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Type 3 cytokines in liver fibrosis and liver cancer

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ABSTRACT

The type 3 cytokines IL-17 and IL-22 play a crucial, well synchronized physiological role in wound healing and repairing tissue damage due to infections or injury at barrier surfaces. These cytokines act on epithelial cells to induce secretion of early immune mediators, recruitment of inflammatory cells to the site of injury, and to trigger tissue repair mechanisms. However, if the damage persists or if these cytokines are dysregulated, then they contribute to a number of inflammatory pathologies, autoimmune conditions and cancer. The liver is a multifunctional organ that plays an essential role in metabolism, detoxification, and immune surveillance. It is also exposed to a variety of pathogens, toxins and injuries. Over the past decade, IL-17 and IL-22 have been implicated in various aspects of liver inflammation. IL-17 is upregulated in chronic liver injury and associated with liver disease progression. In contrast, IL-22 was shown to be hepatoprotective during acute liver injury but exhibited inflammatory effects in other models. Furthermore, IL-22 and IL-17 are both associated with poor prognosis in liver cancer. Finally, the regulatory mechanisms governing the physiological versus the pathological role of these two cytokines during acute and chronic liver injury remain poorly understood. In this review, we will summarize the current state of knowledge about IL-17 and IL-22 in wound healing during acute and chronic liver injury, their contribution to pathogenesis, their regulation, and their role in the transition from advanced liver disease to liver cancer.

1. Introduction

Inflammation, the body's first response to injury, serves an essential physiological role in eliminating invading pathogens and tissue repair. However, persistent or dysregulated inflammation results in various immunopathologies and is a major risk for developing cancer [1]. Early studies stratified functionally distinct CD4 T cell subsets according to the type of cytokines they produce into Th1 (IFNγ producers) and Th2 (IL-4 producers) [2,3]. This grouping later expanded to include IL-17 producing CD4 T cells, termed Th17 cells [4]. Increasing data over the past two decades have underscored the capacity of various innate and adaptive immune cells to produce multiple cytokines leading to a shift in the classical Th1/Th2/Th17 paradigm. Hence, a more general term encompassing all cellular subsets was proposed as type 1, 2 and 3 immunity. Type 1 immunity is characterized by production of IFNγ and is mediated by cells expressing the T-box transcription factor (T-bet) including CD4 Th1 cells, CD8 cytotoxic T cells (Tc1), type 1 innate lymphoid cells (ILC1s) and natural killer (NK) cells. Type 1 immune cells are responsible for immunity against intracellular pathogens and are implicated in inflammatory autoimmune conditions. Type 2 immunity is characterized by the production of IL-4, IL-5 and IL-13 and is mediated by cells expressing the transcription factor GATA-binding protein 3 (GATA3) including CD4 Th2 cells, CD8 (Tc2) cells and type 2 ILCs (ILC2s). Type 2 immune cells protect against helminths and venoms, orchestrate tissue repair and are implicated in asthma, allergic reactions, and fibrosis [5]. Type 3 immunity is characterized by the production of Th17-associated cytokines IL-17A-F, IL-21, IL-22 and IL-26. Production of type 3 cytokines is mediated by cells expressing the retinoic acid-related orphan receptor-γt (RORγt) [6]. IL-22 production is dependent on expression of the aryl hydrocarbon receptor (AHR) [7]. Type 3 immune cells include CD4 Th17 cells, CD8 Tc17 cells, type 3 ILCs (ILC3s), mucosal associated invariant T cells (MAIT), NKT cells, and γδ T cells [8,9]. Type 3 cytokines mediate immunity against extracellular bacteria and fungi at barrier surfaces and are essential for tissue repair [5,10]. Dysregulated type 3 responses have been implicated in chronic inflammation, and have been associated with inflammatory disorders, autoimmunity [11,12], and cancer [13].

The liver is a multifunctional organ that plays a key role in metabolism and detoxification as well as immune surveillance [14]. The liver is continuously being exposed to self and foreign antigens carried by blood from the gut and is thus a potential gateway for numerous pathogens. Hence, it is not surprising that it is enriched in type 3 immune cells that are able to mount an effective immune response against invading pathogens and mediate tissue protection *via* the type 3 cytokines (IL-17 and IL-22) [15–17]. However, these same repair and protective mechanisms were associated with pathogenesis of chronic liver disease and liver cancer, known as hepatocellular carcinoma (HCC) [18–21]. Here, we provide an overview of type 3 immunity and

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cytokines, specifically IL-17 and IL-22, in wound healing during acute and chronic liver injury, their implication in the pathogenesis of liver disease, and their role in the development of liver cancer.

2. Biology of type 3 cytokines

2.1. IL-17

The IL-17 family of cytokines comprises six cytokines IL-17A-F, of which IL-17A and IL-17F are the most studied. IL-17A and IL-17F share 55% homology in amino acid sequence [22]. This homology translates into functional similarities with both cytokines sharing cellular sources, target tissues, receptor, and inducing the same pro-inflammatory pathways [23]. In this review, we will focus on IL-17A, hereinafter referred to as IL-17.

IL-17 is produced by Th17 (CD4+CD161+CCR6+CD26+) helper T cells that also produce IL-17F, IL-21, IL-22 and occasionally IFNγ [24]. Other key producers of IL-17 are CD8 T cells (Tc17), γδ T cells, neutrophils, mast cells and ILC3s [25–27]. IL-17 production is regulated by the RORγt transcription factor [6,28] and to a lesser extent by RORα [29]. Th17 cells differentiate from naïve CD4 T cells in response to antigenic stimulation and the cytokines IL-6 and TGF-β. This early differentiation is accompanied by upregulation of RORγt, the chemokine receptor CCR6, and the IL-23 receptor. Signaling *via* IL-23 stabilizes the Th17 phenotype and is essential for the development of pathogenic Th17 cells producing both IL-17 and IFNγ [30–32]. Differentiation of Th17 cells and production of the associated cytokines is regulated by positive and negative regulators. The most prominent positive regulators include signal transduction and activation of transcription 3 (STAT-3), basic leucine zipper ATF-Like transcriptional factor (BATF), interferon regulatory factor 4 (IRF4) and AHR [23]. Negative regulators include T-bet and FOXP3 that drive Th1 and regulatory T cells (Tregs) differentiation, respectively [23]. Interestingly, TGF-β is essential for development of both Th17 and Tregs and thus may play a dual role in polarizing naïve CD4 T cells depending on the context of stimulation and the level of TGF-β and other cytokines. It is also noteworthy that Th17 cells are endowed with a certain level of plasticity as they can produce cytokines associated with the Th1 lineage (ex. IFNγ) or IL-10 associated with Tregs [33]. A shift towards IL-10 production by Th17 is considered a mechanism of regulating Th17 inflammatory activity. Finally, IL-10 produced by Tregs can also inhibit proliferation and differentiation of Th17 cells and contributes to the regulation of Th17 functions [34].

