Cancer is one of the leading causes of death worldwide. When cancer patients are diagnosed with metastasis, meaning that the primary tumor has spread to at least one different site, their life expectancy decreases dramatically. In the past decade, the immune system’s role in fighting cancer and metastasis has been studied extensively. Importantly, immune cells and inflammatory reactions generate potent antitumor responses but also contribute to tumor development. However, the molecular and cellular mechanisms underlying this dichotomic interaction between the immune system and cancer are still poorly understood. Recently, a spotlight has been cast on the distinct subsets of immune cells and their derived cytokines since evidence has implicated their crucial impact on cancer development. T helper 17 cell (TH17) cells, which express the master transcriptional factor Retinoic acid-receptor-related orphan receptor gamma t, are among these critical cell subsets and are defined by their production of type 3 cytokines, such as IL-17A, IL-17F, and IL-22. Depending on the tumor microenvironment, these cytokines can also be produced by other immune cell sources, such as T cytotoxic 17 cell, innate lymphoid cells, NKT cells, or γδ T cells. To date, a lot of data have been collected describing the divergent functions of IL-17A, IL-17F, and IL-22 in malignancies. In this comprehensive review, we discuss the role of these TH17- and non-TH17-derived type 3 cytokines in different tumor entities. Furthermore, we will provide a structured insight into the strict regulation and subsequent downstream mechanisms of these cytokines in cancer and metastasis.
Introduction

The history of the IL-17 family

Heptadecaphobia (derived from the Ancient Greek ‘hepta’ = seven, ‘deca’ = ten, and ‘phobos’ = fear) describes the pathologic fear of the number 17, which is widely spread in Italy and other countries of Latin origin. When the proinflammatory cytokine interleukin (IL)-17A, formerly called cytotoxic T lymphocyte-associated protein 8, was described for the first time in 1993 without a clear function [1], there was little evidence that this discovery might fuel the fear of superstitious scientists. Soon, it became apparent that IL-17A was only the first of six genetically related cytokines, conveniently named IL-17B, IL-17C [2], IL-17D [3], IL-17E [4], and IL-17F [5], collectively termed the IL-17 superfamily [6]. While IL-17E shares the lowest degree of genomic sequence conservation with the main member of the family, IL-17A [4], IL-17F shares the highest [7]. Later on, it was found that IL-17A and IL-17F are not only capable of forming homodimers, but they can also assemble into IL-17A/IL-17F heterodimers in mice [8] and humans [9], describing a formation in which one monomer consists of IL-17A and the other of IL-17F.

Cellular sources of type 3 cytokines

Early on, it was shown that IL-17A could be produced by T cells [1,10]. However, the groundwork for a new T-cell subset was not provided until the year 2000, when the structural distinction between IL-12 and IL-23 became apparent [11]. Shortly after, this distinction enabled recognition of the different functions of these particular cytokines [12]. Subsequently, this led to the discovery that IL-23 itself can promote the differentiation of a new IL-17A producing T-cell lineage, which expresses the cluster of differentiation (CD) 4 and is referred to as T helper 17 (T\textsubscript{H}17) cell lineage [13]. In 2001, retinoic acid receptor-related orphan receptor gamma t (ROR\textgreek{t}) was identified as an indispensable transcriptional factor for the differentiation of T\textsubscript{H}17 cells [14], distinguishing this CD4-positive T-cell subset from others. Further research revealed other cytokines that are coproduced by T\textsubscript{H}17 cells, among them IL-17F [8] and IL-22 [15]. IL-22 is a cytokine of the IL-10 family [16], first described in 2000 [17]. Together, IL-17A, IL-17F, and IL-22 form the group of type 3 cytokines [18].

Of note, other subsets of cells are equally capable of producing IL-17A, IL-17F, or IL-22. Among them are CD8-positive cytotoxic T cells, termed T cytotoxic 17 (T\textsubscript{c}17) cells [19], type 3 innate lymphoid cells (ILC3s) [20,21], natural killer T (NKT) cells [22,23], and a subset of γδ T cells [24,25], which are also referred to as γδ T17 cells when secreting IL-17A. T helper 22 (T\textsubscript{H}22) cells are yet another source of IL-22 and are defined as CD4-positive T cells lacking the production of IL-17A [26].

Regulation of type 3 cytokines

Differentiation and positive regulation toward type 3 cytokine-secreting cells are often initiated by a combination of the cytokines IL-1β, Transforming growth factor-beta (TGF-β), and IL-23 [22,27,28]. Depending on the microenvironment and the specific cell subset, multiple enhancing factors might come into play. For example, it was demonstrated that IL-7 could exclusively enhance the production of IL-17A by γδ T cells in neonate mice and by γδ T cells derived from human cord blood [29]. Likewise, spatiotemporal regulation of IL-17A, IL-17F, and IL-22 is required to insure a targeted immune response avoiding overt inflammation. One possible mechanism lies in regulating the migration of the cells producing these cytokines, such as T\textsubscript{H}17. Interestingly, T\textsubscript{H}17 is recruited to and controlled in the small intestine during an overwhelming T\textsubscript{H}17 immune response, for instance, during sepsis [30,31]. This attraction of T\textsubscript{H}17 is dependent on their expression of C-C chemokine receptor (CCR) 6 [30]. In the same fashion, γδ T17 cells often expressing CCR6 [32] can be allured to inflammation sites [33]. Vice versa, negative regulation of many type 3 cytokine-producing cells is needed and often occurs via IL-10 [34,35]. However, there are also other ways to control T\textsubscript{H}17 cells. For example, these cells may be washed out through the intestinal lumen during intensive tissue damage. Finally, T\textsubscript{H}17 can change their phenotype, acquire regulatory functions [30], and even fully transdifferentiate into regulatory T cells (T\textsubscript{regs}) [36]. Interestingly, IL-22 is not only regulated on a transcriptional level, but its activity is also controlled by IL-22-binding protein (BP), an endogenous antagonist, that binds and neutralizes IL-22 [37].

Downstream signaling of IL-17A and IL-17F

Even 25 years after the discovery of IL-17A [1], the precise mechanisms of signal transduction of IL-17A and IL-17F are not yet fully understood. In a similar fashion to their ligands, the receptors of the IL-17 family form a family of their own, comprising of interleukin-17 receptor A (IL-17RA) all the way through to IL-17RE [6]. While IL-17RA was already described to
mediate IL-17A signaling back in 1995 [38], it took another 11 years to discover IL-17RC as the second part of the functional IL-17RA/IL-17RC receptor [39]. Shortly after, it was confirmed that both IL-17A and IL-17F could bind to both IL-17RA and IL-17RC in mice [40] and humans [41] and thus induce downstream signaling directly mediated by nuclear factor kappa-B activator 1 [42] and tumor necrosis factor receptor-associated factor 6 [43]. Eventually, IL-17A and IL-17F were found to induce transcriptional factors such as nuclear factor kappa-light-chain-enhancer of activated B cells [38] and mediate transcription of proinflammatory and hematopoietic cytokines such as IL-6, IL-8, and granulocyte-colony-stimulating factor (G-CSF) [10]. Nevertheless, the long-lasting paradigms describing IL-17A signaling were significantly challenged since a recent report suggested signaling of the IL-17A homodimer through a newly described pairing of the receptors IL-17RA and IL-17RD [44]. However, further implications of this newly found heterodimeric match are yet to be elucidated.

