impaired wound healing in wildtype mice. On the other hand, increase of intestinal IL-22 expression via a gene delivery system boosted the recovery of the injured intestine [24]. Interestingly, another study showed that IL-22 deficiency leads to altered intestinal microbiota and therefore increases the severity of the disease in a mouse model of experimental colitis. This IL-22-mediated changed microbiota can be transferred to co-housed wild type mice, which subsequently become more susceptible to experimental colitis, suggesting that IL-22 is essential for maintaining the balance between immunity and intestinal microbiota [52].

Although the beneficial role of IL-22 in wound healing is well documented, in some cases the delicate balance between protection and harm shifts in favor of the pathogenic direction leading to carcinogenesis. A tumor-promoting function of IL-22 via STAT3 stimulation has already been identified in cancers such as hepatocellular carcinoma and lung cancer [53,54]. Recent studies suggest that in the absence of close regulation, IL-22 also promotes colon carcinogenesis via STAT3 activation [55]. To this end, Huber et al. recently reported that IL-22 is involved in colitis associated colon cancer in a dual manner. On the one hand, IL-22 deficiency can delay tissue repair, thereby sustaining inflammation and leading to tumor development. On the other hand, high levels of IL-22 in Il22bp−/− mice may prolong the regenerative program and promote colon carcinogenesis [56]. Clinical data show an association between high serum IL-22 levels and resistance to chemotherapy in patients with colorectal cancer, an observation which was further confirmed in vitro [57,58]. Recently, Kryczek et al. suggested that IL-22 can enhance colon cancer stemness. Specifically, IL-22 was found to activate STAT3 in human colon cancer cells, resulting in the expression of the H3K9-specific N-methyltransferase DOT1L, which subsequently induced the expression of core stem cell genes such as SOX2, NANOG, and POU5F1. This pathway promoted colon carcinogenesis and the expression of the implicated genes was associated with poor patient prognosis [59]. IL-22 is known to promote and sustain the survival of normal intestinal stem cells in mice [60]. Therefore, a similar function resulting in maintaining the cancer stem cell niche is likely to be one of the main contributions of IL-22 to colorectal carcinogenesis. Other studies showed that high expression of RORγt, which is essential for IL-22 production, and IL-17A, which is commonly found in association with IL-22, indicates poor prognosis in patients with colorectal cancer [39].

3.3. Effects of TNF-α on Wound Healing

Upon inflammation-induced disruption of the intestinal mucosal barrier, intestinal epithelial cells (IECs) need to orchestrate the process of tissue restitution and regeneration. To this end, a crosstalk between epithelial and immune cells needs to take place. TNF-α, an important pro-inflammatory cytokine, is one of the implicated molecules, playing a key role during inflammation and subsequent wound healing [61]. Two forms of TNF-α, the soluble and its precursor, transmembrane one, participate in the inflammatory process. Transmembrane TNF-α acts via cell-to-cell contact, whereas soluble TNF-α performs its biological effects at distant sites from the TNF-α-secreting cells [62]. Transmembrane TNF-α acts both as a ligand by interacting with TNF-α receptors as well as a receptor
that receives and transfers signals back into the same transmembrane TNF-α-expressing cells [63]. During intestinal inflammation, TNF-α is produced by immune cells such as T\textsubscript{H}17 cells, stromal cells, and IECs and subsequently interacts with the latter via two receptors: TNF-R1 (TNFRSF1A) and TNF-R2 (TNFRSF1B). TNF-α signaling mediates the production of inflammatory molecules, regulates cell survival, proliferation, and death, and affects epithelial wound healing. Wound healing is a complicated process involving cellular migration, re-differentiation, and proliferation. TNF-α/TNF-R2 signaling mediates epithelial migration and enhances the survival and proliferation of IECs [64]. Furthermore, TNF-α promotes intestinal wound healing by protecting against epithelial apoptosis via ErbB pathway activation. TNF-α also enhances re-epithelialization and thus wound healing by promoting the FGF-7 production. TNF-α induced effects depend on concentration and duration of exposure. Specifically, low levels of TNF-α promote inflammation and stimulate the production of macrophage-derived growth factors facilitating wound healing. However, long exposure to high levels of TNF-α can have a negative impact on healing, as TNF-α can lead to reduced production of ECM components while promoting the synthesis of metalloproteinases (MMP-1, MMP-2, MMP-3, MMP-9, MMP-13, and MT1-MMP). In line with this, TNF-α levels are increased in chronic wounds. Infection can further promote TNF-α accumulation by prolonging inflammation.

A frequent consequence of IBD and especially ulcerative colitis is colon cancer. Although initially, TNF-α was considered to serve as a tumor-suppressive factor, due to its conditional pro-apoptotic function, it was recently found to promote colitis-associated tumor development by linking inflammation and cancer [65–67]. TNF-α can interact strongly with intestinal epithelial cells, which express high levels of TNFR1, leading to the activation of NF-κB-dependent oncogenic pathways. Recently, Popivanova et al. identified TNF-α as a key factor for the development of colitis-related colon cancer. Specifically, upon DSS/AOM-induced colon carcinogenesis, the expression of TNF-α and the intestinal recruitment of leukocytes expressing the main TNF receptor, namely TNF-Rp55, were boosted, resulting in the formation of several intestinal tumors. Absence of TNF-Rp55 or specific blocking of TNF-α led to reduced mucosal injury and inflammation followed by decreased tumor formation [67]. In other studies, TNF-α deficiency was associated with severe colitis and cancer along with increased blood levels of IL-6, IFN-γ, and IL-17A. Similarly, recent studies showed that TNF-α mRNA expression was increased in colorectal tumors compared to surrounding healthy intestinal tissue. Interestingly, TNF-α was overexpressed in Stage III and IV tumors, suggesting that high TNF-α expression in tumor cells can be associated with advanced stages of carcinogenesis [68]. Additionally, a genetic link between TNF-α and colorectal cancer has been identified recently. Furthermore, TNF was found to play a key role in the colon cancer promoting effect of obesity [69]. Finally, TNF may also enhance metastasis by promoting epithelial to mesenchymal transition (EMT) in colorectal cancer [70].

4. Control of T\textsubscript{H}17 Cells

T\textsubscript{H}17 cells were originally discovered in an autoimmune setting. In a mouse model of multiple sclerosis, experimental autoimmune encephalomyelitis (EAE), and a mouse model of arthritis, both formerly linked to an uncontrolled T\textsubscript{H}1 response, it was discovered that not IL-12, the cytokine driving T\textsubscript{H}1 differentiation, but IL-23 was essential for disease development [71,72]. From in vitro studies, it has been shown that IL-23 can induce the production of IL-17 from effector and memory T cells [73]. Finally, in 2005, Langrish et al. demonstrated that IL-23 induced IL-17 producing T cells displayed stronger pathogenic properties in EAE than T\textsubscript{H}1 cells, and that these T\textsubscript{H}17 cells have a distinct gene-expression profile [74]. Besides the described protective properties of T\textsubscript{H}17 cells, this cell type is apparently also associated with autoimmune diseases, chronic inflammatory conditions, and carcinogenesis. Multiple sclerosis, rheumatoid arthritis, IBD, and psoriasis are amongst the diseases with a strong T\textsubscript{H}17 cell involvement [75–78]. Additionally, as discussed above, uncontrolled IL-22, IL-17, and TNF-α level can promote carcinogenesis. Therefore, the immune system needs control mechanisms to keep T\textsubscript{H}17 cells in check. There are several layers to control T\textsubscript{H}17 cells, which are discussed in the next sections.
4.1. T<sub>H</sub>17 Cell Differentiation