The main targets of IL-17 are epithelial cells, endothelial cells, and fibroblasts at barrier/mucosal surfaces [35–37]. Macrophages were also recently shown to respond to IL-17 [38]. The IL-17 receptor (IL-17R) is a heterodimer of IL-17RA and IL-17RC. Engagement of the IL-17R leads to activation of the transcription factors nuclear factor kappa B (NF-κB), and CCAAT-enhancer-binding proteins (C/EBP) [23]. It also activates mitogen-activated protein kinases (MAPKs) signaling including p38 kinase and Jun N-terminal kinase (JNK) [23]. Collectively, these pathways regulate the expression of pro-inflammatory cytokines, neutrophil chemo-attractants, antimicrobial peptides (AMPs) including defensins, angiogenic factors, and matrix metalloproteinases (MMPs) [39]. As such, IL-17 orchestrates tissue responses to invading extracellular bacteria and fungi in the skin, lungs, vagina, kidneys and gastrointestinal system including the liver [40]. Most IL-17-producing cells reside in non-lymphoid tissues where they act as sentinels against microbial invasion [41].

IL-17, on its own, is not a potent inducer of inflammation but synergizes with other cytokines (type 3 and others) in the tissue microenvironment to induce a potent pro-inflammatory response [39]. For example, IL-17 synergizes with IL-22, or TNF-α to enhance induction of inflammatory cytokines, neutrophil and Th17 infiltration, and expression of AMPs [42]. These effects were associated with both host protection and immunopathology [42]. Pathogenic Th17 cells producing both IL-17 and IFNγ were associated with inflammatory autoimmune conditions like multiple sclerosis, inflammatory bowel disease (IBD) and rheumatoid arthritis [30,32,43,44].

2.2. IL-22

IL-22 is a member of the IL-10 family of cytokines [45]. IL-22 is produced essentially by IL-17-producing cells including Th17 cells, subpopulations of activated Th1 cells and CD8 T cells, ILC3s, MAIT cells, γδ T cells, NK, NKT cells, and neutrophils. One notable exception is the population of CD4+ Th22 cells that are enriched in the blood and skin and express IL-22 but not IL-17 [46]. IL-22 production is largely dependent on the expression of AHR [7].

The IL-22 receptor (IL-22R) is a heterodimer of the IL-10Rβ and the IL-22RA1 chains. IL-22RA1 is expressed on epithelial cells and fibroblasts including hepatocytes and hepatic stellate cells (HSCs), but not immune cells thus restricting its target cellular population [47]. This compartmentalization determines the unidirectional signaling of IL-22 from the immune system to the tissues. IL-22 binding to its receptor induces the Jak1-Tyk2 pathway leading mainly to canonical activation of STAT-3 and induction of the MAPKs pathway [47]. Downstream target genes of IL-22 signaling include those encoding innate immunity mediators (acute phase proteins, AMPs, mucins, pro-inflammatory cytokines and chemokines) that are key in the innate immune defense of tissues against fungal and bacterial pathogens. IL-22 also induces modulators of pro-proliferative, and anti-apoptotic programs [48]. Thus, it is associated with enhanced proliferation and survival of epithelial cells that promote wound healing and tissue regeneration. At the same time, induction of these genes has the collateral effect of favoring proliferation and survival of transformed cells and promoting tumorigenesis [49–53].

IL-22 production can be regulated by microRNA 15a/16-1 (miR-15a/16-1) acting on the AHR locus [54]. IL-22 activity is regulated by the soluble IL-22RA2 receptor known as IL-22 binding protein (IL-22BP) [55–57] typically produced by dendritic cells (DCs), T cells and eosinophils [34]. The affinity of IL-22 for IL-22BP is 20 to 1000-fold higher than its affinity to its membrane bound IL-22RA1 [58]. This dramatic difference in binding affinities suggest that tight regulation of IL-22 signaling is important. Most likely, for limiting the pro-inflammatory and proliferative effects of this cytokine [59].

3. Acute and chronic liver injury

The liver is a multifunctional organ that plays essential roles in metabolism of carbohydrates, lipids, and proteins; detoxification; production and secretion of bile, and immune surveillance [14]. As the major recipient of blood from the gut, the liver is constantly exposed to a myriad of harmless antigens from diet and commensal bacteria, as well as food-borne pathogens and toxins. Very unique mechanisms have evolved for ensuring tolerance to innocuous antigens while retaining the ability to respond to infection and other insults [60].

The liver could be subjected to acute injury such as drugs, toxins, bacterial infections, and acute resolving viral infections like hepatitis A virus (HAV). Following acute injury, the earliest response is that of hemostasis, where platelets are rapidly recruited to the site of injury to form a temporary clot and close the wound. Then a highly orchestrated self-resolving wound healing response is set in motion to first eliminate the tissue damaging agent(s) and then to restore normal tissue architecture and function. This response is composed of three overlapping phases: inflammation, proliferation/repair, and tissue remodeling (Fig. 1A). Following the injury, inflammation is triggered in response to recognition of pathogen associated molecular patterns (PAMPs), and/or damage associated molecular patterns (DAMPs). Circulating or tissue resident pro-inflammatory cells like monocytes, neutrophils and macrophages are recruited to the site of injury/infection and mediate removal of the damaging agent. Next, the proliferative phase is initiated,