**Downstream signaling of IL-22**

In contrast, the mechanisms underlying IL-22 signaling are better understood. IL-22 binds to a heterodimeric receptor, consisting of the universally expressed IL-10R2 and IL-22RA1 [17], whose expression is exclusive to non-hematopoietic cells [45]. Further downstream effects are mainly mediated by signal transducer and activator of transcription (STAT) 3, although it was also reported that STAT1 and STAT5 could be activated via IL-22 in a hepatoma cell line [46]. These effects include the enhanced production of antimicrobial peptides [45], the promotion of tissue regeneration and wound healing [47], and the protection from genotoxic stress [48].

**State of the art**

Today, the roles of TH17 cells and their secreted cytokines have been extensively examined in different diseases. Particularly, reports show that type 3 cytokine-producing cells are capable of exerting ambiguous roles in multiple settings. Often enough, they were found to display a pathogenic behavior and thus provide scientists with sound evidence to further fear and despise the number 17. In this review, we aim to rationalize and objectify the partially bad reputation of TH17 cells and associated cytokines during carcinogenesis and metastatic development. Worldwide, tumor development in the lung, colon, breast, liver, and stomach causes the most cancer-related deaths, with a combined death toll of four million in 2018 alone [49]. Therefore, this review will be centered on the four primary entities mentioned above, while the impact of type 3 cytokines in stomach cancer will be briefly addressed at the end. Likewise, metastases in the liver and lung rank among the most common sites for distant tumor seeding [50]. Therefore, metastasis development in these two organs will be outlined in detail. Finally, we will point out unresolved questions that need to be addressed and discuss possible therapeutic targets.

**Colorectal cancer**

**Overview**

Colorectal cancer (CRC) ranks as the third most common cancer-related cause of death in the Western world [51]. CRCs most commonly develop over the span of many years, often arising from benign polyps [52]. Over time and after accumulation of mutations in genes such as adenomatous polyposis coli (APC), (Kirsten) rat sarcoma viral oncogene homolog ([K] RAS), or tumor protein p53 [53], these benign polyps transform into cancerous tissues, which subsequently infiltrate adjacent structures. In the last stage of their development, these malignant lesions can then spread to other organs and form metastases.

**Overall impact of IL-17A**

The role of TH17 cells and their associated cytokines, especially IL-17A and IL-22, has been examined and reviewed extensively in the past [54–58]. While IL-17A has been described as mostly pro-tumorigenic in the colonic environment, the functions of IL-22 are more divergent (Fig. 1). One of the first observations regarding the role of IL-17A during CRC was made by crossing Il17a-deficient mice with APCMin/+ mice. These mice harbor the multiple intestinal neoplasia (Min) mutation in one of their APC loci and, thus, are prone to spontaneous development of CRC. By using this model, it was discovered for the first time that the lack of IL-17A expression protects mice against CRC [59]. A similar observation was made a year later, where Il17a-deficient mice presented with a decreased colitis-associated CRC burden compared with wild-type mice in the azoxymethane (AOM)-dextran sodium sulfate (DSS) mouse model [60]. Another genetic CRC mouse model based on a different APC mutation revealed that treatment with an antibody-inhibiting IL-17A resulted in a reduced colonic tumor burden compared with an isotype control [61]. In humans, it was found that patients suffering from
CRC display higher levels of IL-17A in their serum [62] and that IL-17A expression in tumor tissues increases during the transformation from adenoma toward dysplasia [63,64]. Furthermore, IL-17A is negatively correlated with overall survival in these patients [65], highlighting this cytokine’s CRC-promoting capabilities.

**Cellular sources of IL-17A**

The cellular sources of IL-17A were found to include not only TH17 cells, but also γδ T17 cells as a second producer. This was discovered in APCMin/+ mice that had been colonized with the human gut bacterium, enterotoxigenic *Bacteroides fragilis* (ETBF), to enhance...
tumor growth [66]. In humans, the exact contributions of the different sources of IL-17A are not yet fully elucidated. Indeed, one study detected both T_{H17} cells, as well as γδ T17 cells, in colonic tumor tissues [66]. After analyzing two different patient cohorts, it was shown that roughly 80% of tumor-infiltrating IL-17A-producing T cells represented T_{H17} cells. However, another study reported that despite the detection of an increased number of T_{H17} cells, γδ T17 cells were the major source of IL-17A in colonic tissues of patients suffering from CRC [67]. Here, the authors found an absolute number of γδ T17 cells that more than doubled the detected amount of T_{H17} cells in the tissue. The study further correlated the abundance of γδ T17 cells with distinct CRC progression features, including tumor stage, tumor size, tumor invasion, lymph node metastasis, and serum level of carcinoembryonic antigen (CEA). More recently, however, it was reiterated that the major source of IL-17A in CRC is T_{H17} cells, which could exert both pro- and antitumorigenic effects in vitro [68]. Therefore, it is conceivable that both γδ T17 cells and T_{H17} cells significantly contribute to IL-17A production in CRC. Nonetheless, the precise functions of these cell subsets might differ, leading to different effects during carcinogenesis. Of note, T cells expressing the major transcription factor forkhead box P3 (Foxp3), termed T_{reg}, were described to exert pathogenic properties via the production of IL-17A, as well [69,70].

Regulatory mechanisms of IL-17A

The regulation of IL-17A-producing cells during CRC is highly dependent on the colonic microbiome and its ability to induce IL-23 production [71]. Early on, IL-23 production by myeloid cells was suspected to enhance CRC growth via upstream and downstream signaling of STAT3, partially by inhibiting antitumor immunity via promotion of T_{reg} [72]. Some years later, this suggested circuit was expanded by demonstrating that early colonic adenocarcinoma stages can lead to an intestinal barrier defect. This favors an efflux of microbes and microbial peptides from the lumen toward the colon’s outer layers in mice. Subsequently, this mechanism triggers an enhanced production of IL-23 by tumor-associated myeloid cells, which then leads to an increase of IL-17A expression in the tumor [71]. Although the secretion of IL-17A in CRC is also highly dependent on IL-1β, its deficiency only slightly affects colonic tumor burden. This might be explained by potent antitumorigenic effects of IL-1β compensating its pro-tumorigenic effects, involving the control of local tumor-enhancing microbiota [73].

In humans, it was equally demonstrated that the gut’s microbiome, and more specifically, a distinct colonic bacterium, called ETBF, can induce colonic tumor growth via the induction of T_{H17} cells [74]. Strikingly, this mechanism seems to be partially mediated by T_{reg} since depletion of these cells in a murine colon cancer model reduced tumor development promoted by IL-17A [75]. Interestingly, this T_{reg}-dependent effect could be bypassed by the inhibition of IL-2, indicating that T_{reg} might stimulate T_{H17} cells in CRC by depriving them of IL-2.

Intriguingly, it was further postulated that a subset of IL-17A-producing T_{reg} in CRC had compromised anti-inflammatory properties due to the coexpression of RORγt [76]. Since T_{H17} cells can transdifferentiate into T_{reg} as a response to systemic infections [36], it would be of high interest to determine whether regular T_{H17} cells can fully convert from RORγt+ Foxp3+ T cells to RORγt− Foxp3+ T cells as a direct response to CRC development [77]. This suspected form of plasticity might indicate a regulatory mechanism initiated by the host’s immune system to dampen the tumor-promoting effects of T_{H17} cells.