The first level of control already occurs under physiological conditions by regulating T<sub>H</sub>17 cell differentiation. In the past decade, intensive studies have further elucidated the signaling pathways leading to the differentiation of T<sub>H</sub>17 cells. Noteworthy, IL-23 signaling is not essential for the induction of T<sub>H</sub>17 cells from naïve T cells, since naïve T cells only express very low amounts of IL-23R [79]. Nonetheless, IL-23 signaling is crucial for the terminal differentiation, expansion, and maintenance of T<sub>H</sub>17 cells. IL-23R-deficient T<sub>H</sub>17 cells fail to maintain IL-17 expression in vivo and cannot induce EAE [80]. IL-6 signaling can induce the expression of IL-23R, a crucial step in the early priming phase of T<sub>H</sub>17 cells. This leads to the activation of STAT3. Translocation of phosphorylated STAT3 dimers to the nucleus results in induction of T<sub>H</sub>17-related genes such as Rorc, Il17, and also Il23r. The induction of Rorc (encoding RORγt) is indispensable for T<sub>H</sub>17 cell development [81–83]. RORγt is the master transcriptional regulator of T<sub>H</sub>17 cells, demonstrated by the absence of IL-17 producing T cells in RORγt-deficient mice [17].

TGF-β is another cytokine contributing to the development of T<sub>H</sub>17 cells, even though its part in this process is still controversial. In low concentrations, TGF-β can inhibit T<sub>H</sub>1 and T<sub>H</sub>2 differentiation by inhibiting IL-2 dependent STAT5 activation and expression of T-bet and GATA3, the master regulators of T<sub>H</sub>1 and T<sub>H</sub>2, respectively [84]. Nonetheless, higher concentrations of TGF-β result in downregulation of IL-23R and consequently counter regulate T<sub>H</sub>17 cell expansion [79]. Additionally, in 2010, it was demonstrated that T<sub>H</sub>17 cells can occur in the absence of TGF-β signaling in the gut mucosa in vivo [85]. On the contrary, TGF-β signaling can induce the differentiation of inducible regulatory T cells (pTreg). TGF-β is dispensable for T<sub>H</sub>17 cell differentiation but non-redundant for the induction of pTregs [85]. TGF-β signaling induces both FOXP3, the master transcription factor of Treg cells, and RORγt expression. However, in the absence of IL-6 signaling, FOXP3 abrogates the effects of RORγt [79,86,87]. Additionally, IL-2 signaling can both enhance FOXP3 expression and induce STAT5, which leads to impaired binding of STAT3 to IL-17 related genes and inhibits T<sub>H</sub>17 cell differentiation [88–90]. In the absence of pro-inflammatory cytokines, such as IL-6 or IL-1β, TGF-β favors the development of regulatory T cells to maintain immune homeostasis. T<sub>H</sub>17 cells and Treg cells are cell subsets with opposite functions for the immune system, however, they share common pathways for their differentiation. This close relationship demonstrates the important and delicate balance the immune system has to maintain to guarantee immune homeostasis in the presence of foreign antigens from commensal microorganisms and food and to guarantee effective protection against pathogens. Besides TGF-β, the cytokine IL-27 is known to negatively regulate T<sub>H</sub>17 cell induction. IL-27 signaling inhibits the expression of RORγt and therefore suppresses T<sub>H</sub>17 cell differentiation [91]. On the other hand, IL-27 can induce the differentiation of another regulatory T cell subset, type one regulatory T cells (TR<sub>1</tr>1). These cells are characterized by high expression levels of IL-10, they, however, lack FOXP3 expression [92,93]. In summary, the differentiation of the two major regulatory T cell subsets is inversely related with T<sub>H</sub>17 cell induction, a phenomenon not known for other effector T cell subsets, such as T<sub>H</sub>1 and TR<sub>1</tr>1.

Furthermore, IL-1β is important for the differentiation of T<sub>H</sub>17 cells, which was already established in human T cells in 2007 [94,95]. Unlike TGF-β signaling, it was demonstrated by using mice that IL-1β signaling was crucial for T<sub>H</sub>17 cell induction in all tissues in vivo [96]. IL-1β signaling has multiple effects on the differentiation of T<sub>H</sub>17 cells. However, one essential consequence is the induction of the transcription factor IRF4, which is strictly needed for RORγt expression [97]. Interestingly, T<sub>H</sub>17 cells, which differentiated in the absence of TGF-β signaling, seem to have an altered phenotype. Since TGF-β is required for the suppression of T-bet expression in T<sub>H</sub>17 cells, IL-1β induced T<sub>H</sub>17 cells are also T-bet positive and co-express IFN-γ, the signature cytokine of T<sub>H</sub>1 cells [85]. These IFN-γ producing T<sub>H</sub>17 cells are frequently linked with the occurrence of autoimmune disease such as multiple sclerosis [98].

Finally, the microbiota plays an important role in T<sub>H</sub>17 cell differentiation. Under physiological conditions, T<sub>H</sub>17 cells are most abundant in the lamina propria of the small intestine [17] due to the
presence of intestinal microbiota. Studies demonstrated that germ free mice have dramatically reduced levels of T\textsubscript{H}17 cells, which can be induced by colonization with conventional microbiota \cite{99}. SFB were identified as contributing to the expansion of T\textsubscript{H}17 cells in the small intestine due to the induction of serum amyloid A (SAA), which can stimulate DCs to release IL-6 and IL-23 and finally promote T\textsubscript{H}17 cell differentiation \cite{16}. Another effect of the microbiota is the induction of IL-1\beta, further contributing to T\textsubscript{H}17 cell development \cite{100}.

Last, but not least, ligands for the aryl hydrocarbon receptor (AHR) also derive from diet or are products of the intestinal microbiota. AHR is another transcription factor which plays a non-redundant role for T\textsubscript{H}17 cell biology. It has been reported that AHR can promote T\textsubscript{H}17 cell differentiation and is already highly expressed during the early T\textsubscript{H}17 cell polarization \cite{101,102}. However, contradicting studies reported an increase in T\textsubscript{H}17 cells in AHR-deficient mice, especially in the small intestine, demonstrating that AHR is not essential for T\textsubscript{H}17 cell development \cite{103}. Nonetheless, AHR expression is crucial for IL-22 secretion by T\textsubscript{H}17 cells and therefore important for some tissue regenerative functions of T\textsubscript{H}17 cells \cite{101,104,105}.

In conclusion, T\textsubscript{H}17 cell differentiation is strongly influenced by the cytokine environment in different tissues of the body and the presence or absence of environmental factors such as microbiota. In the last decade, immense efforts have been made to understand the regulation of T\textsubscript{H}17 cell induction. Environmental factors, such as microbiota or diet, can directly or indirectly via DCs influence the development and phenotype of T\textsubscript{H}17 cells. Various cytokines are involved in the differentiation of T\textsubscript{H}17 cells and a complex transcriptional network orchestrates this process. Understanding the whole picture could facilitate the design of new therapeutic strategies targeting T\textsubscript{H}17 cells.