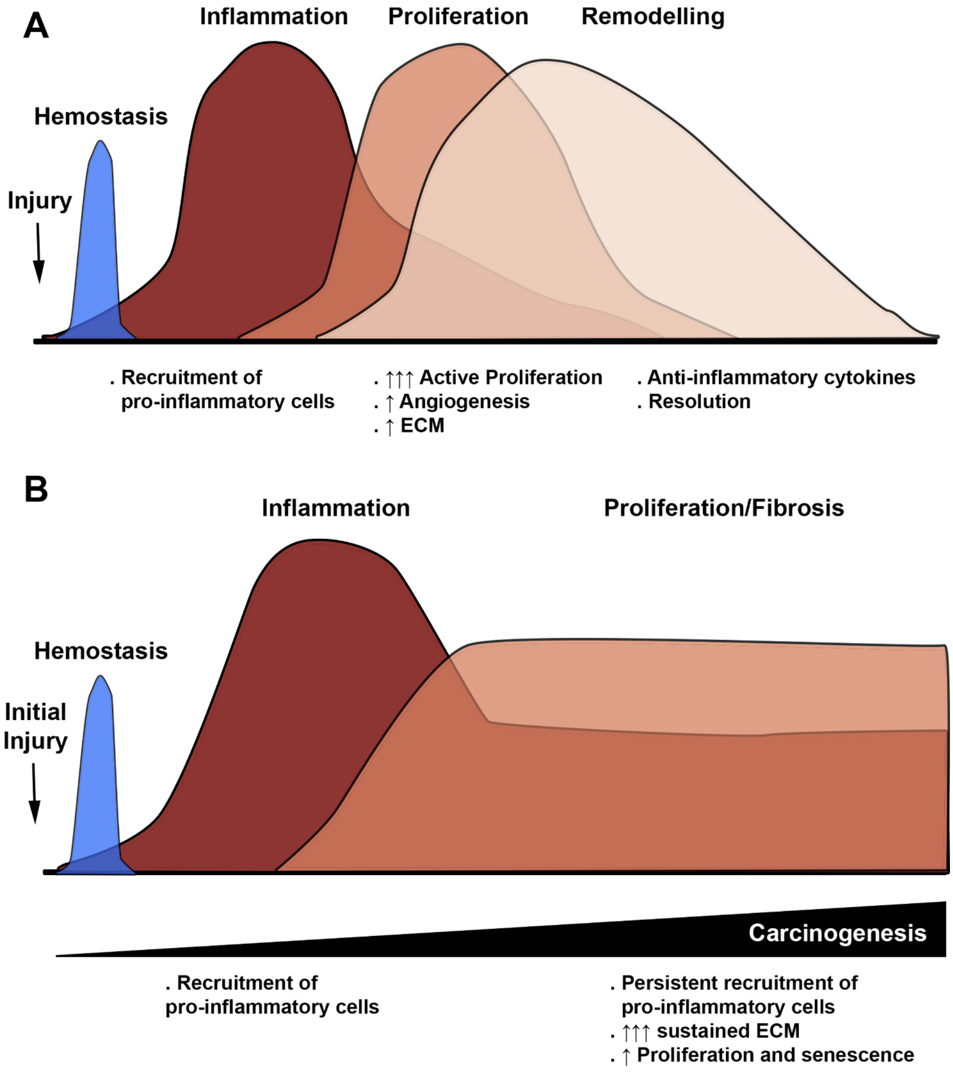

Fig. 1. Normal vs. Pathological Wound Healing. (A) Upon acute injury, hemostatic mechanisms are quick to react to contain the wound. The sensing of PAMPs and DAMPs initiates a wound healing response that can be divided into three phases: inflammation, proliferation/repair, and remodeling. The inflammatory phase is characterized by the orderly influx of neutrophils, monocytes, and lymphocytes into the infection/inflammation site. Subsequent clearing of pathogens or toxins, and elimination of necrotic tissue reduces inflammation and initiates repair. During the proliferation/repair phase in response to liver injury, HSCs get fully activated, proliferate and generate a temporary matrix which supports new tissue and vessel formation. This process is assisted by pro-resolving macrophages through production of growth factors and anti-inflammatory mediators. Finally, during tissue remodeling the ECM is remodeled back to its homeostatic configuration, HSCs get deactivated or killed, and immune cells leave the site. (B) Persistent exposure to injurious agents leads to perpetuation of inflammation and tissue damage, and therefore chronic activation of HSCs and fibrosis. With time, chronic inflammation, fibrosis, and pathological tissue remodeling increase the risk of malignant transformation.

where tissue repair and regeneration takes place. Tissue repair involves proliferation, migration, and reorganization of cells in order to restore the basic architecture of the tissue with formation of a temporary extracellular matrix (ECM). It also involves angiogenesis and formation of new blood vessels. Finally, during the tissue remodeling phase, cells that are no longer needed are either inactivated or killed, and the ECM is remodeled back or matured to its normal configuration. This phase can continue for a long time until the tissue heals completely (reviewed in [61–63]).

The liver could also be subjected to chronic types of injury due to persistent infections like viral hepatitis B and C, malaria and schistomiasis. Furthermore, chronic liver injury can result from alcoholic steatohepatitis (ASH) or fat deposition during non-alcoholic steatohepatitis (NASH). Persistence of the damaging agent or injury results in prolongation of the inflammation phase, sustained recruitment of pro-inflammatory cells and exacerbation of the tissue repair/regeneration mechanisms including continuous activation and proliferation of epithelial cells leading to senescence. In addition, sustained production of extracellular matrix and dysregulation of MMPs leads to matrix deposition and fibrosis. Chronic inflammation and tissue fibrosis increase the risk of carcinogenic transformation (Fig. 1B) [62].

4. Type 3 immunity in acute liver injury

Following acute liver injury, innate sensing of PAMPs, and/or DAMPs released by dying hepatocytes triggers inflammatory responses [64]. Several liver specific immune cells and the unique architecture of the liver contribute to this process. Kupffer cells (KCs), the liver-resident macrophages strategically positioned in the liver sinusoids, act as first responders during the early stages of inflammation through secretion of pro-inflammatory cytokines and chemokines [65]. Liver sinusoidal endothelial cells (LSECs) are also activated in the inflammatory microenvironment, further amplifying this response [66,67]. The resulting gradient of chemokines attract inflammatory cells to the site of injury. Notably, neutrophils and pro-inflammatory monocytes that are further activated by the cytokine milieu. These phagocytes provide early immune control through ingestion of microbes and their products as well as apoptotic bodies from injured and dying cells. Furthermore, they produce key inflammatory cytokines (IL-1β, IL-6 and TNFα) and antimicrobial peptides to protect the site of injury from opportunistic infections [68–71]. This inflammatory loop is essential to protect the epithelium and to recruit and activate effector cells to initiate tissue repair at the site of injury [72]. The type 3 cytokines IL-17 and IL-22 can be rapidly secreted during the inflammation phase, most likely by tissue resident Th17, MAIT, γδ T and NKT cells [17,41,73–76] and are critical for containing infections and tissue repair. IL-17 and IL-22 both induce a variety of AMPs and acute phase proteins that preserve and protect epithelial integrity [77–82].