Targets of IL-17A

Mechanistically, the interactions among IL-17A, myeloid cells, and colonic cancer cells were demonstrated to be of extreme importance in mediating the mostly pro-tumorigenic effects of IL-17A. For example, one established axis describes a mechanism by which the IL-17A-mediated production of granulocyte macrophage-colony-stimulating factor (GM-CSF) favorably recruit myeloid-derived suppressor cells (MDSCs) to the tumor site. These cells are then capable of suppressing antitumorigenic effector cells [67]. As a second mechanism, it was suggested that IL-17A could enhance the migration properties of a colon cancer cell line [78], as well as cell-cycle progression [79] in vitro. Accordingly, in vivo observations found a reduced tumor burden in mice with a specific depletion of IL-17A on colonic epithelial cells [61]. Moreover, IL-17A might synergize with IL-4 to induce hydrogen peroxide production and damage DNA in colon and pancreatic cancer cell lines [80]. Of note, it was suggested that IL-17A signaling might play a role in mediating the effects of cisplatin resistance [81]. However, convincing in vivo data is currently missing to corroborate the impact of IL-17A on cancer cells.

Overall impact of IL-17F

While the effect of IL-17A on CRC has been well examined for decades, evidence of an involvement of
IL-17F is scarce. However, different polymorphisms of IL-17A, IL-17F, and IL-23R were reported to correlate with distinct clinical characteristics of CRC [82,83], pointing toward an important role of these T_{H17} cell-associated cytokines. Nonetheless, a mechanistic study from 2012 shows a protective effect of IL-17F in CRC. Here, the authors used IL-17F overexpressing cancer cell lines, which were subcutaneously implanted into the host, and the inflammation-associated AOM-DSS model [84]. Since the levels of the pro-angiogenic factor vascular endothelial growth factor (VEGF) were increased in Il17f-deficient mice, the authors concluded that mechanistically, IL-17F might inhibit angiogenesis by directly or indirectly reducing VEGF. Intriguingly, the authors discovered a high expression of IL-17F in epithelial cells and healthy colon tissue, whereas the expression of IL-17F was reduced in the tumor tissue. However, a more recent study described conflicting observations, where elevated levels of IL-17F were found in colon tumor tissues [85]. Conclusively, further studies, including bigger sample sizes, are necessary to draw conclusions.

**Overall impact of IL-22**

In contrast to IL-17F, the role of IL-22 during CRC has been defined more precisely. In comparison with IL-17A, the role of IL-22 is strikingly more divergent. This becomes most apparent by the observation that IL-17A, IL-22, and IL-23R were reported to correlate with distinct clinical characteristics of CRC [82,83], pointing toward an important role of these T_{H17} cell-associated cytokines. However, using a different murine model of CRC, another report described IL-22 and nitric oxide-mediated damage of DNA, which subsequently led to a decreased dysplasia of tumors in Il17f-responsive mice [82]. Finally, the last factor enhancing the production of IL-22 is mediated by IL-22BP, a soluble receptor with a high binding affinity for IL-22 [82]. It was demonstrated that a dysregulated activity of IL-22 by depletion of IL-22BP leads to a drastic increase in tumor burden [47]. In fact, it was recently described that IL-22BP production relies on the induction of IL-22 by depletion of IL-22BP.[92] Conversely, tight negative regulation of IL-22 is needed to prevent potential harmful effects. Physiological inhibition of IL-22 is mediated by IL-22BP, a soluble receptor with a high binding affinity for IL-22 [94]. It was demonstrated that a dysregulated activity of IL-22 by depletion of IL-22BP leads to a drastic increase in tumor burden [47]. In fact, it was recently described that IL-22BP production relies on the induction of lymphotoxin, in which case, inhibition of the lymphotoxin beta receptor leads to an increased CRC development in mouse models [95]. Interestingly, high levels of lymphotoxin and IL-22BP were associated with a significantly improved survival rate in patients with CRC. Moreover, high levels of IL-22BP were associated with a less advanced tumor stage and less distant metastasis.

**Cellular sources of IL-22**

IL-22 derived from ILC3 [86] and T_{H22} [87,88] cells was found to be pathogenic in different mouse models of CRC. Additionally, another recent report assigned a pathogenic role to IL-17A and IL-22 double producing T_{H17} cells [89]. An increase of T_{H22} cells in tumor tissue and tumor-infiltrated lymph nodes was equally detected in humans [90]. In contrast, a different study reports a tumor-protective function of ILC3 and γδ T cell-derived IL-22 [48]. Thus, it seems likely that the multiple circuits that regulate IL-22 production and assure gut homeostasis have divergent effects when faced with threats such as cancer development.

**Regulatory mechanisms of IL-22**

The spatiotemporal regulation and induction of IL-22-producing cells are not only mediated by cytokines and dietary components, but they also occur through commensal bacteria in the digestive tract [91]. Similar to the regulation of IL-17A, IL-23 was shown to be capable of inducing IL-22 production of lamina propria-derived ILC3s in vitro. Moreover, it was recently reported that transforming growth factor (TGF)-β1, together with ligands of the aryl hydrocarbon receptor (AhR), can enhance pathogenic IL-22 production in T_{H17} cells but not T_{H22} cells, and thus, can promote carcinogenesis in colitis-associated CRC [89]. Ligands of the AhR can also be provided by the diet and subsequently induce production of IL-22 from ILC3 and γδ T cells [48]. Strikingly, in this setting, IL-22 has an antitumorigenic effect protecting intestinal stem cells from DNA damage-mediated apoptosis [48]. However, using a different murine model of CRC, another report described IL-22 and nitric oxide-mediated damage of DNA, which subsequently led to a decreased dysplasia of tumors in IL-22-depleted mice [92]. Finally, the last factor enhancing the production of IL-22 involves the microbiome. Administering fecal samples of patients suffering from CRC to mice led to an upregulation of different cytokines, such as IL-17A and IL-22. Consequently, their tumor burden was found to be increased in an AOM-only model [93].
Targets of IL-22
Mechanistically, IL-22 can protect both malignant epithelial cells and healthy epithelial stem cells from extracellular and intracellular threats, leading to both pro- [96] and antitumorigenic [48] effects. Furthermore, IL-22 signaling increased colonic cancer cell proliferation [97,98], partially by synergizing with mutated KRAS [99]. Additionally, IL-22 can induce an upregulation of nicotinamide N-methyltransferase and CEA gene expression in multiple cancer cell lines, promoting proliferation and migration in turn [100].

Taken together, more conclusive studies are needed to decipher the dual role of IL-22 during colonic carcinogenesis. Since most data suggest that IL-22 signaling on cancer cells mediates highly pro-tumorigenic effects, the pathogenic effect of IL-22 might rely on a high tumor burden and advanced tumor stage. In this case, direct inhibition of IL-22 or overexpression of IL-22BP [101] might be considered in advanced cases of CRC.

