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Review

IL-18/IL-18BP and IL-22/IL-22BP: Two interrelated couples with therapeutic potential

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ABSTRACT

Interleukin (IL)-18 and IL-22 are key components of cytokine networks that play a decisive role in (pathological) inflammation, host defense, and tissue regeneration. Tight regulation of cytokine-driven signaling, inflammation, and immunoactivation is supposed to enable nullification of a given deleterious trigger without mediating overwhelming collateral tissue damage or even activating a cancerous face of regeneration. In fact, feedback regulation by specific cytokine opponents is regarded as a major means by which the immune system is kept in balance. Herein, we shine a light on the interplay between IL-18 and IL-22 and their opponents IL-18 binding protein (IL-18BP) and IL-22BP in order to provide integrated information on their biology, pathophysiological significance, and prospect as targets and/or instruments of therapeutic intervention.

1. Introduction

Inflammation, an ancient effector program of innate immunity, is initiated by infection and/or tissue damage and aims to inactivate/remove or leastwise seal off infectious agents, foreign bodies, or necrotic cell debris [1]. Simultaneously, acute inflammatory processes may set the stage for activation of adaptive immunity by providing a precious time window along with a defining microenvironment. For the latter task production of key Th1- (e.g. interleukin (IL)-12, IL-18, interferon (IFN)-γ), Th2- (e.g. IL-4, thymic stroma lymphopoietin), or Th17- (e.g. IL-1β, IL-6, IL-23) inducing cytokines is of decisive importance [2,3].

Exuberant collateral tissue damage, transition to chronic inflammation or autoimmunity, fibrosis, and eventually loss of organ function are serious consequences of unleashed inflammation of diverse causes. In order to generally avoid those unwanted outcomes, a successful inflammatory program inherently sets in motion specific means to curb the pathological arm of inflammation. Recent progress in this research area demonstrates that inflammation resolution is not merely a passive process achieved by simple removal of initiating triggers. In fact, successful reparative resolution actively involves (gene expression) programs mediating anti-inflammation, repair, regeneration, and in some cases induction of immune tolerance. Key determinants in this context include neutrophil infiltration and survival, macrophage differentiation towards an M2-pro-reparative phenotype, promotion of regulatory T cells, and activation of growth factor- and signal transducer and activator of transcription (STAT)-3-driven tissue regeneration. This latter process appears particularly relevant for reparative inflammation in liver and intestine [4–8].

Modulation of cytokine networks [9] must be regarded as a critical mechanism driving successful resolution of inflammation. However, the counterintuitive fact that inflammatory signaling likewise is an inherent prerequisite for activation of pro-resolution pathways implements a significant degree of complexity. For example, pro-inflammatory tumor necrosis factor (TNF)-α can be viewed as a pathological but also as a

Abbreviations: APAP, acetaminophen; ALI, acute liver injury; AOSD, adult-onset Still's disease; bcl, B-cell lymphoma; JNK, c-jun N-terminal kinase; ConA, concanavalin A; CsA, cyclosporin A; DC, dendritic cells; DSS, dextran sulfate sodium; ERK, extracellular signal-regulated kinases; FasL, Fas ligand; GAS, γ-activated site; HPS, hemophagocytic syndrome; HCC, hepatocellular carcinoma; IBD, inflammatory bowel diseases; IFN, interferon; IRF1, interferon regulatory factor-1; IL, interleukin; IL-10R, IL-10 receptor; IL-18BP, IL-18 binding protein; IL-18R, IL-18 receptor; IL-22BP, IL-22 binding protein; IL-22ra2, IL-22 Receptor Subunit α2; IRI, ischemia-reperfusion injury; IRAK, IL-1 receptor associated kinase; IVA, influenza A virus; iNOS, inducible nitric oxide synthase; ILC, innate lymphoid cells; LPS, lipopolysaccharide; MMP, matrix metalloproteinase; MAP, mitogen-activated protein; MDDC, monocyte-derived dendritic cells; MyD88, myeloid differentiation primary response-88; NK cells, natural killer cells; NF-AT, nuclear factor of activated T cells; NF-κB, Nuclear factor-κB; NLRP, nucleotide-binding domain leucin-rich repeat (NLR) pyrin domain containing; PAMP, pathogen-associated molecular pattern; PBMC, peripheral blood mononuclear cells; PP, Peyer's patches; PKB, protein kinase B; RANK-L, receptor activator of NF-κB ligand; SAA, serum amyloid A; STAT, signal transducer and activator of transcription; TCR, T cell receptor; Th, T helper cells; TLR, toll-like receptor; TNBS, trinitrobenzene sulphonic acid; TTP, tristetraprolin; TNF, tumor necrosis factor

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pro-resolution factor which is well documented for acute liver injury (ALI) [10–14]. Notably, pro-resolving hepatic functions of TNFα likely involve downstream induction of STAT3-activating cytokines [8,10].