4.2. Regulation of T\textsubscript{H}17 Cells Expansion

A second mechanism is to control the expansion of T\textsubscript{H}17 cells via regulatory T cells. Upon tissue damage and infections with extracellular bacteria or fungi, T\textsubscript{H}17 cell immunity is strictly required. A pro-inflammatory environment favors the differentiation of T\textsubscript{H}17 cells over regulatory T cells. Nonetheless, this immune response must be regulated to prevent the onset of chronic inflammatory conditions. Likewise, during wound healing the inflammatory phase needs to be ended. Very little is known about the direct role of T\textsubscript{H}17 cells in the inflammatory phase. However, it was demonstrated that the absence of regulatory T cells results in decreased inflammation resolution after myocardial infarct injury and delayed wound healing in skin, further underlining the non-redundant role of CD4\textsuperscript{+} T cells in regulation of wound repair and regeneration \cite{106,107}. Regulatory T cells, both T\textsubscript{R} cells and T\textsubscript{R}1 cells, are key to terminate T\textsubscript{H}17 cell associated immune responses by suppressing the expansion of T\textsubscript{H}17 cells. Both regulatory T cell subsets can suppress T\textsubscript{H}17 cell expansion in vivo \cite{108,109}. A major suppressive mechanism of regulatory T cells is the release of anti-inflammatory factors, such as TGF-\beta and IL-10. IL-10 signaling is a key factor to dampen inflammatory responses. IL-10 deficiency leads to severe inflammatory diseases in humans \cite{110}. T\textsubscript{H}17 cells express IL-10 receptor and can be directly controlled via IL-10 released by regulatory T cells \cite{111}. Another effect of IL-10 signaling is the reinforcing of regulatory T cell stability \cite{112,113}. An environment high in IL-10 will therefore directly inhibit or terminate a T\textsubscript{H}17 cell immune response and amplify anti-inflammatory T cell subsets.

4.3. T\textsubscript{H}17 Cell Plasticity

A third mechanism to regulate T\textsubscript{H}17 cell immune responses lies within the T\textsubscript{H}17 cells themselves. T\textsubscript{H}17 cells display a great plasticity depending on their cytokine environment. The acquisition of IFN-\gamma production occurs frequently during inflammation and is linked to disease progression in multiple human diseases \cite{114–116}. T\textsubscript{H}17 cells can also acquire the production of the T\textsubscript{H}2 signature cytokine, IL-4 \cite{117}. These cells are present in patients suffering from allergic asthma, and in mice it has been demonstrated that these IL-4 producing T\textsubscript{H}17 cells have greater potential to induce asthma than conventional T\textsubscript{H}2 cells \cite{117,118}. However, T\textsubscript{H}17 cells can also acquire a regulatory phenotype. T\textsubscript{H}17 cells can start producing IL-10 themselves, and it has been demonstrated that these regulatory
**4.4. Regulation of IL-22 via IL-22BP**

Finally, there are ways to control the activity of Th17 cell associated cytokines, such as IL-22. Apart from its protective characteristics, IL-22 is known to play a pathogenic role in autoimmune diseases, several cancers, and chronic liver damage. In order to successfully maintain the balance between protection and harm, endogenous mechanisms controlling the activity of IL-22 are required. IL-22 binding protein (IL-22BP, IL-22Ra2) is a soluble IL-22 receptor and inhibitor. It has been shown that IL-22BP binds to IL-22 and blocks its interaction with the membrane bound IL-22R1 in vitro using human and mouse cells. In vivo studies using mouse models have concluded that the effect of IL-22BP is dependent on the presence of IL-22, revealing a specific in vivo binding of IL-22BP to IL-22 with higher affinity than to the membrane-bound IL-22R1 [121–124]. IL-22BP is present in lymphatic organs, the gastrointestinal system, the lung, the skin, the liver, and in the female reproductive system. Normally, cellular sources of IL-22BP detected in lymphoid organs and the intestine are conventional dendritic cells (DCs), T cells, and eosinophils. It has been shown previously that endogenous IL-22BP is responsible for controlling IL-22-induced effects in the intestine. Recently, Pelczar et al. identified the role of IL-22BP in the development of IBD [125]. It was shown that T cell derived IL-22BP promotes IBD development. CD4+ T cells from patients with IBD were found to produce high levels of IL-22BP. Interestingly, reduced IL-22BP expression was found in intestinal CD4+ T cells derived from IBD patients treated with anti-TNF-α antibodies. Therefore, these studies suggest that the regulation of IL-22 by IL-22BP is crucial and may serve as a therapeutic target in diseases like IBD.

**5. Concluding Remarks and Future Perspective**

Adaptive immunity plays a non-redundant role not only for defense against infections, but also for wound healing, tissue regeneration, or carcinogenesis. However, adaptive immunity has both beneficial and potential pathogenic characteristics. The immune system performs a constant balancing act to maintain beneficial properties over pathogenic ones. Th17 cells have been a main focus of immunological research since their discovery in 2005. As described above, Th17 cells and Th17 cell related cytokines can act in a beneficial fashion during wound repair and regeneration, but they can also cause chronic inflammation and carcinogenesis. Therefore, the immune system developed several control mechanisms to regulate Th17 cell mediated immunity. However, failure of these control mechanisms results in chronic inflammatory diseases and cancer. Thus, new therapeutic strategies targeting Th17 cells have been a main focus of clinical research in recent years. Nonetheless, there are many remaining open questions regarding the involvement and regulation of Th17 cells during tissue regeneration and wound healing. It has long been known that αβ CD4+ T cells infiltrate the wound bed, however, recent research lacks detailed analysis of these cells during wound healing. Th17 cells are especially of great interest in this matter, since they can attract neutrophils and other innate immune cells and induce anti-microbial peptides from epithelial cells. Therefore, Th17 cells could help to prevent spreading infections in a wound. Additionally, Th17 cell associated cytokines such as IL-22 can promote epithelial cell proliferation. However, the basic question if the inflammatory phase during wound healing is altered in the absence of Th17 cells has not been fully addressed yet. A detailed characterization of Th17 cell immune responses during wound healing in different tissues is needed. Th17 cells are most abundant in the intestine and other barrier organs such as lung and skin, therefore it can be assumed that Th17 cells are most important during wound healing in these organs. Besides the beneficial properties of Th17 cells, these cells are strongly associated with chronic inflammatory conditions. Prolonged inflammation is a common hallmark for chronic wounds, which represent an
increasing health threat and a therapeutic challenge. Whether or not an uncontrolled Th17 cell immune response plays an important part during this process is unknown so far. However, if this is the case, it is crucial to understand control mechanisms of Th17 cells that could allow the reprogramming of the immune system so that this chronic inflammatory stage can be resolved. Establishing a better understanding of this process and the underlying mechanisms could potentially facilitate the design of new therapeutic approaches for a wide variety of diseases including infections, cancer, and immune mediated inflammatory diseases.

Acknowledgments: This work was supported by the ERC (ERC Stg 337251 to SH).