4.1. IL-17 in acute liver injury

IL-17 acts on epithelial cells and fibroblasts to induce secretion of pro-inflammatory chemokines including: macrophage inflammatory protein 1-alpha (MIP-1α/CCL3), growth related oncogene-alpha (GRO-α/CXCL1), IFN-γ-inducible protein 10 (IP-10/CXCL10), and IL-8 (CXCL8), involved in recruitment of monocytes and neutrophils to the site of injury [19,83]. Furthermore, IL-17 collaborates with IL-1β and IL-6 to enhance activation of recruited and tissue resident pro-inflammatory phagocytes leading to exacerbation of inflammation as well as clearance of the injurious agent [20,83,84]. As the cause of inflammation is cleared, the macrophage population undergoes gradual functional and phenotypic changes from pro-inflammatory to a pro-wound-healing, pro-fibrotic phenotype. These phenotypic and functional changes are associated with increased production of factors that promote fibroblast activation and tissue repair followed by a pro-resolving, anti-inflammatory, anti-fibrotic, and tissue-regenerating phenotype that ensures that the tissue-damaging inflammatory response is suppressed and normal tissue architecture is restored [85]. During tissue repair, IL-17 may indirectly contribute to hepatocyte proliferation through the induction of IL-6 which consequently activates the key proliferative STAT3 pathway [86–88]. In parallel, activation of angiogenic pathways induces migration and proliferation of LSECs that form new vessels. IL-17 was reported to be a potent inducer of vascular endothelial growth factor (VEGF) in a variety of cancers including HCC [18,89]. So, it is reasonable to speculate that IL-17 may participate in angiogenesis during tissue repair in the liver but sufficient evidence is still lacking. During the repair phase, HSCs are fully activated and migrate to the site of injury where they proliferate and secrete fibrillar collagens [90]. Activation and differentiation of HSCs is induced by TGF-β and platelet derived growth factor (PDGF) and maintained by pro-inflammatory cytokines. IL-17 may indirectly contribute to the fibrogenic process through activation of KCs, monocytes and neutrophils leading to additional recruitment of inflammatory cells and further production of IL-17 and other cytokines in an inflammatory loop [19,20,83,84,88]. IL-17 may also sensitize HSCs to suboptimal doses of TGF-β by upregulating the expression of the TGF-β-RII on HSCs [21]. Activation of HSCs initiates production of ECM. The formation of a temporary matrix promotes hepatocyte survival through integrin signaling, support re-epithelialization, and limits pathogen/toxin spreading [91]. Once the site of injury is repopulated and the basic architecture of the tissue is restored, ECM remodeling takes place through the secretion of MMPs, and reduction in the expression of tissue inhibitors of metalloproteinases (TIMPs) in order to degrade the temporary scar. A number of studies have identified IL-17 as a potent inducer of MMPs in a variety of inflammatory conditions and cancer but its potential involvement in ECM remodeling upon acute liver injury is yet to be determined [92–96].

In contrast to the pro-inflammatory functions of IL-17 described above, IL-17 has also been associated with reduction of inflammation and tissue damage in several models of acute hepatitis. In a mouse model of α-galactosylceramide (αGalCer)-induced hepatitis, hepatic CD4+ invariant NKT (iNKT) cells were identified as key producers of IL-17. Neutralization of IL-17 exacerbated hepatitis and liver damage and was associated with increased hepatic recruitement of neutrophils and pro-inflammatory monocytes. The authors demonstrated that hepatic iNKT cells specifically activated with α-GalCer rapidly produced IL-17, and this IL-17 inhibited the development of hepatitis [97]. Similarly, a protective role was attributed to γδ T cells-derived IL-17 in a model of Concanavalin A (ConA) induced hepatitis in hepatitis B virus surface antigen transgenic (HBs-Tg) mice [98]. In this study, ConA induced activation of liver resident γδ T cells and early release of IL-17. Mice deficient in γδ T cells exhibited reduced hepatic expression of IL-17 and accelerated IFN-γ production by CD4 T cells after ConA treatment leading to worsening of inflammation. In both studies, early release of IL-17 by tissue resident innate-like lymphocytes (iNKT or γδ T cells) was key to inhibiting the development of type 1 inflammation. Similarly, a protective role for IL-17 was described in acute T-cell mediated colitis, whereby IL-17 acts directly on T cells to regulate differentiation of pathogenic Th1 T cells [99]. Altogether, these studies underscore the multifaceted and complex role of IL-17 both as an inflammatory mediator and as a regulator of other types of inflammation.

4.2. IL-22 in acute liver injury

IL-22 plays a crucial, hepatoprotective role during the inflammation phase following liver injury through the induction of the anti-apoptotic molecules Bcl-2 and Bcl-xL in hepatocytes [100–102] and promoting proliferation of liver stem/progenitor cells (LPCs) [103]. Lack of IL-22 during ConA acute liver injury leads to increased inflammation, necrosis and delayed tissue repair [100,102]. During the proliferation/regeneration phase, IL-22, as a potent activator of STAT-3, contributes directly to the proliferation of hepatocytes [100,102,104,105]. As discussed above, IL-22 signaling is tightly regulated through the expression of its decoy receptor IL-22BP. In the liver, under normal condition the IL-22/IL-22BP ratio is low [49]. The significance of endogenous IL-22BP and IL-22/IL-22BP ratio during acute liver injury is not fully understood. However, it was demonstrated in the gut that increased IL-22/IL-22BP ratio is required to promote efficient tissue repair [49]. Interestingly, one recent study demonstrated that IL-22BP plays a protective role during acute liver injury. Lack of IL-22BP leads to dysregulated IL-22 signaling that indirectly promotes necrosis through CXCL10 mediated recruitment of inflammatory monocytes [106]. In conclusion, these studies demonstrate the importance of IL-22 regulation through secretion of its decoy receptor.

The hepatoprotective role of IL-22 has been challenged in several acute liver injury models where the inflammatory/pathogenic properties of IL-22 prevail over the benefits associated to its tissue protective function. IL-22 neutralization reduced tissue damage and liver inflammation in HBV transgenic mice following adoptive transfer of HBV specific CD8 T cells [107]. Depletion of IL-22 in this model led to reduced recruitment of inflammatory cells [107]. These observations may be relevant in chronic HBV infected patients, where IL-22 may exacerbate hepatitis through enhanced recruitment of pro-inflammatory immune cells. Similarly, using a rat allogeneic liver transplantation model, Zhang Y. et al showed that IL-22 is protective during the ischemia-reperfusion injury stage of liver transplantation (day one) but detrimental during the acute rejection stage (day 7) [108]. In this study, IL-22-mediated tissue protection was associated with inhibition of apoptosis and promotion of hepatocyte proliferation. In contrast, IL-22 signaling at day 7 resulted in enhanced expression of pro-inflammatory cytokines and chemokines, increased Th17/Tregs ratio, and more extensive tissue damage that was ameliorated by neutralization of IL-22 [108]. Further confirmation of the pathogenic role of IL-22 during acute liver injury was demonstrated using IL-22 binding protein deficient mice (IL-22BP-/-) in models of ischemia-reperfusion injury and acetaminophen-induced liver injury. In both models, lack of IL22BP, and therefore dysregulated IL-22, led to increased hepatocellular death [106]. Uncontrolled IL-22 signaling, due to lack of IL-22BP, resulted in increased CXCL10 gene expression in hepatocytes and enhanced recruitment of tissue destructive inflammatory monocytes [106]. These data suggest that the protective versus pathogenic role of IL-22 may be dependent on the specific context in which it is expressed, regulation by IL-22BP and the particular signaling pathways activated in target cells (pro-survival/regeneration vs. pro-inflammatory).