Feedback regulation of inflammatory cytokine pathways is established on diverse levels. Crucial mechanisms are, among others, a lipid mediator switch towards resolvins and lipoxins, generation of cortisol, adenosine and N. vagus-derived acetylcholine, as well as production of anti-inflammatory cytokines such as transforming growth factor-β, IL-10 [5–7], or IL-37 [15]. Besides that, regulation by specific cytokine opponents is of particular interest. Those include receptor antagonists such as IL-1 receptor antagonist targeting IL-1 receptor type I as well as IL-36 receptor antagonist [16] and IL-38 [17], the latter two addressing the inflammatory IL-36 receptor chain IL-1 receptor-related protein 2 (IL-1Rrp2). Neutralization of cytokine activity is likewise achieved by soluble receptors proteolytically shed from cell membranes. Well-known examples are soluble TNF receptors (whose function is actually dependent on the microenvironment) [18,19] and soluble IL-1 receptors, in particular inhibitory IL-1 receptor type II [16].

Further remarkable parameters are two immunoregulatory binding proteins, specifically IL-18 binding protein (IL-18BP) [20,21] and IL-22BP [22]. These secreted proteins bind to and nullify their target cytokines (IL-18 and IL-22) with high affinity, do not originate from membrane-derived receptors but are encoded by separate genes loci. Both, IL-18 and IL-22, are regarded as key determinants of (innate and adaptive) host defense, inflammation, tissue repair and regeneration, as well as cancer. Herein, current knowledge on the IL-18/IL-18BP and IL-22/IL-22BP systems and their potential therapeutic application is reviewed.

2. IL-18

IL-18 [23] (previously known as IL-1F4 or IFNγ-inducing factor) is an IL-1 related cytokine [16,24] with some outstanding properties discriminating this protein from other paradigmatic IL-1 family members. First of all, IL-18 is, even in health, a constitutively expressed protein not only detectable in human peripheral blood mononuclear cells (PBMC) [25], monocytes [26], and macrophages [27] but also in epithelial cells, among others renal intercalated cells [28], keratinocytes [29] and intestinal epithelial cells [30]. High constitutive IL-18 protein, particularly in monocytes/macrophages, separates IL-18 from other major inflammatory cytokines like IL-1β or TNFα and suggests that its rapid release is located proximal in the inflammatory cytokine cascade. Accordingly, leukocytic IL-18 biological activity is supposed to be regulated foremost post-translationally but characteristically not on the level of mRNA expression.

Posttranslational regulation of IL-18 is similar to that of IL-1β. Both cytokines are produced as inactive pro-forms that demand processing to become biologically active [16,31,32]. Here, caspase-1, a cysteine-aspartic acid protease activated in the context of specialized intracellular protein platforms called inflammasomes, is crucial. Inflammasomes capable of processing proIL-18 include: nucleotide-binding domain leucin-rich repeat (NLR) pyrin domain containing-1 (NLRP1) – activated e.g. by lethal factor of *B. anthracis*; NLRP3 – activated e.g. by ATP/$P2X_7$, crystals, pore-forming bacterial toxins, and parasites-derived hemozoin; NLR family card domain containing-4 (NLRC4) – activated e.g. by intracellular flagellin; absent in melanoma-2 (AIM2) – activated e.g. by dsDNA; and pyrin - activated e.g. by Rho-modifying toxins. Among inflammasomes, NLRP3 is best characterized. For example, paradigmatic activation of $P2X_7$ by extracellular ATP is coupled to K^+-efflux and rising cytosolic and mitochondrial Ca^{2+} levels that subsequently generate reactive oxygen species (ROS) and oxidized (ox)-mitochondrial (mt)-DNA [33,34]. Ox-mtDNA in turn directly activates NLRP3 [35]. NLRP3 simultaneously cleaves pore-forming gasdermin-D which allows for cell-death associated and possibly also cell-death independent release of IL-1β and IL-18 [34,36,37]. Interestingly, NLRP3-dependent release of mature IL-18 from monocytes/macrophages is enhanced under short-term influence of pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharide (LPS) (supposedly via toll-like receptor (TLR)-4) or flagellin (supposedly via TLR5) or Pam3CSK4 (synthetic PAMP-like molecule; supposedly via TLR1/2). Priming by these TLR agonists does not involve IL-18 gene induction (or a translational mechanism in general) but is supposed to act via myeloid differentiation primary response-88 (MyD88)/IL-1 receptor associated kinase (IRAK)-1/4 and c-jun N-terminal kinase (JNK) which generate ROS (via MyD88/IRAK-1/4) or phosphorylate NLRP3 at Ser198 (via JNK) to establish full inflammasome activity [34]. Notably, low concentrations of flagellin amplify release of mature monocytic IL-18 [38] likely via TLR5/JNK [39]. Flagellin can, moreover, mediate processing of proIL-18 by direct activation of NLRC4 – after being transferred into the host cytosol in the context of bacterial infection and activation of the type III secretion system [40]. Of note, 'sterile' exposure of macrophages to high flagellin concentrations can likewise result in cytosolic levels able to activate NLRC4 with subsequent processing of IL-18 [41]. Besides caspase-1-containing inflammasomes, proIL-18 can be activated by some extracellular proteases, among others proteinase-3 [42] and mast cell chymase [43]. However, the pathophysiological significance of these observations still needs to be fully established.