Author Contributions: Leonie Brockmann and Anastasios D. Giannou wrote the manuscript, Nicola Gagliani and Samuel Huber supervised and revised the manuscript.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Dvorak, H.F. Tumors: Wounds that do not heal. Similarities between tumor stroma generation and wound healing. N. Engl. J. Med. 1986, 315, 1650–1659. [PubMed]
2. Minutti, C.M.; Knipper, J.A.; Allen, J.E.; Zaiss, D.M. Tissue-specific contribution of macrophages to wound healing. Semin. Cell Dev. Biol. 2017, 61, 3–11. [CrossRef] [PubMed]
3. Avitabile, S.; Odorisio, T.; Madonna, S.; Eyrelich, S.; Guerra, L.; Eyrelich, K.; Zambruno, G.; Cavani, A.; Cianfarrani, F. Interleukin-22 promotes wound repair in diabetes by improving keratinocyte pro-healing functions. J. Investig. Dermatol. 2015, 135, 2862–2870. [CrossRef] [PubMed]
4. Xiao, W.A.; Hu, Z.Y.; Li, T.W.; Li, J.J. Bone fracture healing is delayed in splenectomized rats. Life Sci. 2017, 173, 55–61. [CrossRef] [PubMed]
5. Broekman, W.; Amatngalim, G.D.; de Mooij-Eijk, Y.; Oostendorp, J.; Roelofs, H.; Taube, C.; Stolk, J.; Hiemstra, P. TNF-α and IL-1β-activated human mesenchymal stromal cells increase airway epithelial wound healing in vitro via activation of the epidermal growth factor receptor. Respir. Res. 2016, 17, 3. [CrossRef] [PubMed]
6. Gosain, A.; DiPietro, L.A. Aging and wound healing. World J. Surg. 2004, 28, 321–326. [CrossRef] [PubMed]
7. Fishel, R.S.; Barbul, A.; Beschorner, W.E.; Wasserkrug, H.L.; Efron, G. Lymphocyte participation in wound healing. Morphologic assessment using monoclonal antibodies. Ann. Surg. 1987, 206, 25–29. [CrossRef] [PubMed]
8. Hofmann, U.; Beyersdorf, N.; Weirather, J.; Podolskaya, A.; Bauersachs, J.; Ertl, G.; Kerkau, T.; Frantz, S. Activation of CD4+ T lymphocytes improves wound healing and survival after experimental myocardial infarction in mice. Circulation 2012, 125, 1652–1663. [CrossRef] [PubMed]
9. Park, J.E.; Barbul, A. Understanding the role of immune regulation in wound healing. Am. J. Surg. 2004, 187, 115–165. [CrossRef]
10. Swift, M.E.; Burns, A.L.; Gray, K.L.; DiPietro, L.A. Age-related alterations in the inflammatory response to dermal injury. J. Investig. Dermatol. 2001, 117, 1027–1035. [CrossRef] [PubMed]
11. Antonio, N.; Bonnellykke-Behrndtz, M.L.; Ward, L.C.; Collin, J.; Christensen, I.J.; Steineiche, T.; Schmidt, H.; Feng, Y.; Martin, P. The wound inflammatory response exacerbates growth of pre-neoplastic cells and progression to cancer. EMBO J. 2015, 34, 2219–2236. [CrossRef] [PubMed]
12. Mosmann, T.R.; Coffman, R.L. Th1 and Th2 cells: Different patterns of lymphokine secretion lead to different functional properties. Annu. Rev. Immunol. 1989, 7, 145–173. [CrossRef] [PubMed]
13. Khader, S.A.; Gaffen, S.L.; Kolls, J.K. Th17 cells at the crossroads of innate and adaptive immunity against infectious diseases at the mucosa. Mucosal Immunol. 2009, 2, 403–411. [CrossRef] [PubMed]
14. Pickert, G.; Neufert, C.; Leppkes, M.; Zheng, Y.; Wittkopf, N.; Warnolten, M.; Lehr, H.A.; Hirth, S.; Weigmann, B.; Wirtz, S.; et al. STAT3 links IL-22 signaling in intestinal epithelial cells to mucosal wound healing. J. Exp. Med. 2009, 206, 1465–1472. [CrossRef] [PubMed]
15. Savage, D.C. Microbial ecology of the gastrointestinal tract. Annu. Rev. Microbiol. 1977, 31, 107–133. [CrossRef] [PubMed]
16. Ivanov, I.I.; Atarashi, K.; Manel, N.; Brodie, E.L.; Shima, T.; Karaoz, U.; Wei, D.; Goldfarb, K.C.; Santee, C.A.; Lynch, S.V.; et al. Induction of intestinal Th17 cells by segmented filamentous bacteria. *Cell* 2009, 139, 485–498. [CrossRef] [PubMed]

17. Ivanov, I.I.; McKenzie, B.S.; Zhou, L.; Tadokoro, C.E.; Lepelley, A.; Lafaille, J.J.; Cua, D.J.; Littman, D.R. The orphan nuclear receptor rorgammat directs the differentiation program of proinflammatory IL-17+ T helper cells. *Cell* 2009, 139, 485–498. [CrossRef] [PubMed]

18. Ivanov, I.I.; Moseley, T.A.; Haudenschild, D.R.; Rose, L.; Reddi, A.H. Interleukin-17 family and IL-17 receptors. *Cytokine Growth Factor Rev.* 2003, 14, 155–174. [CrossRef]

19. Ouyang, W.; Karim, R.; Dunussi-Ioannopoulos, K.; Collins, M.; Fouser, L.A. Interleukin-22 and IL-17 are coexpressed by Th17 cells and cooperatively enhance expression of antimicrobial peptides. *J. Exp. Med.* 2006, 203, 2271–2279. [CrossRef] [PubMed]

20. Archer, N.K.; Adappa, N.D.; Palmer, J.N.; Cohen, N.A.; Harro, J.M.; Lee, S.K.; Miller, L.S.; Shirtliff, M.E. IL-17A (IL-17A) and IL-17F are critical for antimicrobial peptide production and clearance of staphylococcus aureus nasal colonization. *Infect. Immun.* 2016, 84, 3575–3583. [CrossRef] [PubMed]

21. Hymowitz, S.G.; Filvaroff, E.H.; Yin, J.P.; Lee, J.; Cai, L.; Risser, P.; Maruoka, M.; Mao, W.; Foster, J.; Kelley, R.F.; et al. IL-17s adopt a cystine knot fold: Structure and activity of a novel cytokine, IL-17f, and implications for receptor binding. *EMBO J.* 2001, 20, 5332–5341. [CrossRef] [PubMed]

22. Quesniaux, V.R.; Ryffel, B.; Di Padova, F. IL-17, IL-22 and Their Producing Cells: Role in Inflammation and Autoimmunity, 2nd ed.; Springer: Basel, Switzerland, 2013.
35. Martin-Orozco, N.; Muranski, P.; Chung, Y.; Yang, X.O.; Yamazaki, T.; Lu, S.; Hwu, P.; Restifo, N.P.; Overwijk, W.W.; Dong, C. T helper 17 cells promote cytotoxic T cell activation in tumor immunity. *Immunity* **2009**, *31*, 787–798. [CrossRef] [PubMed]

36. Wu, S.; Rhee, K.J.; Albesiano, E.; Rabizadeh, S.; Wu, X.; Yen, H.R.; Huso, D.L.; Brancati, F.L.; Wick, E.; McAllister, F.; et al. A human colonic commensal promotes colon tumorigenesis via activation of T helper type 17 T cell responses. *Nat. Med.* **2009**, *15*, 1016–1022. [CrossRef] [PubMed]

37. Housseau, F.; Wu, S.; Wick, E.C.; Fan, H.; Wu, X.; Llosa, N.J.; Smith, K.N.; Tam, A.; Ganguly, S.; Wanyiri, J.W.; et al. Redundant innate and adaptive sources of IL17 production drive colon tumorigenesis. *Cancer Res.* **2016**, *76*, 2115–2124. [CrossRef] [PubMed]

38. Hyun, Y.S.; Han, D.S.; Lee, A.R.; Eun, C.S.; Yoon, J.; Kim, H.Y. Role of IL-17A in the development of colitis-associated cancer. *Carcinogenesis* **2012**, *33*, 931–936. [CrossRef] [PubMed]

39. Tosolini, M.; Kirilovsky, A.; Mlecnik, B.; Fredriksen, T.; Mauger, S.; Bindea, G.; Berger, A.; Bruneval, P.; Hyun, Y.S.; Han, D.S.; Lee, A.R.; Eun, C.S.; Youn, J.; Kim, H.Y. Role of IL-17A in the development of colon tumorigenesis. *Cancer Res.* **2011**, *71*, 1263–1277. [CrossRef] [PubMed]

40. Bindea, G.; Mlecnik, B.; Tosolini, M.; Kirilovsky, A.; Waldner, M.; Obenauf, A.C.; Angell, H.; Fredriksen, T.; Lafontaine, L.; Berger, A.; et al. Spatiotemporal dynamics of intratumoral immune cells reveal the immune landscape in human cancer. *Immunity* **2013**, *39*, 782–795. [CrossRef] [PubMed]