Breast cancer

Overview
Breast cancer is the most commonly diagnosed cancer entity of women and ranks second among women’s cancer-related deaths, only after lung cancer [102]. In the last decades, progress in breast cancer diagnosis and treatment has led to a decline in mortality by 40% since 1989 [102]. Nevertheless, there is still room for refinement of existing therapies and establishment of new ones. Breast cancer can be divided into subsets classified by the expression of the estrogen receptor, the progesterone receptor, and the human epidermal growth factor receptor 2 [103]. Indeed, if one of these receptors is expressed by breast cancer, targeted therapies might be of use. For example, these targeted therapies can deprive receptors of their ligand or can antagonize the receptor signaling itself [103]. This game-changing therapeutic concept has greatly improved the overall prognosis of these breast cancer entities during recent years. Conversely, breast cancers that do not express one of these three receptors, hence labeled as triple-negative breast cancer (TNBC), have a poor prognosis due to a lack of specific therapeutic options [104].

Overall impact of IL-17A

Positive regulation of IL-17A production in breast cancer occurs through diverse mechanisms, one of which is through direct signaling of TGF-β [113]. Of note, TGF-β signaling on breast cancer cells can exert antitumorigenic functions since it was shown that it could inhibit the secretion of chemokines attracting pro-tumorigenic immune cells [118]. Furthermore, an increasing amount of evidence has been provided addressing the regulation of IL-17A through levels of salt (sodium chloride) intake [119–122]. In a recent report, mice fed with a high-salt diet displayed an accelerated subcutaneous growth of breast cancer cells as well as higher levels of IL-17A-producing T effector cells [122]. In line with this, in vitro observations report a synergistic role of IL-17A and sodium chloride in enhancing breast cancer growth and cell-cycle release [119,120] and production of pro-angiogenic factors like VEGF [121]. However, antitumorigenic functions reviewed extensively [105]. Overall, the published data suggest a rather pro-tumorigenic influence of this cytokine by exerting multiple pro-tumorigenic actions (Fig. 2). Specifically, treatment of mice with recombinant IL-17A increases the tumor burden of previously implanted breast cancer cell lines [106], and IL-17A antibody treatment reduces the tumor size [107]. Likewise, IL-17A levels are increased in patients suffering from breast cancer compared with healthy controls [108], and infiltration of IL-17A-positive cells presents itself as a poor prognostic factor in humans [109–111].

Cellular sources of IL-17A
Detailed studies surprisingly found that T effector cell infiltration was likely to be associated with a more favorable prognosis [112], thus making pathogenic effects of other IL-17A-producing cells more likely. For example, one study reported an important role of IL-17A derived from cytotoxic T cells in an orthotopic mouse model of breast cancer [113]. Another study showed that macrophages were able to produce IL-17A in human breast cancer [114]. In line with these findings, a more recent report found pathogenic crosstalk between macrophages and cancer cells involving the activation of the IL-17A signaling pathway [115]. Although γδ T cells were shown to have an overall antitumorigenic role in breast cancer [116,117], not much is known about the effect of γδ T cell-derived IL-17A. Conclusively, a possible pathogenic source of IL-17A that might confirm the role of IL-17A as a poor prognostic factor has not yet been determined.

Regulatory mechanisms of IL-17A

Positive regulation of IL-17A production in breast cancer occurs through diverse mechanisms, one of which is through direct signaling of TGF-β [113]. Of note, TGF-β signaling on breast cancer cells can exert antitumorigenic functions since it was shown that it could inhibit the secretion of chemokines attracting pro-tumorigenic immune cells [118]. Furthermore, a growing amount of evidence has been provided addressing the regulation of IL-17A through levels of salt (sodium chloride) intake [119–122]. In a recent report, mice fed with a high-salt diet displayed an accelerated subcutaneous growth of breast cancer cells as well as higher levels of IL-17A-producing T effector cells [122]. In line with this, in vitro observations report a synergistic role of IL-17A and sodium chloride in enhancing breast cancer growth and cell-cycle release [119,120] and production of pro-angiogenic factors like VEGF [121]. However, antitumorigenic functions
of high-salt intake in breast cancer have been recently described as well [123], highlighting the need for further research in this particular area.

**Targets of IL-17A**

Downstream effects of IL-17A involve multiple mechanisms that have only been partially elucidated so far. An important mechanism is the induction of tumor-supporting angiogenesis [106,121]. Depending on the precise type of cancer cell, IL-17A may mediate the reduction of apoptosis [113] or production of neutrophil attracting chemokines [124]. This enhanced migration of neutrophils toward the tumor site is then capable of promoting breast cancer growth on its own [107].

**Overall impact of IL-17F**

Once again, the evidence for the involvement of IL-17F in breast cancer is rare. One study found a lower...
expression of IL-17F in the blood of TNBC patients compared with patients suffering from receptor-positive breast cancer [125]. Surprisingly, a second study reported upregulation of the T<sub>H</sub>17 cell-associated cytokines IL-17A and IL-17F in TNBC [126]. This can be explained by peripheral IL-17F-producing cells specifically recruited to the tumor site of TNBC, therefore lowering their quantity in the blood and increasing them in the tumor. A first study suggested pro-tumorigenic effects of high-salt-diet-induced IL-17F production on cancer cells [122] in vitro. However, further in vivo studies are needed to validate this finding.

**Overall impact of IL-22**

The data collected from different studies on the effects of IL-22 in cancer strongly suggest a dual role of this T<sub>H</sub>17 cell-associated cytokine. An early study suggested a direct tumor-protective role since in vivo treatment with recombinant IL-22 of mice with subcutaneously implanted breast cancer cells significantly reduced tumor growth [127]. Nonetheless, more recent studies have highlighted a pro-tumorigenic effect of IL-22 by analyzing IL-22-treated cancer cells in vitro [128–131] and using in vivo mouse models [132–134]. In humans, an increase of IL-22 in the serum of patients was described [129] and an elevated number of T<sub>H</sub>22 cells in the tumor tissue of TNBC compared with noninfiltrated tissue [130].

**Cellular sources and regulatory mechanisms of IL-22**

The sources of IL-22 in breast cancer have not been extensively examined yet. One study suggested a pathogenic role of IL-22 derived from CD4-positive memory cells [132]. Furthermore, this report showed that an IL-22 induction was mainly mediated by in a murine model. In contrast, IL-1β production from immune cells induced by nucleotide-binding domain leucine-rich repeat and pyrin domain-containing receptor 3 was described by the same study to induce IL-22 production in humans. A different study claimed that ILC3s were the predominant source of IL-22 in breast cancer, and its production was dependent upon IL-1β and IL-23 secretion, whereas IL-22 production was not upregulated in T cells [134].