After binding of mature IL-18 to IL-18Rα and recruitment of IL-18Rβ, inflammatory TLR/IL-1R-like signaling is initiated – here acting particularly through the MyD88-IRAK1/4-NF-κB axis and p38 mitogen-activated protein (MAP) kinase (Fig. 1, left panel) [31,44]. Compared to receptors for IL-1, expression of functional heterodimeric IL-18 receptors is more restricted to specific cell types. With few exceptions, IL-18 signaling primarily connects to lymphoid cells, among others conventional T cells [23], γδT cells [45], natural killer (NK) cells [46,47], NKT cells [48], and innate lymphoid cells (ILC) [49,50]. Of note, by upregulating IL-18Rα, IL-12 stands out as key determinant of cellular IL-18 responsiveness [51,52].

Among the functions of IL-18, support of Th1-like inflammation and IFNγ production is outstanding [31,32]. Interestingly, IL-18 not only is

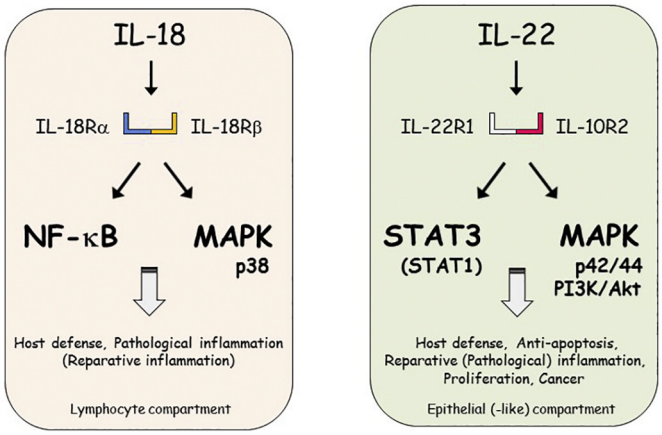

Fig. 1. Schematic overview of cellular IL-18/IL-22 signaling. After ligating their specific heterodimeric receptors, IL-18 and IL-22 initiate signaling that is dominated by activation of NF-κB/p38 and STAT3/ERK1,2/PKB, respectively. Cell type specific receptor expression determines cellular targets with IL-18 addressing primarily lymphocytes and IL-22 primarily epithelial (-like) cells. With regard to function, IL-18 biological activity is mostly connected to Th1/IFNγ-driven host defense and related pathological inflammation. Under defined conditions (particularly in the intestine) IL-18 may also mediate reparative responses by its anti-microbial action and/or by activating the IL-22/IL-6/STAT3-axis as part of its pro-inflammatory nature. IL-22 mediates tissue protection at biological borders (foremost) via STAT3 activation in epithelial cells. However, IL-22 is clearly pathogenic in diseases in which STAT3-driven cell proliferation/survival is key to pathogenesis examples are psoriasis (with proliferation of keratinocytes), rheumatoid arthritis (with proliferation of synoviocytes), and carcinogenesis (due to the oncogenic potential of STAT3).