41. Kirchberger, S.; Royston, D.J.; Boulard, O.; Thornton, E.; Franchini, F.; Szabady, R.L.; Harrison, O.; Powrie, F. Innate lymphoid cells sustain colon cancer through production of interleukin-22 in a mouse model. *J. Exp. Med.* **2013**, *210*, 917–931. [CrossRef] [PubMed]

42. Wu, P.; Wu, D.; Ni, C.; Ye, J.; Chen, W.; Hu, G.; Wang, Z.; Wang, C.; Zhang, Z.; Xia, W.; et al. GammadeltaT17 cells promote the accumulation and expansion of myeloid-derived suppressor cells in human colorectal cancer. *Immunity* **2014**, *40*, 785–800. [CrossRef] [PubMed]

43. Zhuang, Y.; Peng, L.S.; Zhao, Y.L.; Shi, Y.; Mao, X.H.; Chen, W.; Pang, K.C.; Liu, X.F.; Liu, T.; Zhang, J.Y.; et al. CD8+ T cells that produce interleukin-17 regulate myeloid-derived suppressor cells and are associated with survival time of patients with gastric cancer. *Gastroenterology* **2012**, *143*, 951–962. [CrossRef] [PubMed]

44. Wang, K.; Kim, M.K.; Di Caro, G.; Wong, J.; Shalapour, S.; Wan, J.; Zhang, W.; Zhong, Z.; Sanchez-Lopez, E.; Wu, L.W.; et al. Interleukin-17 receptor a signaling in transformed enterocytes promotes early colorectal tumorigenesis. *Immunity* **2014**, *41*, 1052–1063. [CrossRef] [PubMed]

45. Chung, A.S.; Wu, X.; Zhuang, G.; Huo, H.; Kasman, I.; Zhang, J.; et al. Alterations in the microbiota to be transmissible and colitogenic. *Carcinogenesis* **2015**, *36*, 2127–2135. [CrossRef] [PubMed]

46. Boniface, K.; Bernard, F.X.; Garcia, M.; Gurney, A.L.; Lecron, J.C.; Morel, F. IL-22 inhibits epidermal differentiation and induces proinflammatory gene expression and migration of human keratinocytes. *J. Investig. Dermatol.* **2013**, *133*, 1321–1329. [CrossRef] [PubMed]

47. Tong, Z.; Yang, X.O.; Yan, H.; Liu, W.; Niu, X.; Shi, Y.; Fang, W.; Xiong, B.; Wan, Y.; Dong, C. A protective role by interleukin-17F in colon tumorigenesis. *PLoS ONE* **2012**, *7*, e34959. [CrossRef] [PubMed]

48. Khare, V.; Paul, G.; Movadat, O.; Frick, A.; Jambrich, M.; Krajic, A.; Marian, B.; Wrbba, F.; Gasche, C. IL10R2 overexpression promotes IL22/STAT3 signaling in colorectal carcinogenesis. *Cancer Immunol. Res.* **2015**, *3*, 1227–1235. [CrossRef] [PubMed]

49. McGee, H.M.; Schmidt, B.A.; Booth, C.J.; Yancopoulos, G.D.; Valenzuela, D.M.; Murphy, A.J.; Stevens, S.; Flavell, R.A.; Horsley, V. IL-22 promotes fibroblast-mediated wound repair in the skin. *J. Immunol.* **2013**, *183*, 132–1329. [CrossRef] [PubMed]

50. Boniface, K.; Bernard, F.X.; Garcia, M.; Gurney, A.L.; Lecron, J.C.; Morel, F. IL-22 inhibits epidermal differentiation and induces proinflammatory gene expression and migration of human keratinocytes. *J. Investig. Dermatol.* **2005**, *124*, 3695–3702. [CrossRef] [PubMed]

51. Zheng, Y.; Danilenko, D.M.; Valdez, P.; Kasman, I.; Eastham-Anderson, J.; Wu, J.; Ouyang, W. Interleukin-22, a T helper 17 cytokine, mediates IL-23-induced dermal inflammation and acanthosis. *Nature* **2007**, *445*, 648–651. [CrossRef] [PubMed]

52. Zenewicz, L.A.; Yin, X.; Wang, G.; Elinav, E.; Hao, L.; Zhao, L.; Flavell, R.A. IL-22 deficiency alters colonic microbiota to be transmissible and colitogenic. *J. Immunol.* **2013**, *189*, 5306–5312. [CrossRef] [PubMed]
Cua, D.J.; Sherlock, J.; Chen, Y.; Murphy, C.A.; Joyce, B.; Seymour, B.; Lucian, L.; To, W.; Kwan, S.; Wu, Y.; Deng, J.; Rychahou, P.G.; Qiu, S.; Evers, B.M.; Zhou, B.P. Stabilization of snail by NF-κB is required for inflammation-induced cell migration and invasion. Cancer Cell 2009, 15, 416–428. [CrossRef] [PubMed]

50. Hanash, A.M.; Dudakov, J.A.; Hua, G.; O’Connor, M.H.; Young, L.F.; Singer, N.V.; West, M.L.; Jenq, R.R.; Holland, A.M.; Kappel, L.W.; et al. Interleukin-22 protects intestinal stem cells from immune-mediated tissue damage and regulates sensitivity to graft versus host disease. Immunity 2012, 37, 339–350. [CrossRef] [PubMed]

51. Ritsu, M.; Kawakami, K.; Kanno, E.; Tanno, H.; Ishii, K.; Imai, Y.; Maruyama, R.; Tachi, M. Critical role of tumor necrosis factor-α in the early process of wound healing in skin. J. Dermatol. Dermatol. Surg. 2017, 21, 14–19. [CrossRef]

52. Perez, C.; Albert, I.; DeFay, K.; Zachariades, N.; Gooding, L.; Kriegler, M. A nonsecretable cell surface mutant of tumor necrosis factor (TNF) kills by cell-to-cell contact. Cell 1990, 63, 251–258. [CrossRef]

53. Sun, X.; Zhang, J.; Wang, L.; Tian, Z. Growth inhibition of human hepatocellular carcinoma cells by blocking STAT3 activation with decoy-odn. Cancer Lett. 2008, 262, 201–213. [CrossRef] [PubMed]

54. Bi, Y.; Cao, J.; Jin, S.; Lv, L.; Qi, L.; Liu, F.; Geng, J.; Yu, Y. Interleukin-22 promotes lung cancer cell proliferation and migration via the IL-22R1/STAT3 and IL-22R1/AKT signaling pathways. Mol. Cell. Biochem. 2016, 415, 1–11. [CrossRef] [PubMed]

55. Wu, T.; Cui, L.; Liang, Z.; Liu, C.; Liu, Y.; Li, J. Elevated serum IL-22 levels correlate with chemoresistant epithelial-to-mesenchymal transition in colorectal cancer. World J. Gastroenterol. 2014, 20, 18390–18396. [CrossRef] [PubMed]

56. Flores, M.B.; Rocha, G.Z.; Damas-Souza, D.M.; Osorio-Costa, F.; Dias, M.M.; Ropelle, E.R.; Camargo, J.A.; de Carvalho, R.B.; Carvalho, H.F.; Saad, M.J.; et al. Obesity-induced increase in tumor necrosis factor-α is associated with advanced colorectal cancer stages. World J. Gastroenterol. 2014, 20, 18390–18396. [CrossRef] [PubMed]

57. Flores, M.B.; Rocha, G.Z.; Damas-Souza, D.M.; Osorio-Costa, F.; Dias, M.M.; Ropelle, E.R.; Camargo, J.A.; de Carvalho, R.B.; Carvalho, H.F.; Saad, M.J.; et al. Obesity-induced increase in tumor necrosis factor-α leads to development of colon cancer in mice. Gastroenterology 2012, 143, 741–753. [CrossRef] [PubMed]