**Targets of IL-22**

Similar to CRC, cancer cells themselves might present as an important target of IL-22 signaling. An antitumorigenic effect was reported in EMT6 cancer cells due to an increased cell-cycle arrest upon IL-22 stimulation in vitro [127]. However, using different cell lines, a rather pro-tumorigenic effect could be detected, reporting once more an increase in proliferation [128] and cell-cycle entry [129]. Another study described the capability of IL-22 in enhancing cell migration and paclitaxel resistance in a TNBC cell line stimulated in vitro [130]. In contrast, a different study reported that cells could upregulate their expression of the sphingosine-1-phosphate receptor 1 upon IL-22 challenge [131]. Conclusively, extensive data have been accumulated so far, describing a pro-tumorigenic effect of IL-22 on cancer cells. Precise molecular mechanisms might vary between cell lines, possibly explaining the antitumorigenic effects of IL-22 observed in the EMT6 cell line. Moreover, little is known about the effects of IL-22 on other cells during breast cancer that might contribute to mediating the strong pro-tumorigenic effects observed in different in vitro models. Furthermore, human data on the association of IL-22 levels and survival, tumor stage, and metastasis are limited, and further studies are needed to fill the gaps in our knowledge.

**Lung cancer and lung metastasis**

**Overview**

As mentioned above, lung cancer is the most common cancer-related cause of death in men and women in the United States [135]. It can be divided into two main entities, namely non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). SCLC accounts for 15–20% of lung cancer cases, whereas NSCLC is diagnosed in 80–85% of the cases [136,137]. NSCLC can be further split into squamous cell carcinoma, large cell carcinoma, and adenocarcinoma, with the latter entity being histologically diagnosed in 60% of patients suffering from NSCLC [136]. Unsurprisingly, a history of smoking is a causative factor linked to lung cancer in 90% of the cases [138] and dramatically increases relative risks of lung cancer subtypes [139]. However, other risk factors such as genetic predispositions, inhalation of nontobacco procarcinogens, or preexisting lung diseases should not be overlooked [138].

Lung metastasis describes a medical condition in which a tumor from a different primary site has spread to the lung. It is associated with a poor prognosis in nearly every cancer entity, explaining the need for further innovative therapies [140]. Even though tumor entities differ between lung cancer and lung metastasis, the target organ is the same, leading to a similar
tumor microenvironment. Thus, lung cancer and lung metastasis will be discussed in the same section to highlight similarities.

**Overall impact of IL-17A in lung cancer**

In recent years, overwhelming evidence has been collected regarding the pathogenic role of IL-17A in lung cancer, whereas the role of IL-17A in lung metastasis is more divergent (Fig. 3). Suspicions of pro-tumorigenic functions of IL-17A were fueled by an initial report in 2005 using human cells of NSCLC that were implanted into immunodeficient mice [141]. In the following years, murine models harboring KRAS mutations were used to define the role of IL-17A signaling further, corroborating the pro-tumorigenic effects in lung cancer [142,143]. Similarly, subcutaneous implantation of lung cancer cells in mice pretreated with recombinant IL-17A led to an equal observation [144]. Likewise, increased IL-17A-producing cells and elevated expression of IL-17A were found to be associated with decreased survival [145–148]. However, one murine study took advantage of a different genetic lung tumor model and surprisingly found a protective role of IL-17A during lung cancer development [149].

Thus, additional murine models are warranted to dissect possible pro- and antitumorigenic effects of IL-17A in lung cancer.

**Cellular sources and regulatory mechanisms of IL-17A in lung cancer**

Relevant sources of tumor-supporting IL-17A production are Th17 cells [142] and γδ T cells [150,151], in which the latter seems to be tightly regulated by the microbiome. Depletion of the microbiome by antibiotic treatment [150] or use of germ-free mice [151] greatly diminished lung cancer development, an effect that was shown to be associated with decreased IL-17A-producing γδ T cells in both reports. Mechanistically, a microbiome-stimulated secretion of IL-1β and IL-23 by myeloid cells was identified to be the trigger for enhanced IL-17A production [151].

A further regulatory mechanism in lung cancer might be related to the signaling of IL-7, a cytokine that can promote IL-17A production exclusively from γδ T cells [29]. An interesting study revealed a faster tumor growth of subcutaneously implanted lung carcinoma cells in older mice, an observation that was partially attributed to IL-7-mediated expansion of a specific subset of IL-17A-producing γδ T cells [152]. Since the administration of an antibody against IL-7 reduced the proliferation of this particular group of γδ T cells, inhibition of IL-7 qualifies for further extensive examination in other cancer models.

**Targets of IL-17A in lung cancer**

Further downstream mechanisms of IL-17A signaling involve at least three already well-established processes. Firstly, a direct effect of IL-17A on lung cancer cells supports epithelial–mesenchymal transition [153,154], an important step for cancer progression and subsequent metastasis development. Secondly, IL-17A can equally increase the production of VEGF by cancer cells themselves [155–157] and therefore lead to enhanced angiogenesis. Thirdly, IL-17A can recruit tumor-supporting myeloid cells [142] like neutrophils [143] to the lung, thus enhancing cancer development.

**Overall impact of IL-17A in lung metastasis**

Inconsistent with the role of IL-17A in lung cancer, multiple studies suggest a dual role of this cytokine in lung metastasis. On the one hand, some reports found a reduced development of lung metastasis of different murine and human lung cancer cell lines in Il17a-deficient mice [158,159] or a reduction of lung cancer metastasis by an antibody-mediated inhibition of IL-17A [160]. In the same fashion, treatment with an anti-IL-17A-antibody reduced metastatic burden in a sophisticated murine lung metastasis model [161]. On the other hand, a contrasting observation was made when melanoma cells were intravenously injected into the tail vein of Il17a-deficient mice [162], which generally leads to subsequent metastasis formation in the lung. Moreover, another well-known study claims that IL-17A mediates antimetastatic effects in lung metastasis [163], leading to increased lung metastasis of a colon carcinoma cell line in Il17a-deficient mice. Nonetheless, this observation remains highly controversial since other laboratories did not obtain similar results [164].

**Cellular sources of IL-17A in lung metastasis**

One possible explanation concerning these unclear metastatic functions of IL-17A might lay within this cytokine’s different sources. Indeed, multiple cells like Th17 cells, T cytotoxic 17 cell (Tc17 cells), and γδ T cells produce IL-17A in the lung. While IL-17A derived from γδ T cells was assigned a clear pathogenic role in two studies [159,161], IL-17A-secreting Tc17 cells were shown to possess a protective effect, although not through their
production of IL-17A [165]. When comparing these two subsets, IL-17A-producing T_{H}17 cells might mediate more divergent functions, being capable of both promoting [160] and inhibiting [162] lung metastasis.

Regulatory mechanisms of IL-17A in lung metastasis

As expected, induction of IL-17A production in γδ T cells occurs through the signaling of IL-1β [161].
follow-up study elaborated this cascade by the finding that tumor cells induce IL-1β production of macrophages via upregulation of the C-C motif chemokine ligand (CCL) 2. Subsequently, the blocking of CCL2 reduced IL-1β secretion and decreased the abundance of IL-17A-producing γδ T cells [166]. Surprisingly, IL-23 is dispensable for IL-17A induction in some lung metastasis models [161] and can even exert IL-17A independent pro-metastatic effects in lung metastasis [167].