Once tissue repair is near completion, proliferation subsides and tissue remodeling is initiated. During this phase the number of activated HSCs is limited either by inducing their reversion to a quiescent phenotype or their elimination through direct killing and/or induction of apoptosis [72,109–111]. IL-10, from various sources, plays a crucial role during this phase. First, it induces further polarization of macrophages to an anti-inflammatory or pro-fibrogenic phenotype, sometimes termed regulatory macrophages, that will then orchestrate the tissue remodeling phase (reviewed in [112,113]). These regulatory macrophages secrete IL-10 which contributes directly to the inactivation and elimination of activated HSCs in cooperation with NK cell-mediated cytotoxicity. Finally, the temporary scar, no longer required, is degraded by MMPs produced by macrophages [114,115].

The role of IL-22 in the tissue remodeling phase of acute liver injury remains undefined. Nevertheless, IL-22 has been reported to induce expression of MMP-1 in keratinocytes *via* p38 and STAT-3 dependent mechanisms [116]. IL-22 was reported to inhibit [117], activate [118] or induce senescence of HSCs [119]. Hence, its action in limiting activity of HSCs remains controversial. These data suggest an active role for IL-22 in inducing mediators that enhance resolution of hepatic fibrosis following acute injury and re-stablishing liver homeostasis but the exact mechanisms remain to be elucidated [120].

5. Type 3 immunity in chronic liver injury

Persistence of the liver damaging agent beyond the acute phase leads to chronic inflammation and sustained activation of the repair/regenerative response without ever resolving the injury. Irrespective of the underlying etiology, the ongoing repair response leads to fibrosis characterized by an imbalance between deposition and degradation of ECM in response to injury. Activated HSCs are the main fibrogenic cellular population in liver [121]. The crosstalk between HSCs, immune cells, and other liver resident cells regulates the fibrogenic process. As discussed above, during the wound healing response to acute liver injury, activation of HSCs is transient, reversible, and is meant to support the tissue repair process. In this case, the temporary fibrous scar is degraded during the remodeling phase and activated HSCs are either killed or revert to an inactivated state. In contrast, during chronic injury, activation of HSCs is sustained and perpetuated by persistent inflammatory signals and growth factors like TGF-β leading to hyperproliferation, and accumulation of scar tissue [90].

5.1. IL-17 in chronic liver injury

IL-17 is upregulated in chronic liver disease and correlates with disease progression in chronic HBV [122,123], HCV [124], ASH [19] and NASH [125,126]. IL-17 can have direct effects as a proinflammatory cytokine or indirect effects by enhancing the role of other inflammatory or fibrogenic signals.

5.1.1. IL-17-mediated inflammation in chronic liver disease

High levels of IL-17 were detected in chronic HBV patients and have been linked to exacerbation of inflammation and tissue damage [122,123]. Furthermore, hepatic and peripheral Th17 frequencies were increased in these patients and were identified as cellular sources of IL-17 [122,123]. *In vitro* studies suggested that IL-17 mediates the activation of inflammatory monocytes and macrophages leading to increased secretion of the hepatic damaging cytokines IL-1β, IL-6, and TNFα [122,123]. IL-17RA deficient mice exhibited reduced neutrophil influx, pro-inflammatory cytokines, hepatocellular necrosis, inflammation, and fibrosis as compared to controls in a CCl_4 injection model of chronic liver injury [127]. Similarly, IL-17 produced mainly by neutrophils and T cells was upregulated in ASH patients and correlated with lobular inflammation [19]. Finally, induction of liver infiltrating neutrophils by IL-17 was identified as the main pathological driver of disease progression in NASH [128]. Accordingly, in the liver of NASH patients, IL-17+ cells were detected in close proximity to ballooning hepatocytes and macrovesicular lesions providing *in situ* evidence for a pathogenic role of IL-17 in NASH. Subsequent *in vivo* work showed that Th17 cells were enriched in the liver of mice on high fat diet compared to controls [125]. Blockade of IL-17 ameliorated LPS-induced inflammation in this model [125].

5.1.2. Pro-fibrogenic activity of IL-17 in chronic liver disease

The density of intrahepatic IL-17+ cells, as well as the levels of peripheral Th17 cells, correlated positively with fibrosis staging in chronic HBV [122,123,129], chronic HCV [124], ASH [19] and NASH [125,126,130,131]. Using the cholestatic bile duct ligation and hepatotoxic CCl_4 models of liver injury in IL-17RA$^{-/-}$ mice, Meng et al demonstrated that lack of IL-17 signaling conferred resistance to liver fibrosis as measured by decreased collagen deposition and expression of alpha smooth muscle actin (α-SMA), Col-α1, MMP-3, TIMP1, TGF-β and TNFα [20]. In addition, using bone marrow chimeric mice devoid of IL-17 signaling in immune cells including KC, the authors demonstrated that IL-17 signaling to KCs and HSCs, but not to hepatocytes nor to LSECs, was critical for promoting fibrosis [20].

Even though the current data suggest that IL-17 is pro-fibrogenic in the liver, the mechanisms underlying this effect are still controversial. Two studies have reported that IL-17 directly activates HSCs in a STAT-3 dependent manner [20,127]. Conversely, in two other studies the fibrogenic activity of IL-17 was attributed to indirect effects. Our group has demonstrated that IL-17 sensitizes HSCs to the action of TGF-β by increasing cell surface expression of TGF-β-RII and TGF-β signaling *via* SMAD2/3 in a JNK-dependent manner [21]. In addition, Lemmers et al. have demonstrated that IL-17-activated HSCs produced neutrophil chemoattractants potentially leading to tissue damage and the resultant fibrosis [19]. More studies are needed in order to clarify the mechanism by which IL-17 activates HSCs.

5.2. IL-22 in chronic liver injury

As previously stated, data from a variety of acute liver injury models demonstrate that IL-22 is hepatoprotective. IL-22 acts mainly by promoting survival of hepatocytes through the induction of anti-apoptotic and pro-proliferative pathways in a STAT-3-dependent manner [48,102]. This effect is limited in time and is tightly controlled through action of IL-22BP [106]. However, dysregulation of IL-22 in chronic disease has been associated with the pathogenesis of several autoimmune diseases mainly due to the pro-inflammatory potential of IL-22, and its ability to induce proliferation of myofibroblasts [47]. The balance between IL-17 and IL-22 can also contribute to pathogenesis, as recently demonstrated in a mouse model of NASH whereby IL-22 protected mice from NASH development but only in absence of IL-17 [132]. Opposite effects of IL-22 have been reported in the lung and the liver depending on the duration of injury and aetiology [119,133,134]. IL-22 signaling was also associated with increased fibrosis in pancreatitis [135]. Thus, the protective versus pathogenic function of IL-22 is context dependent.