58. Huang, L.; Wang, X.; Wen, C.; Yang, X.; Song, M.; Chen, J.; Wang, C.; Zhang, B.; Wang, L.; Iwamoto, A.; et al. Hsa-miR-19a is associated with lymph metastasis and mediates the TNF-α induced epithelial-to-mesenchymal transition in colorectal cancer. Sci. Rep. 2015, 5, 13350. [CrossRef] [PubMed]

59. Cua, D.J.; Sherlock, J.; Chen, Y.; Murphy, C.A.; Joyce, B.; Seymour, B.; Lucian, L.; To, W.; Kwan, S.; Churakova, T.; et al. Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain. Nature 2003, 421, 744–748. [CrossRef] [PubMed]
72. Murphy, C.A.; Langrish, C.L.; Chen, Y.; Blumenschein, W.; McClanahan, T.; Kastelein, R.A.; Sedgwick, J.D.; Cua, D.J. Divergent pro- and antiinflammatory roles for IL-23 and IL-12 in joint autoimmune inflammation. J. Exp. Med. 2003, 198, 1951–1957. [CrossRef] [PubMed]

73. Aggarwal, S.; Ghilardi, N.; Xie, M.H.; de Sauvage, F.J.; Gurney, A.L. Interleukin-23 promotes a distinct CD4 T cell activation state characterized by the production of interleukin-17. J. Biol. Chem. 2003, 278, 1910–1914. [CrossRef] [PubMed]

74. Langrish, C.L.; Chen, Y.; Blumenschein, W.M.; Mattson, J.; Basham, B.; Sedgwick, J.D.; McClanahan, T.; Kastelein, R.A.; Cua, D.J. IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. J. Exp. Med. 2005, 201, 233–240. [CrossRef] [PubMed]

75. Fouser, L.A.; Wright, J.F.; Dunussi-Joannopoulos, K.; Collins, M. T(H)17 cytokines and their emerging roles in inflammation and autoimmunity. Immunol. Rev. 2008, 226, 87–102. [CrossRef] [PubMed]

76. Harbour, S.N.; Maynard, C.L.; Zindl, C.L.; Schoeb, T.R.; Weaver, C.T. T(H)17 cells give rise to T(H)1 cells that are required for the pathogenesis of colitis. Proc. Natl. Acad. Sci. USA 2015, 112, 7061–7066. [CrossRef] [PubMed]

77. Jimeno, R.; LeCeta, J.; Garin, M.; Ortiz, A.M.; Mellado, M.; Rodriguez-Frade, J.M.; Martinez, C.; Perez-Garcia, S.; Gomariz, R.P.; Juarranz, Y. T(H)17 polarization of memory Th cells in early arthritis: The vasoactive intestinal peptide effect. J. Leukoc. Biol. 2015, 98, 257–269. [CrossRef] [PubMed]

78. Babaloo, Z.; Aliparasti, M.R.; Babaiea, F.; Almasi, S.; Baradaran, B.; Farhoudi, M. The role of T cell activation state characterized by the production of interleukin-17. J. Immunol. 2017, 188, 1402–1412. [CrossRef] [PubMed]

79. Zhou, L.; Lopes, J.E.; Chong, M.M.; Ivanov, I.I.; Min, R.; Victoria, G.D.; Shen, Y.; Du, J.; Rubtsov, Y.P.; Rudensky, A.Y.; et al. TGF-β-induced Foxp3 inhibits T(H)17 cell differentiation by antagonizing rorgamat function. Nature 2008, 453, 236–240. [CrossRef] [PubMed]

80. McGeachy, M.J.; Chen, Y.; Tato, C.M.; Laurence, A.; Joyce-Shaikh, B.; Blumenschein, W.M.; McClanahan, T.K.; O’Shea, J.J.; Cua, D.J. The interleukin 23 receptor is essential for the terminal differentiation of interleukin 17-producing effector T helper cells in vivo. Nat. Immunol. 2009, 10, 314–324. [CrossRef] [PubMed]

81. Bettelli, E.; Carrier, Y.; Gao, W.; Korn, T.; Strom, T.B.; Oukka, M.; Weiner, H.L.; Kuchroo, V.K. Reciprocal developmental pathways for the generation of pathogenic effector T(H)17 and regulatory T cells. Nature 2006, 441, 235–238. [CrossRef] [PubMed]

82. Mangan, P.R.; Harrington, L.E.; O’Quinn, D.B.; Helms, W.S.; Bullard, D.C.; Elson, C.O.; Hatton, R.D.; Wahl, S.M.; Schoeb, T.R.; Weaver, C.T. Transforming growth factor-β induces development of the T(H)17 lineage. Nature 2006, 441, 231–234. [CrossRef] [PubMed]

83. Harbour, S.N.; Maynard, C.L.; Zindl, C.L.; Schoeb, T.R.; Weaver, C.T. T(H)17 cells give rise to T(H)1 cells that are required for the pathogenesis of colitis. Proc. Natl. Acad. Sci. USA 2015, 112, 7061–7066. [CrossRef] [PubMed]

84. Qin, H.; Wang, L.; Feng, T.; Elson, C.O.; Niyongere, S.A.; Lee, S.J.; Reynolds, S.L.; Weaver, C.T.; Roarty, K.; Serra, R.; et al. TGF-β promotes T(H)17 cell development through inhibition of SOCS3. J. Immunol. 2009, 183, 97–105. [CrossRef] [PubMed]

85. Ghoreschi, K.; Laurence, A.; Yang, X.P.; Tato, C.M.; McGeachy, M.J.; Konkel, J.E.; Ramos, H.L.; Wei, L.; Davidson, T.S.; Bouladoux, N.; et al. Generation of pathogenic T(H)17 cells in the absence of TGF-β signalling. Nature 2010, 467, 967–971. [CrossRef] [PubMed]

86. Hori, S.; Nomura, T.; Sakaguchi, S. Control of regulatory T cell development by the transcription factor Foxp3. Science 2003, 299, 1057–1061. [CrossRef] [PubMed]

87. Selvaraj, R.K.; Geiger, T.L. A kinetic and dynamic analysis of Foxp3 induced in T cells by TGF-β. J. Immunol. 2007, 178, 7667–7677. [CrossRef] [PubMed]

88. Davidson, T.S.; DiPaolo, R.J.; Andersson, J.; Shevach, E.M. Cutting edge: IL-2 is essential for TGF-β-mediated induction of Foxp3+ T regulatory cells. J. Immunol. 2007, 178, 4022–4026. [CrossRef] [PubMed]

89. Brandenburg, S.; Takahashi, T.; de la Rosa, M.; Janke, M.; Karsten, G.; Muzzolini, T.; Orinska, Z.; Bulfone-Paus, S.; Scheffold, A. IL-2 induces in vivo suppression by CD4⁺CD25⁺Foxp3⁺ regulatory T cells. Eur. J. Immunol. 2008, 38, 1643–1653. [CrossRef] [PubMed]

90. Laurence, A.; Tato, C.M.; Davidson, T.S.; Kanno, Y.; Chen, Z.; Yao, Z.; Blank, R.B.; Meylan, F.; Siegel, R.; Henninghausen, L.; et al. Interleukin-2 signaling via STAT5 constrains T helper 17 cell generation. Immunity 2007, 26, 371–381. [CrossRef] [PubMed]
91. Diveu, C.; McGeachy, M.J.; Boniface, K.; Stumhofer, J.S.; Sathe, M.; Joyce-Shaikh, B.; Chen, Y.; Tato, C.M.; McClanahan, T.K.; de Waal Malefyt, R.; et al. IL-27 blocks rorc expression to inhibit lineage commitment of Th17 cells. *J. Immunol.* **2009**, *182*, 5748–5756. [CrossRef] [PubMed]