**Targets of IL-17A in lung metastasis**

Moreover, the different effects of IL-17A might be explained by the multiple targets of this cytokine. These may further differ depending on the lung metastasis model used. Forced metastasis models, such as intravenous injections of cancer cells, are generally distinguished from spontaneous models, namely the subcutaneous or orthotopic implantation of cancer cells or tumor fragments. Different implantation sites and the bypassed step of extravasation in intravenous models may clarify why, on the one hand, IL-17A was shown to enhance cytotoxic antitumorigenic T-cell responses [162], while on the other hand, IL-17A was demonstrated to suppress cytotoxic T cells indirectly by recruiting immunosuppressive neutrophils via the production of G-CSF [161]. Furthermore, IL-17A can act directly on cancer cells in lung metastasis [160], leading to different outcomes depending on the cancer entity. Nevertheless, possible explanations for the observed dual role may exceed different sources and target cells of IL-17A and might also include the microbiota. In some studies, Il17a-deficient mice and wild-type mice were not cohoused [159,163], indicating that a possible protective effect of an altered microbiome in Il17a-deficient mice may be lost when cohousing mice. However, further studies are needed to address this issue before a conclusion can be drawn.

**Overall impact of IL-17F in lung cancer and lung metastasis**

In direct comparison with IL-17A, the role of IL-17F in lung cancer and metastasis had not been studied as well. One study discovered a higher expression of IL-17F in NSCLC with a negative correlation to tumor stage and lymph node metastasis, which hints toward a protective effect of this cytokine in lung cancer risk [168]. In line with this finding, a genetic polymorphism of IL-17F was shown to increase lung cancer [169]. Overall, a high expression of IL-17F was associated with a better prognosis [170], further highlighting the involvement of IL-17F in lung cancer. Contrastingly, a first mechanistic study suggested that IL-17F is capable of skewing macrophages toward a tumor-supporting M2-phenotype, which can promote angiogenesis, thus promoting cancer growth [171]. However, using a murine model with a lung-specific KRAS mutation, depletion of IL-17F did not impact the overall tumor burden [142]. Undoubtedly, further in vivo studies are required to explain the contradictory observations between humans and mouse models. Of note, the role of IL-17F in lung metastasis is currently unclear.

**Overall impact of IL-22 in lung cancer and lung metastasis**

In line with the mainly pro-tumorigenic aspects of IL-22 in other cancer entities, this cytokine follows a similar pattern in lung cancer. A genetic mouse model in which a specific KRAS mutation targets Clara cells revealed a pro-tumorigenic effect of IL-22 [172]. Equally to other cancer subsets, IL-22 expression in NSCLC patients was upregulated in pleural effusion [173] and plasma levels [173,174], with expression levels corresponding to the stage of NSCLC [175]. Another study reported that patients with higher levels of IL-22 in their bronchoalveolar lavage fluid have a decreased probability of survival [176]. However, whether IL-22 levels detected in bronchoalveolar lavage fluid are elevated or decreased in lung cancer patients currently remains unclear since different studies report conflicting observations [176,177]. Moreover, IL-22-expression in different lung tumor entities does not seem to correlate with patients’ overall survival [178].

In the KRAS-mutated mouse model, the sources of IL-22 were determined to consist of γδ T cells mainly and partially of CD4-positive cells [172]. Conversely, a study from human lung cancer tissue also demonstrated that ILC3 in the tumor could produce IL-22 upon activation [179]. The consecutive effects of IL-22 signaling have mainly been examined in cancer cells, where it was shown that in vitro stimulation of lung cancer cells can enhance proliferation [178], reduce apoptosis [173] and intensify migration, invasiveness [180], and stemness [172]. A more recent study confirmed that these IL-22-dependent consequences might even mediate resistance to gefitinib treatment [181], a tyrosine-kinase inhibitor used for targeted therapy in advanced stages of lung cancer. Further distinct studies investigating the role of IL-22 in lung metastasis are warranted, as little is known on this particular aspect.
Hepatocellular carcinoma and liver metastasis

Overview

Hepatocellular carcinoma (HCC) is the most common liver-derived tumor and nearly always arises from a cirrhotic liver. Liver cirrhosis defines a pathological condition consisting of chronic inflammation and fibrotic tissue remodeling. While early therapeutic regimes include surgical removal and liver transplantation or ablative procedures, more advanced tumors can only be treated palliatively [182]. Despite the rather new clinical use of multikinase-inhibitors, the overall prognosis of HCC remains poor [183].

Liver metastasis describes the last stage of cancer, in which tumors of several entities have spread to the organ. Since the venous system of the digestive tract converges to the portal vein, which diverges into the liver, metastases of gastrointestinal malignancies are among the most common in the liver [184,185]. CRC-derived liver metastases are the primary type due to their high prevalence compared with other malignant entities. Unsurprisingly, the prognosis of liver metastasis is poor independently of the primary tumor [186].

Overall impact of IL-17A in HCC

The role of IL-17A in HCC has been assessed in multiple studies in the past years (Fig. 4). Different reports have suggested a pro-tumorigenic role of IL-17A in murine models of HCC since Il17a-deficient mice display a decreased tumor burden [187], and inhibition of IL-17A prevents tumor development in another model [188]. In humans, increased pretherapeutic levels of IL-17A-producing cells or elevated levels of IL-17A in serum are associated with a worse prognosis [189–191]. Additionally, higher expression of IL-17A indicates an increased chance of an early recurrence of a curatively treated HCC [192].

Cellular sources of IL-17A in HCC

Multiple cellular sources have been reported to contribute to IL-17A production in murine models of HCC. Among them are not only Th17 cells in a model of nonalcoholic steatohepatitis [188] and γδ T cells in a model of intrahepatic injection of HCC cells [187], but also ILC3s [193]. Additionally, Tc17 cells were described to produce IL-17A in humans [194]. Considering the different causes of and mechanisms for liver cirrhosis, a common foundation for HCC, further studies using different mouse models are required to elucidate the contributions of different cellular sources of IL-17A.

Regulatory mechanisms of IL-17A in HCC

As it was also demonstrated for other cancer entities, IL-23 mediates the upregulation of IL-17A in HCC in different murine models [193]. Furthermore, a compelling study suggested a direct impact of the microbiome on controlling Th17 cells in the context of HCC development [195]. Mice were fed ad libitum with probiotics starting either 1 week before or on the day of tumor induction. Indeed, this treatment decreased the growth of subcutaneously implanted HCC cells during both feeding intervals with probiotics. However, antibody-mediated blocking of IL-17A inhibited tumor growth even more. This suggests the influence of further factors than just the microbiome controlling IL-17A production during carcinogenesis in the liver. Conversely, the microbiota can facilitate HCC growth and enhance liver metastasis due to mechanisms independent of IL-17A signaling [196].

Targets of IL-17A in HCC

Similar to other entities, target cells of IL-17A comprise cancer cells, in which IL-17A signaling leads to increased invasion [197], proliferation [198], and reduced apoptosis [199]. Another mechanism includes the attraction of neutrophils, which in turn exert pro-tumorigenic effects by inducing angiogenesis [200]. Likewise, it was shown that IL-17A expression in the tissue of HCC correlates with a specific marker for activation of monocytes [201], which subsequently could dampen a cytotoxic immune response of T cells in vitro. These observations deliver some further insights into IL-17A-induced circuits of pro-tumorigenic immunosuppression, which might also be transferable to other tumor entities.