The role of IL-22 during chronic liver disease remains unclear. IL-22 is upregulated in the livers of patients with chronic HBV and HCV suggesting that it may play a role in liver disease progression [79,107,133,136]. The IL-22 pathway was the second top up-regulated pathway in microarray analysis of liver tissue from chronic HBV patients versus normal controls. Furthermore, total IL-22 density in the liver positively correlated with liver damage and fibrosis degree [133]. Similarly, increased infiltration of IL-22-producing cells was observed in the livers of HBV cirrhotic patients and positively correlated with the inflammatory score [79]. By contrast, another study with a better stratified cohort composed of patients with acute HBV, chronic HBV, and asymptomatic HBV carriers, reported increased IL-22 in the serum of acutely infected patients compared to healthy controls but not in chronic or asymptomatic carriers [107]. These contradictory results observed in chronic HBV may reflect that IL-22 is locally produced in the liver to avoid systemic effects. It could also be a consequence of the intrinsic heterogeneity of the disease and the patient cohorts studied, and the context dependent role of IL-22.

The role of IL-22 in chronic HBV has also been investigated *in vivo* using liver-specific HBV transgenic mice and T cell mediated hepatitis. In this model, blockade of IL-22 reduced tissue damage, inflammation, and fibrosis in a Th17-dependent manner, assigning a pro-inflammatory and profibrogenic role to IL-22 [133]. These results contradict observations made in IL-22 transgenic mice [119] or mice treated with IL-

22 [20], where IL-22 reduced fibrosis in response to CCl_4 treatment.

In chronic HCV, Kang et al observed enrichment of IL-22+ and IL-22+IFNγ+ CD4 T cells in the liver but their correlation with fibrosis stage was not established [136]. A study by Sertorio et al. in a large cohort established that IL-22 plays a protective role. This study identified polymorphic variants of the IL-22BP gene that are associated with higher transcript levels of this modulator of IL-22 activity. Chronic HCV patients expressing these genetic variants had a more severe fibrosis indicating that IL-22 was protective probably by mediating tissue repair in response to HCV associated tissue damage [137]. In contrast, another study found a positive correlation between frequency of IL-22 producing cells in the liver and the fibrosis score. *In vitro* work showed that IL-22 treatment of HSCs induced markers of activation, proliferation, survival, and upregulated expression of fibrillar collagens [118].

In summary, it is too early to conclude on the role of IL-22 on fibrosis progression in chronic liver disease, since increased IL-22 in advanced fibrosis could be explained both as playing an active pathogenic role, or simply as an attempt to repair the exacerbated damage that goes along with fibrosis progression. Even though there are important differences between the models studied so far, the opposite effects of IL-22 observed are perplexing and may highlight the context dependent activity of IL-22. More research is needed to identify the determinants that tilt the balance from IL-22 mediated protection to pathogenesis. Better animal models will be very helpful in this endeavor.

6. Type 3 immunity in HCC

HCC is the second leading cause of cancer-related death worldwide [138]. More than 80% of HCC cases occur in individuals with advanced fibrosis or cirrhosis due to chronic viral hepatitis, NASH, and ASH [139]. The IL-17 and IL-22 pathways have been linked to HCC development and progression [13,18,140].

6.1. IL-17 in HCC

IL-17-producing cells are enriched in many solid tumors including HCC [13,141]. IL-17-induced inflammation, angiogenesis, and tissue remodeling, while necessary and beneficial during acute injury for clearing the pathogen and restoring the normal tissue architecture, may create a tumor promoting inflammatory environment [131]. Persistent or dysregulated IL-17 signaling can enhance recruitment of inflammatory neutrophils [142], tumor vascularization [18], and invasiveness [95]. Furthermore, the profibrogenic effect of IL-17 and its association with fibrosis progression may have a crucial impact on HCC development.

All studies so far have associated poor prognosis with high intratumoral levels of IL-17 regardless of the underlying liver disease [18,131,143–145]. Mechanistically, the major impact of IL-17 on tumor progression is through enhancement of tumor angiogenesis [18,146–149]. Accordingly, in a cohort of HBV-associated HCC patients, total IL-17+ cells and Th17 cells were found to be enriched in the tumor and correlated with microvessel density (MVD) and poor survival [18]. In another study involving 87 HBV-associated HCC patients, immunohistochemistry analysis revealed increased density of intratumoral IL-17+ cells and positive correlation with p-STAT-3 intensity, neutrophil frequency, and MVD [143]. Subsequent *in vitro* work showed that IL-17 promotes migration and invasion of hepatoma cells with no impact on the proliferation rate. Moreover, gene expression analysis revealed that IL-17 induces pro-angiogenic factors such as MMP-2 and VEGF, and proinflammatory CXCL8 and IL-6 [143]. All these effects were inhibited by silencing STAT-3 in hepatoma cells [143]. Furthermore, overexpression of IL-17, promoted tumor growth, and expression of MMP-2 and IL-6 in a heterotopic xenograft model [143]. Additional support for the role of IL-17 in new vessel formation in HCC was provided by Tu et al. showing colocalization of IL-17+ cells and CD34+ endothelial cells but no stereological analysis of the distance between IL-17+ cells and endothelial cells was performed [150]. Moreover, in this study mast cells were identified as the main cellular source of IL-17 in HBV-associated HCC [150]. Altogether, these results strongly support the idea that IL-17 promotes HCC *via* enhancing tumor angiogenesis in a STAT-3-dependent manner. At present, we do not know whether or not IL-17-associated tumor angiogenesis plays a major role in other HCC aetiologies such as chronic HCV, ASH or NASH.

IL-17 has been linked to HCC invasiveness and metastasis by promoting pathological tissue remodeling. Specifically, MMPs, induced by IL-17, break down matrix barriers that limit tumor spreading [95]. Indeed, increased density of IL-17+ cells was reported in metastatic HBV-associated HCC versus non-metastatic HCC [95]. Gene expression analysis in 50 paired tumor/non-tumor specimens showed a positive correlation between IL-17 and expression of MMP-2 and MMP-9. In addition, *in vitro* stimulation of hepatoma cell lines with IL-17 resulted in increased expression of MMP-2 and MMP-9 and increased cell migration and invasion [95]

Given its profibrogenic role, IL-17 may be involved in fibrosis-dependent hepatocarcinogenesis since advanced fibrosis is the main risk factor for the development of HCC. Despite the paucity of data about the role of IL-17 in fibrosis and HCC independently, the role of IL-17 in progression from fibrosis to HCC remains elusive. This is likely due to the limited ability to follow cohorts longitudinally through advanced fibrosis and incidence of HCC. Collaborative efforts to establish such cohorts are required. Studies in mouse models that compare incidence and invasiveness of HCC in IL-17 deficient mice are needed.