92. Awasthi, A.; Carrier, Y.; Peron, J.P.; Bettelli, E.; Kamanaka, M.; Flavell, R.A.; Kuchroo, V.K.; Oukka, M.; Weiner, H.L. A dominant function for interleukin 27 in generating interleukin 10-producing anti-inflammatory T cells. *Nat. Immunol.* **2007**, *8*, 1380–1389. [CrossRef] [PubMed]

93. Acosta-Rodriguez, E.V.; Napolitani, G.; Lanzavecchia, A.; Sallusto, F. Interleukins 1β and 6 but not transforming growth factor-β are essential for the differentiation of interleukin 17-producing human T helper cells. *Nat. Immunol.* **2007**, *8*, 942–949. [CrossRef] [PubMed]

94. Kebir, H.; Ifergan, I.; Alvarez, J.I.; Bernard, M.; Poirier, J.; Arbou, N.; Duquette, P.; Prat, A. Preferential recruitment of interferon-gamma-expressing Th17 cells in multiple sclerosis. *Ann. Neurol.* **2009**, *66*, 390–402. [CrossRef] [PubMed]

95. Shaw, M.H.; Kamada, N.; Kim, Y.G.; Nunez, G. Microbiota-induced IL-1β, but not IL-6, is critical for the development of steady-state Th17 cells in the intestine. *J. Exp. Med.* **2012**, *209*, 251–258. [CrossRef] [PubMed]

96. Li, Y.; Innocentin, S.; Withers, D.R.; Roberts, N.A.; Gallagher, A.R.; Grigorieva, E.F.; Wilhelm, C.; Veldhoen, M. Exogenous stimuli maintain intraepithelial lymphocytes via aryl hydrocarbon receptor activation. *Cell* **2011**, *147*, 629–640. [CrossRef] [PubMed]

97. Li, Y.; Innocentin, S.; Withers, D.R.; Roberts, N.A.; Gallagher, A.R.; Grigorieva, E.F.; Wilhelm, C.; Veldhoen, M. Exogenous stimuli maintain intraepithelial lymphocytes via aryl hydrocarbon receptor activation. *Cell* **2011**, *147*, 629–640. [CrossRef] [PubMed]

98. Yeste, A.; Mascanfroni, I.D.; Nadeau, M.; Burns, E.J.; Tukpah, A.M.; Santiago, A.; Wu, C.; Patel, B.; Kumar, D.; Quintana, F.J. IL-21 induces IL-22 production in CD4⁺ T cells. *Nat. Commun.* **2014**, *5*, 3753. [CrossRef] [PubMed]

99. Cochez, P.M.; Michiels, C.; Hendrickx, E.; Van Belle, A.B.; Lemaire, M.M.; Dauguet, N.; Warnier, G.; de Heusch, M.; Togbe, D.; Ryffel, B.; et al. AhR modulates the IL-22-producing cell proliferation/recruitment in imiquimod-induced psoriasis mouse model. *Eur. J. Immunol.* **2016**, *46*, 1449–1459. [CrossRef] [PubMed]

100. Li, Y.; Innocentin, S.; Withers, D.R.; Roberts, N.A.; Gallagher, A.R.; Grigorieva, E.F.; Wilhelm, C.; Veldhoen, M. Exogenous stimuli maintain intraepithelial lymphocytes via aryl hydrocarbon receptor activation. *Cell* **2011**, *147*, 629–640. [CrossRef] [PubMed]

101. Wierstamer, J.; Hofmann, U.D.; Beyersdorf, N.; Ramos, G.C.; Vogel, B.; Frey, A.; Ertl, G.; Kerkau, T.; Frantz, S. FoxP3⁺ CD4⁺ T cells improve healing after myocardial infarction by modulating monocyte/macrophage differentiation. *Circ. Res.* **2011**, *115*, 66–77. [CrossRef] [PubMed]

102. Nash, M.I.; Prevel, E.N.; McGeachy, M.J.; Hardcastle, J.T.; O’Shea, J.J.; Hunter, C.A. Interleukins 27 and 6 induce STAT3-mediated T cell production of interleukin 10. *Nat. Immunol.* **2007**, *8*, 1363–1371. [CrossRef] [PubMed]

103. Cochez, P.M.; Michiels, C.; Hendrickx, E.; Van Belle, A.B.; Lemaire, M.M.; Dauguet, N.; Warnier, G.; de Heusch, M.; Togbe, D.; Ryffel, B.; et al. AhR modulates the IL-22-producing cell proliferation/recruitment in imiquimod-induced psoriasis mouse model. *Eur. J. Immunol.* **2016**, *46*, 1449–1459. [CrossRef] [PubMed]

104. Littman, D.R.; Rudensky, A.Y. T cell development, cytokine profile and function of human interleukin 17-producing helper T cells. *Nat. Immunol.* **2007**, *8*, 942–949. [CrossRef] [PubMed]

105. Wilson, N.J.; Boniface, K.; Chan, J.R.; McKenzie, B.S.; Blumenschein, W.M.; Mattson, J.D.; Basham, B.; Smith, K.; Chen, T.; Morel, F.; et al. Development, cytokine profile and function of human interleukin 17-producing helper T cells. *Nat. Immunol.* **2007**, *8*, 950–957. [CrossRef] [PubMed]

106. Brasier, S.; Hagen, J.; Urbanek, B.; Lemaire, M.; Veldhoen, M.; Petrozzino, J.; Stahl, L.; Bohle, H.; von Andrian, U.H. A dominant function for interleukin 27 in generating interleukin 10-producing anti-inflammatory T cells. *Nat. Immunol.* **2007**, *8*, 1380–1389. [CrossRef] [PubMed]

107. Stumhofer, J.S.; Silver, J.S.; Laurence, A.; Porrett, P.M.; Harris, T.H.; Turka, L.A.; Ernst, M.; Saris, C.J.; O’Shea, J.J.; Hunter, C.A. Interleukins 27 and 6 induce STAT3-mediated T cell production of interleukin 10. *Nat. Immunol.* **2007**, *8*, 1363–1371. [CrossRef] [PubMed]

108. Kebir, H.; Ifergan, I.; Alvarez, J.I.; Bernard, M.; Poirier, J.; Arbou, N.; Duquette, P.; Prat, A. Preferential recruitment of interferon-gamma-expressing Th17 cells in multiple sclerosis. *Ann. Neurol.* **2009**, *66*, 390–402. [CrossRef] [PubMed]

109. Sham, M.H.; Kamada, N.; Kim, Y.G.; Nunez, G. Microbiota-induced IL-1β, but not IL-6, is critical for the development of steady-state Th17 cells in the intestine. *J. Exp. Med.* **2012**, *209*, 251–258. [CrossRef] [PubMed]

110. Li, Y.; Innocentin, S.; Withers, D.R.; Roberts, N.A.; Gallagher, A.R.; Grigorieva, E.F.; Wilhelm, C.; Veldhoen, M. Exogenous stimuli maintain intraepithelial lymphocytes via aryl hydrocarbon receptor activation. *Cell* **2011**, *147*, 629–640. [CrossRef] [PubMed]

111. Littman, D.R.; Rudensky, A.Y. T cell development, cytokine profile and function of human interleukin 17-producing helper T cells. *Nat. Immunol.* **2007**, *8*, 942–949. [CrossRef] [PubMed]