Overall impact of IL-17A in liver metastasis

Notably, the implications of IL-17A production in liver metastasis have been examined less extensively than in lung metastasis. First observations in the murine liver point toward a rather pro-metastatic effect of IL-17A compared with this cytokine’s divergent effects in murine models of lung metastasis (Table 1). One study observed a reduction of liver metastasis of intrahepatically injected CRC cells upon the administration of
IL-17A blocking antibody [202]. In line with these results, another report detected a reduction of liver metastatic burden in IL-17A-deficient mice previously injected intrasplenically with cancer cells [203]. In addition, a high ratio of T<sub>reg</sub> to T<sub>H17</sub> cells in the CRC tumor tissue of patients was reported to be associated with a lower likelihood of metastasis generation 2 years after primary resection [204]. In line with this finding, it was equally reported that a higher expression of IL-17A in the primary tumor of CRC patients correlates with a higher prevalence of metastasis [205], further outlining a potentially pathological role of IL-17A during the development of liver metastasis. Mechanistically, some studies suggest a pro-metastatic effect of IL-17A on metastasized cancer cells promoting angiogenesis [202], as well as a suppressive effect on antitumor natural killer (NK) cells [203]. Furthermore, the microbiome’s importance in mediating the growth of liver metastasis by inducing IL-17A production was recently highlighted in a compelling study [206]. However, further insights regarding sources, regulatory mechanisms, and targets remain limited and highlight the necessity for further research.
Overall impact of IL-17F in HCC and liver metastasis

In consonance with the restricted knowledge of IL-17A in liver metastasis, the involvement of IL-17F in liver pathologies is even more unexplored. A study reported an enhanced detection of IL-17F in HCC samples compared with adjacent healthy tissue [207]. In contrast, an older report suggested an antitumorigenic effect of IL-17F due to a decreased subcutaneous tumor growth of HCC cells transfected with IL-17F retroviral vectors [208]. Last but not least, one study implicated an equally pathogenic role of IL-17F compared with IL-17A in a murine model of nonalcoholic fatty liver disease [209], a disease which may precede HCC. However, how this finding may translate to carcinogenesis in the liver is currently unclear since mechanistic studies regarding the role of IL-17F in HCC and liver metastasis are missing.

Overall impact of IL-22 in HCC and liver metastasis

On the contrary, the contribution of IL-22 in supporting HCC has been studied more extensively. In 2011, the chemical induction of HCC in an IL-22 overexpressing mouse strain revealed a higher susceptibility for HCC when exposed to higher IL-22 levels [210]. Correspondingly, it was demonstrated in the same year that IL-22-deficient mice were protected from HCC development [211], thus delivering the first proof of a HCC-promoting effect of IL-22. Since then, much incriminating evidence has been collected. In patients, IL-22-secreting cells are enriched in HCC tissue, and a high number of IL-22-producing cells in the tumor are associated with reduced disease-free survival [212]. Likewise, high serum levels of IL-22 can equally be correlated to a poor prognosis in HCC [213]. Surprisingly, in a patient cohort that underwent transarterial chemoembolization, IL-22 detection in the peripheral blood was associated with an increased probability of survival [214]. This underlines a possible protective role of IL-22, for example, by mediating repair of healthy liver tissue, depending on the progression of HCC.

Table 1. Overall impact of type 3 cytokines in lung and liver metastasis in human and mouse models. Summarized roles of the corresponding cytokines according to current literature.

| Entity          | Cytokine | Human | Mouse models                                               |
|-----------------|----------|-------|-----------------------------------------------------------|
| Lung metastasis | IL-17A   | Unknown effects | Strong pro-tumorigenic effects [158–161,164,166] Possible antitumorigenic effects [162,163,165] |
|                 | IL-17F   | Unknown effects | Unknown effects                                            |
|                 | IL-22    | Unknown effects | Unknown effects                                            |
| Liver metastasis| IL-17A   | Potential pro-metastatic effects [204,205] | Unknown effects                                          |
|                 | IL-17F   | Unknown effects | Unknown effects                                          |
|                 | IL-22    | Unknown effects | Unknown effects                                          |

Other malignancies

An overwhelming number of studies have been conducted investigating the roles of T\textsubscript{H}17 cells and their associated cytokines in other malignant entities. In many malignancies, only a few studies have addressed type 3 cytokines and their producing cells, making it very difficult to draw a preliminary conclusion on their overall effect in that entity. For instance, a recent report described a reduced IL-22 expression in the tissue of esophageal cancer patients. However, it did not answer its functional role in that type of cancer [218]. Contrarily, the pathogenicity of IL-17A and IL-22 in
pancreatic cancer is well described. IL-17A can promote pancreatic neoplasia in a genetic murine model [219], partially by inducing stem cell characteristics leading to an increased proliferation [220]. IL-22 might serve again as a valid prognostic marker since the high intratumoral expression of this cytokine [221] and increased TH22 cells [222] are associated with a poor prognosis. Moreover, multiple in vitro studies suggest a direct effect of IL-22 on pancreatic cancer cells [223,224]. In contrast, a recent compelling study was able to verify the proposed pathogenic role of IL-22 in a mouse model [225].

Likewise, a pathogenic role for IL-22 in gastric cancer has been suggested multiple times. While the impact of IL-17A on gastric cancer has not been fully addressed [226], two studies suggest a reverse correlation between the amount of circulating and intratumoral IL-22-producing cells and the patient’s survival. Moreover, several studies suggest a direct pro-tumorigenic influence of IL-22 on gastric cancer cells [229,230]. A further mechanistic study recently revealed that IL-22 deficiency did not lead to an ameliorated disease outcome in a genetic murine model of gastric cancer [231], thus hinting toward a more divergent role of IL-22 in this entity.

Unresolved questions

Naturally, many aspects concerning TH17 cells and their associated cytokines in cancer and metastasis require further attention. Much is yet to be investigated, and studies addressing the following queries in this field may provide new game-changing insights.

Firstly, functional distinctions between cell subsets and signature cytokines are needed. While the pathological function of a cell subset is often ascribed to its signature cytokine, this assumption might not always be correct. For example, a study revealed antitumorigenic functions of Th17 cells, which were surprisingly not mediated by IL-17A [165]. Thus, a more detailed characterization of these distinct subsets is required, especially to determine whether ‘upstream-inhibition’ of subset-shaping factors like IL-1β and IL-23 or ‘downstream-inhibition’ of subset-secreted cytokines like IL-17A, IL-17F, or IL-22 turns out to be more beneficial to treat cancer and metastasis.

Secondly, a possible IL-17A/IL-17F heterodimer formation mediating distinct effects should be taken into consideration. It is well accepted that IL-17A and IL-17F can form heterodimers in mice [8] and humans [9]. Nonetheless, the IL-17A/IL-17F heterodimer’s specific role in comparison with their homodimers has only been addressed marginally so far. This may be partially attributed to the fact that specific mouse lines impairing this heterodimer’s specific formation are currently lacking. Thus, it proves highly difficult to specifically examine the impact of the heterodimer on cancer and metastasis.