In summary, IL-17 promotes HBV-associated HCC through fostering angiogenesis and pathological tissue remodeling. Th-17 cells, neutrophils, and mast cells were identified as cellular sources of IL-17 and linked to advanced tumor pathology, but the exact mechanisms by which they induce such pathological features and the time of their recruitment into the tumor microenvironment (TME) are unknown. Further investigation is required to define the IL-17-modulated pathways that are involved in HCC progression in the context of other underlying liver diseases like chronic HCV, NASH and ASH.

6.2. IL-22 in HCC

As discussed above, IL-22 protects epithelial barriers through transient activation of inflammation in response to invading microbes or toxins, and by mediating tissue repair once the pathogens/toxins are cleared. However, in the context of cancer, these pathways are chronically activated, potentially encouraging a tumor promoting inflammatory environment, and the survival and proliferation of cancer cells. Indeed, IL-22 promotes liver cancer development in patients with underlying cirrhosis, which suggests that its protective function is detrimental on the long-term with persistent injury [140,151]. IL-22 is upregulated in the liver and serum of HCC patients and has been associated with tumor progression [140,144,151,152]. A subset of IL-22 producing CD4 T cells co-expressing IFNγ and/or IL-17 were enriched in HCC tumors [140]. IFNγ+/IL-22+ T helper cells were enriched in peritumoral liver tissue, and IL-17+/IL-22+ T helper cells were enriched in HCC tissue and correlated with poor prognosis [140]. The activity of IL-22 is regulated by IL-22BP and the IL-22/IL-22BP may influence the tumorigenic potential of IL-22 within the inflamed tissue. Indeed, incidence of colon cancer is increased in IL-22BP deficient mice [49], in turn the TME promotes further polarization of IL-22+ cells [140]. However, it is unknown how the IL-22/IL-22BP ratio is regulated during the transition from fibrosis to HCC.

In the liver, IL-22 can act on several cell types as the IL-22R is expressed on hepatocytes, cholangiocytes, and HSCs. The individual contribution of each cell subset to the pathological effects of IL-22 is unknown and merits further investigation. IL-22-driven survival and proliferation of hepatocytes is crucial for repopulating the damaged tissue upon injury. However, since IL-22 also induces these pathways in