112. Cochez, P.M.; Michiels, C.; Hendrickx, E.; Van Belle, A.B.; Lemaire, M.M.; Dauguet, N.; Warnier, G.; de Heusch, M.; Togbe, D.; Ryffel, B.; et al. AhR modulates the IL-22-producing cell proliferation/recruitment in imiquimod-induced psoriasis mouse model. *Eur. J. Immunol.* **2016**, *46*, 1449–1459. [CrossRef] [PubMed]

113. Weirstamer, J.; Hofmann, U.D.; Beyersdorf, N.; Ramos, G.C.; Vogel, B.; Frey, A.; Ertl, G.; Kerkau, T.; Frantz, S. FoxP3⁺ CD4⁺ T cells improve healing after myocardial infarction by modulating monocyte/macrophage differentiation. *Circ. Res.* **2011**, *115*, 66–77. [CrossRef] [PubMed]

114. Bosson, A.; Prevel, E.N.; Truong, H.A.; Mehta, P.; Etttinger, M.; Scharschmidt, T.C.; Ali, N.H.; Pauli, M.L.; Abbas, A.K.; Rosenblum, M.D. Cutting edge: Regulatory T cells facilitate cutaneous wound healing. *J. Immunol.* **2016**, *196*, 2010–2014. [CrossRef] [PubMed]

115. Roncarolo, M.G.; Battaglia, M. Regulatory T-cell immunotherapy for tolerance to self antigens and alloantigens in humans. *Nat. Rev. Immunol.* **2007**, *7*, 585–598. [CrossRef] [PubMed]
110. Glocker, E.O.; Frede, N.; Perro, M.; Sebire, N.; Elawad, M.; Shah, N.; Grimbacher, B. Infant colitis—It’s in the genes. Lancet 2010, 376, 1272. [CrossRef]

111. Huber, S.; Gagliani, N.; Esplugues, E.; O’Connor, W., Jr.; Huber, F.J.; Chaudhry, A.; Kamanaka, M.; Kobayashi, Y.; Booth, C.J.; Rudensky, A.Y.; et al. \( \text{T}_{H}17 \) cells express interleukin-10 receptor and are controlled by Foxp3\(^+\) and Foxp3\(^+\) regulatory CD4\(^+\) T cells in an interleukin-10-dependent manner. Immunity 2011, 34, 554–565. [CrossRef] [PubMed]

112. Chaudhry, A.; Samstein, R.M.; Treuting, P.; Liang, Y.; Pils, M.C.; Heinrich, J.M.; Jack, R.S.; Wunderlich, F.T.; Bruning, J.C.; Muller, W.; et al. Interleukin-10 signaling in regulatory T cells is required for suppression of \( \text{T}_{H}17 \) cell-mediated inflammation. Immunity 2011, 34, 566–578. [CrossRef] [PubMed]

113. Brockmann, L.; Gagliani, N.; Steglich, B.; Giannou, A.D.; Kempski, J.; Pelczar, P.; Gefken, M.; Mfarrej, B.; Huber, F.; Herkel, J.; et al. IL-10 receptor signaling is essential for TR1 cell function in vivo. J. Immunol. 2017, 198, 1130–1141. [CrossRef] [PubMed]

114. Annunziato, F.; Cosmi, L.; Santarlasci, V.; Maggi, L.; Liotta, F.; Mazzinghi, B.; Parente, E.; Fili, L.; Ferri, S.; Frosali, F.; et al. Phenotypic and functional features of human \( \text{T}_{H}17 \) cells. J. Exp. Med. 2007, 204, 1849–1861. [CrossRef] [PubMed]

115. Huber, S.; Gagliani, N.; Esplugues, E.; O’Connor, W., Jr.; Huber, F.; Herkel, J.; et al. Evidence of the transient nature of the \( \text{T}_{H}17 \) phenotype of CD4\(^+\)CD161\(^+\) T cells in the synovial fluid of patients with juvenile idiopathic arthritis. Arthritis Rheumatol. 2011, 63, 2504–2515. [CrossRef] [PubMed]

116. Cosmi, L.; Cimaz, R.; Maggi, L.; Santarlasci, V.; Capone, M.; Borriello, F.; Frosali, F.; Querci, V.; Simonini, G.; Barra, G.; et al. Identification of a novel subset of human circulating memory CD4\(^+\) T cells that produce both IL-17A and IL-17F. J. Allergy Clin. Immunol. 2010, 125, 222–230. [CrossRef] [PubMed]

117. Cosmi, L.; Cimaz, R.; Maggi, L.; Santarlasci, V.; Capone, M.; Borriello, F.; Frosali, F.; Querci, V.; Simonini, G.; Barra, G.; et al. Identification of a novel subset of human circulating memory CD4\(^+\) T cells that produce both IL-17A and IL-17F. J. Allergy Clin. Immunol. 2010, 125, 222–230. [CrossRef] [PubMed]

118. Wang, Y.H.; Voo, K.S.; Liu, B.; Chen, C.Y.; Uygungil, B.; Spoede, W.; Bernstein, J.A.; Huston, D.P.; Liu, Y.J. A novel subset of CD4\(^+\) \( \text{T}_{H}12 \) memory/effector cells that produce inflammatory IL-17 cytokine and promote the exacerbation of chronic allergic asthma. J. Exp. Med. 2010, 207, 2479–2491. [CrossRef] [PubMed]

119. Esplugues, E.; Huber, S.; Gagliani, N.; Hauser, A.E.; Town, T.; Wan, Y.Y.; O’Connor, W., Jr.; Rongvaux, A.; Van Rooijen, N.; Haberman, A.M.; et al. Control of \( \text{T}_{H}17 \) cells occurs in the small intestine. Nature 2011, 475, 514–518. [CrossRef] [PubMed]

120. Gagliani, N.; Amezcuvas Vesely, M.C.; Iseppon, A.; Brockmann, L.; Xu, H.; Palm, N.W.; de Zoete, M.R.; Licona-Limon, P.; Paiva, R.S.; Ching, T.; et al. \( \text{T}_{H}17 \) cells transdifferentiate into regulatory T cells during resolution of inflammation. Nature 2015, 523, 221–225. [CrossRef] [PubMed]

121. Dumoutier, L.; Lejeune, D.; Colau, D.; Renauld, J.C. Cloning and characterization of IL-22 binding protein, a natural antagonist of IL-10-related T cell-derived inducible factor/IL-22. J. Immunol. 2001, 166, 7090–7095. [CrossRef] [PubMed]

122. Kotenko, S.V.; Izotova, L.S.; Mirochnitchenko, O.V.; Esterova, E.; Dickensheets, H.; Donnelly, R.P.; Pestka, S. Identification, cloning, and characterization of a novel soluble receptor that binds IL-22 and neutralizes its activity. J. Immunol. 2001, 166, 7096–7103. [CrossRef] [PubMed]

123. Wei, C.C.; Ho, T.W.; Liang, W.G.; Chen, G.Y.; Chang, M.S. Cloning and characterization of mouse IL-22 binding protein. Genes Immun. 2003, 4, 204–211. [CrossRef] [PubMed]

124. Weber, G.F.; Schlautkotter, S.; Kaiser-Moore, S.; Altmaier, F.; Holzmann, B.; Weighardt, H. Inhibition of interleukin-22 attenuates bacterial load and organ failure during acute polymicrobial sepsis. Infect. Immun. 2007, 75, 1690–1697. [CrossRef] [PubMed]

125. Pelczar, P.; Witkowski, M.; Perez, L.G.; Kempski, J.; Hammel, A.G.; Brockmann, L.; Kleinschmidt, D.; Wende, S.; Haueis, C.; Bedke, T.; et al. A pathogenic role for T cell-derived IL-22BP in inflammatory bowel disease. Science 2016, 354, 358–362. [CrossRef] [PubMed]