Thirdly, the downstream effects and target cells of IL-17A, IL-17F, and IL-22 need to be further elucidated. Many studies currently suggest a pro-tumorigenic role of IL-17A and IL-22 due to direct signaling on the tumor cells. Especially with regard to IL-22, it becomes apparent that mechanisms proving beneficial for cancer cells also exert comparable effects on healthy tissue, thus simultaneously providing an antitumorigenic component. Accordingly, a pathogenic function of different cytokines might rely on a later tumor stage, in which the pathological effects outweigh the physiological, protective ones. Conclusively, a closer look at different targets apart from the tumor cells might reveal new intriguing insights with subsequent therapeutic consequences. In line with this, another key aspect explaining divergent functions might lay within the coproduction of different cytokines from the same source. For example, IL-22 might exert different functions in the presence of IL-17A than it does in its absence, as a recent study indeed suggests [89].

Moreover, concise information regarding the spatiotemporal dynamics of type 3 cytokines in cancer and their producers are still rare. On the one hand, a high abundance of infiltrating TH17 cells could be detected in many malignant entities, whereas healthy tissues of these organs only displayed a few of them. Thus, it is often assumed that TH17 cells are recruited to the malignant site in these entities [232]. However, neither the stages of cancer development in which this recruitment predominantly occurs nor the axis which might be involved is clear. On the other hand, in tissues with a higher abundance of TH17 cells, different mechanisms during the early stages of tumor development might be crucial. For instance, a rapid response shaped by the production of type-3 cytokines by tissue-resident cells might be plausible. Since the generation of tissue-resident TH17 cells can be induced by resolved infections in that specific organ [233,234], it would be highly interesting to determine the effect of previous infections on type-3 cytokines, cancer, and metastasis. Luckily, there are now numerous state-of-the-art methods such as in vivo imaging to explore these questions in the next years.

Additionally, in the age of emerging immunotherapies, it will be of utter importance to better understand the prognostic role of TH17 cells and their cytokines for different therapeutic regimens. In the nearer future, it will be crucial to identify patients for the use of
specific immunotherapy. Whether the amount of infiltrating T17 cells and the expression of their signature cytokines could guide therapies in patients is currently unknown.

Ultimately, more research should be directed toward unraveling the plasticity of T cells as a possible explanation for the dichotomous effects of type 3 cytokine-producing cells. Since it is well known that T17 cells can indeed transform into other T-cell subsets during infections [36], the same mechanism can be easily imagined for cancer of different entities. The several stages of transdifferentiated cells might exert dichotomous functions due to the coproduction of different cytokines, leading to distinct effects regarding tumor growth and metastatic seeding. Although a first study does indeed hint toward plasticity in T cells during cancer development [77], more studies are needed to confirm this interesting finding.

Outlook

Taken together, mounting evidence has been presented regarding the pro-tumorigenic functions of T17 cell-derived cytokines in a lot of primary malignancies affecting mice and humans (Table 2). Consequently, therapeutic approaches may include direct inhibition of IL-17A, IL-17F, or IL-22 and a blockade of the upstream cytokines IL-23 or IL-1β. Luckily, many of these blocking antibodies have been successfully tested and are already approved for several inflammatory diseases. Namely, secukinumab (targeting IL-17A), bimekizumab (targeting IL-17A and IL-17F simultaneously, not yet approved), guselkumab (targeting IL-23), and ustekinumab (targeting IL-12 and IL-23) are currently used, among others, to treat psoriasis [235]. Likewise, Anakinra (targeting IL-1 receptor) is approved for treating rheumatoid arthritis [236], and an antibody directed against IL-22, named fezakinumab, is currently being tested in phase II trials with patients suffering from psoriasis [237].

A further therapeutic approach might lie within the inhibition of regulatory factors of type 3 cytokine production, such as targeting the transcription factor RORγt. One of the first synthetic inverse agonists of RORγt was developed in 2011 and named SR1001 [238]. This study showed that SR1001 was indeed not only able to reduce T17 development and IL-17A secretion, but also led to reduced severity of experimental autoimmune encephalomyelitis when administered intraperitoneally. Another study equally reported decreased IL-17A when cells were treated with another synthesized RORγt antagonist, termed SR2211 [239]. Also, preexisting substances such as the antiarrhythmic agent digoxin were identified as potent RORγt antagonists [240].

With passing time, more and more substances targeting RORγt emerged [241], indicating a great interest regarding their clinical use [242]. Since these expectations are partially based on the overwhelming success of IL-17A antibodies in the psoriasis treatment, major attention will be drawn toward the performance of RORγt antagonists in their actions against certain diseases. In that regard, the first results from mouse and human studies addressing RORγt antagonist treatment in psoriasis could indeed corroborate a positive effect [243–246]. Moreover, interest in treating other autoimmune diseases such as arthritis [247–249] and inflammatory bowel disease [250–252] with RORγt antagonist have begun to emerge as well.

Unfortunately, studies investigating RORγt antagonists in cancer and metastasis remain scarce. Comparable to the treatment of autoimmune diseases, these inhibitors could complement or even replace an immunotherapeutic regime with checkpoint inhibitors or antibodies directed against cytokines. Advantages of RORγt antagonists may start with the possibility of an oral administration compared with the intravenous or subcutaneous injections of most other immunotherapeutic drugs. Moreover, it is thinkable that side effects may be less severe. As small molecule inhibitors, orally administered RORγt antagonists may lead to fewer allergenic reactions than current immunotherapeutic agents. Furthermore, the sheer number of existing agents would allow physicians to switch between dozens of substances in case of drug-related complications. Definitely, further studies addressing these questions are needed.

A final advantage might lie within the fact that RORγt antagonists may target the production of different pathogenic cytokines simultaneously. This might lead to the parallel inhibition of IL-17A and IL-22, which would provide an additional benefit for the treated patient. However, enthusiasm for long-term use of RORγt antagonists might be dampened because RORγt deficiency in mice and RORγt antagonist treatment in rats leads to lymphoma development [253–255].

Another therapeutic option might include the artificial overexpression of physiological regulators of cytokines, for instance, IL-22BP [101]. Ultimately, expression levels of type 3 cytokines were shown to correlate with a poor prognosis in multiple cancer entities, so that a sound evaluation for the use of these cytokines as biomarkers should be conducted. However, despite the need for new, innovative
therapeutic regimes, physiological and sometimes antitumorigenic functions of these cytokines should not be overlooked. Moreover, one should bear in mind that many functions of IL-17A, IL-17F, and IL-22 remain elusive in this field. Hindsight has shown us that scientists might be well advised to show respect for the pathogenic functions of TH17 cells and their associated cytokines in cancer and metastasis. Whether this is reason enough to let one’s fears run wild, culminating eventually into heptadecaphobia, remains questionable.

Acknowledgements

This work was supported in part by the Deutsche Forschungsgemeinschaft (grant SFB841 to SH), the European Research Council (CoG 865466 to SH), European Respiratory Society/short-term fellowship (to ADG), Else Kröner Memorial Stipendium (to ADG), Werner Otto Stiftung (to ADG), Erich und Gertrud Roggenbuck Stiftung (to ADG) and Hamburger Krebsgesellschaft Stiftung (to ADG). SH has an endowed Heisenberg-Professorship awarded by the Deutsche Forschungsgemeinschaft. The authors thank Franziska Bertram, Elaine Hussey, Morsal Sabihi, and Dimitra E. Zazara for carefully proofreading the manuscript. Figures were created with BioRender.com.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

JL conceptualized and wrote the manuscript and designed the figures. AMS, TZ, JK, ADG, and SH provided critical scientific advice and reviewed the manuscript.

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