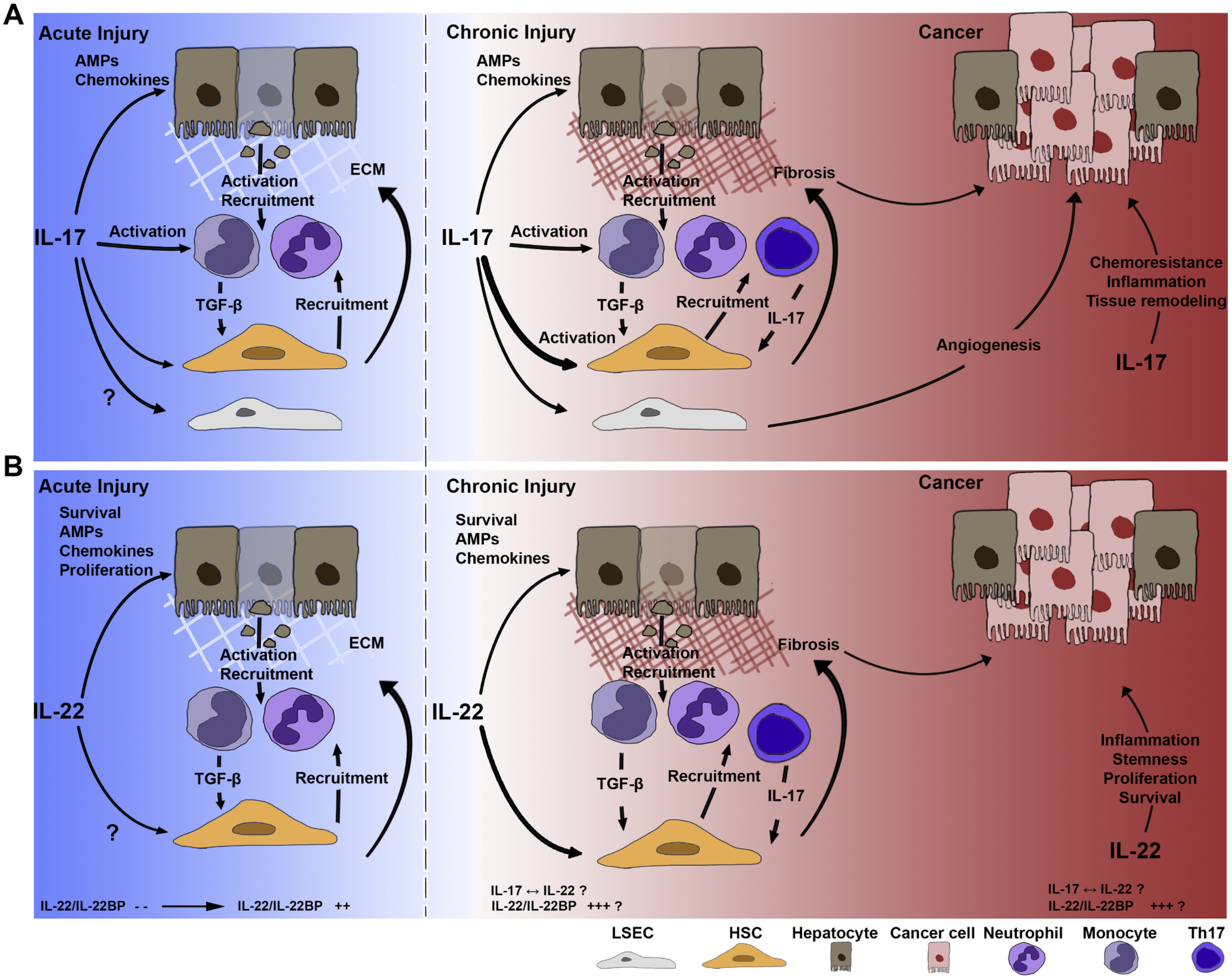

Fig. 2. Type 3 cytokines in Acute vs. Chronic Liver Injury. (A) IL-17 is involved at various levels of the healing response to acute injury. It induces antimicrobial programs in hepatocytes, and simultaneously supports pathogen/toxin removal via the recruitment of inflammatory neutrophils and monocytes to the site of injury. IL-17 enhances activation of HSCs which generate a provisional matrix that supports the repair phase of wound healing. It is plausible that IL-17 acts on endothelial cells to promote angiogenesis. The tissue destructive effects of IL-17 during acute injury are self-limited. In contrast, in chronic injury, dysregulated IL-17 leads to persistent activation of inflammatory cells and long-term tissue damage, ECM deposition and consequently fibrosis. At the extreme of the chronic injury spectrum occupied by cancer, IL-17 promotes tumor progression and aggressiveness by perpetuating inflammation, increasing fibrosis, and inducing angiogenesis and pathological tissue remodeling. (B) During acute injury, IL-22 cooperates with IL-17 by activating antimicrobial programs in the hepatic tissue. Additionally, IL-22 mediates tissue protection by inducing pro-survival, anti-apoptotic, and pro-proliferative pathways in hepatocytes. The role of IL-22 signaling on HSCs in response to acute injury is still unknown, although it may be involved in the proliferation of HSC. Conversely, during chronic injury it is likely that IL-22 mediated protection in the hepatocyte compartment is counterbalanced by the pro-inflammatory potential of IL-22 through recruitment of Th17 cells leading to fibrosis progression. During carcinogenesis, IL-22 enhances survival and proliferation of tumor cells, induces tumor stemness and promotes inflammation within the tumor microenvironment. The activity of IL-22 during acute injury is balanced by IL-22BP to allow repair and to limit the inflammatory effects of IL-22. Dysregulated IL-22/IL-22BP ratio in chronic liver injury may lead to an increase in IL-22 signaling that favors fibrosis and carcinogenesis. The pathogenic effects of IL-22 can be enhanced by IL-17. Not depicted in this model is IL-10 that can be secreted by different cell subsets and can dampen inflammation as well as inhibit IL-17 producing cells.

malignant hepatocytes, IL-22 may promote tumor survival and growth of cancer cells in HCC. Jiang et al. reported that IL-22 expression is upregulated in HCC and correlates with the histological tumor grade [151]. Moreover, recipient mice that were transplanted with patient HCC cells exhibited enhanced tumor growth, and increased expression of anti-apoptotic, and proliferation markers when co-transplanted with IL-22-producing cells [151]. Similarly, *in vitro* stimulation of a hepatoma cell line with IL-22 induced STAT-3-dependent pro-survival, pro-angiogenic, and pro-proliferative pathways [140]. Finally, liver-specific IL-22 transgenic mice do not develop spontaneous tumors but exhibit accelerated tumorigenesis in response to carcinogens as compared to their wild type counterparts. The enhanced tumorigenesis in this model was associated with STAT-3 phosphorylation and expression of cyclin D1, Ki67, and Bcl-xL [79]. Altogether, IL-22-induced tissue repair pathways accelerate tumor development by inhibiting apoptosis and inducing proliferation of cancer cells.

The effect of IL-22 signaling on HSCs during the development of HCC is unknown. Examining the role of IL-22 in HSC activation during fibrosis has generated conflicting results as discussed above [118,119]. Given that IL-22 may have both pro-fibrogenic and anti-fibrogenic activities depending on the context, it may favor tumorigenesis *via* enhancing fibrosis. Indeed, in other organs like the skin [153], lung [134], and pancreas [135], IL-22 has dramatic effects on the proliferation and motility of myofibroblasts during healing and may have a similar effect on HSCs in the liver. It is also noteworthy that some of these effects were dependent on the presence of other signals like IL-17 or could be regulated by IL-22BP or IL-10 from various sources [34]. Further analysis characterizing in detail the inflammatory immune landscape during fibrosis and transition from fibrosis to HCC is required to elucidate these mechanisms.

7. Conclusions

IL-17 and IL-22 have important physiological roles during acute liver injury but can contribute to pathogenesis of chronic liver injury and may predispose or enhance development of HCC. Based on the current state of knowledge, we can propose a model (Fig. 2) whereby during acute injury, IL-17, produced by various cell subsets targets several cellular compartments of the liver and is involved at various levels of the healing response. It induces antimicrobial programs in hepatocytes, and simultaneously supports pathogen/toxin removal by the recruitment of inflammatory neutrophils and monocytes to the site of injury. IL-17 enhances activation of HSCs which generate a provisional matrix that supports the repair phase of wound healing. In addition, observations in other organs support the premise that IL-17 promotes new vessel formation by acting on endothelial cells but its effect on LSECs within the liver is unknown. The tissue destructive effects of IL-17 during acute injury are self-limited. In contrast, in chronic injury, dysregulated IL-17 leads to persistent activation and recruitment of inflammatory cells and long-term tissue damage. This persistent inflammation enhances ECM deposition and consequently fibrosis. IL-17 may also enhance fibrosis by synergizing with other profibrogenic signals activating HSCs. This inflammatory loop may create an environment favorable to oncogenic transformation. Once cancer is initiated, IL-17 promotes tumor progression and aggressiveness by perpetuating inflammation, increasing fibrosis, and inducing angiogenesis and pathological tissue remodeling (Fig. 2A).

During acute injury, IL-22 cooperates with IL-17 by activating antimicrobial programs in the liver. Furthermore, IL-22 mediates tissue protection by inducing pro-survival, anti-apoptotic, and pro-proliferative pathways in hepatocytes. The role of IL-22 signaling on HSCs in response to acute injury is still unknown, but it may induce HSC proliferation, which would be beneficial. The action of IL-22 during acute injury is short and well-regulated *via* IL-22BP, whereby the IL-22/IL-22BP ratio is high during tissue repair and decreases during tissue remodeling and resolution of the injury. During chronic injury, it is likely that IL-22-mediated protection of hepatocytes is counterbalanced by the pro-inflammatory properties of IL-22, and its potential profibrogenic actions. The role of IL22/IL-22BP ratio in that phase is not well understood. According to the current data, we propose that IL-22BP mediated neutralization of IL-22 is insufficient to prevent IL-22 signaling in the context of chronic liver disease. Other inflammatory cytokines and specifically IL-17 may favor the pathogenic effects of IL-22. At the cancer stage, increased IL-22 may accelerate tumor progression as a consequence of enhanced survival, stemness, and proliferation of tumor cells, and tumor promoting inflammation. Both IL-22 and IL-22BP are increased but the IL22/IL-22BP ratio likely remains in favor of IL-22 resulting in a situation that promotes tumorigenesis (Fig. 2B).

8. Future directions

Numerous gaps remain in our knowledge of the role of type 3 cytokines in the liver that warrant additional research. First, the role of non-Th17 cells that produce massive amounts of these cytokines (ex. γδ T cells, MAIT cells, ILCs and neutrophils), their recruitment and their localization during different phases of wound healing within the liver remain elusive. Second, mapping of the inflammatory immune landscape during various stages of liver disease is required to elucidate the overall interaction(s) and cross-regulation between the different immune cell subsets. Third, most studies have examined only one stage of liver disease, mostly in cross-sectional studies. Longitudinal patient cohorts and longitudinal studies in different mouse models are required to decipher the inflammatory immune factors that govern the progression from advanced liver disease to HCC. Given the success of manipulating the IL-17/IL-22 pathways for the treatment of various inflammatory conditions [11,128,154], better understanding of their role in liver disease may accelerate their use as novel therapeutics to limit liver fibrosis and prevent liver cancer.

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