crucial for IFNγ derived from $CD4^+$ or $CD8^+$ T cells [23,31,53] but is likewise seminal for IFNγ production during innate immunoactivation. Specifically, IL-18 supports IFNγ expression by NK [46,47,54], γδT [45], and NKT cells [48], as well as ILC [49,55]. Particularly the combination IL-12/IL-18 can moreover activate 'innate' functions of memory T cells which enable T cell receptor-independent but cytokine-driven IFNγ production [56]. Given that initial innate IFNγ shapes T cell differentiation [57] bridging between innate and adaptive immunity is regarded a pivotal attribute of IL-18. Murine models support a key role of IL-18 in Th1-like inflammation and disease and suggest this cytokine as promising target for anti-inflammatory immunopharmacological intervention [58]. At this point it is noteworthy that IL-18 can mediate specific pro-inflammatory responses independent on IFNγ, which, for example, concerns IL-18-induced TNFα and induction of succeeding downstream genes such as IL-1β or matrix metalloproteinase (MMP)-9 in human PBMC [59,60]. Besides enhancing Th1, IL-18 displays the capability to amplify Th17 responses [61]. It is therefore not surprising that increased IL-18 biological activity associates with uncontrolled inflammation as seen in patients with e.g. hepatitis, Crohn's disease, rheumatoid arthritis, Still's disease, psoriasis, or hemophagocytic syndrome (HPS) [31,32,58,62]. Corresponding clinical studies targeting IL-18 are ongoing and initial results already emphasize the anti-inflammatory/therapeutic potential of IL-18 blockage for the treatment of adult-onset Still's disease (AOSD) [63] and autoinflammatory HPS (or macrophages activation syndrome) [64]. A further facet of IL-18 is activation of the Fas ligand (FasL)/Fas-axis via FasL upregulation – particularly on NK and T cells [32,65]. This pathway (along with induction of IFNγ) not only contributes to IL-18-associated (anti-cancer) cytotoxicity [66]. Enhanced Fas signaling in macrophages moreover enables a caspase-1-independent – caspase-8-dependent – mode of IL-18 processing [67,68] thus implementing a classical positive feedback loop.

It is another interesting facet that, despite being key to efficient Th1 immunity, IL-18 can promote allergic inflammation when active in absence of IL-12. Under those conditions IL-18 is able to enhance pro-allergic function e.g. by action on mast cells and basophils which translates to enhanced production of key factors driving atopic inflammation such as IL-4 and IL-13 [32,69].

3. IL-22

IL-22 [70,71] (previously IL-10-related T cell-derived inducible factor) is a member of the IL-10 cytokine family which is based on structural, biochemical, and functional characteristics [72,73]. Expression of IL-22 specifically connects to lymphocytes. Adaptive (TCR-dependent) production of human IL-22 is achieved by Th1, Th17, and Th22 cells [74,75]. Besides that, aforementioned 'innate' activation of memory $CD4^+$ and $CD8^+$ T cells [56] can drive IL-22. In that context, a key role of IL-1 for induction of human IL-22 in $CD4^+$ T cells has been uncovered using cultured PBMC [76]. Specifically, we [76] and others [77] could demonstrate that IL-1 is pivotal for IL-22 production by PBMC exposed to live *Borrelia burgdorferi* or necroinflammatory-stimuli derived from lysed cancer cells. A similar IL-1 dependency of IL-22 production was recently observed for activated murine $CD4^+$ memory T cells cultured under the influence of splenic dendritic cells (DC) [78]. Among innate-like lymphocytes, γδT [79], NK cells [80], and NKT cells [81] are established sources of IL-22. However, of particular interest are type 3 ILC which generate high amounts of IL-22 during pathological conditions [82] such as infection-driven colitis [83] and pneumonia [84]. Interestingly, intestinal ILC3 as well as dermal and pulmonary γδT cells are significant sources of 'physiological' IL-22 in health. Being activated by environmental cues, such as commensal microbes and their products or nutritional compounds, those cell types generate IL-22 in the steady state thereby enforcing homeostasis, wound healing, and immunological alertness at biological barriers [82,85,86].

Lymphocyte-derived IL-22 is established and maintained by TCR and/or cytokine signaling chiefly involving IL-1 and IL-23 [74,82,86]. Current knowledge on molecular regulation of the *IL22* promoter still is vague. On a transcriptional level STAT3, aryl hydrocarbon receptor (AhR), retinoid orphan receptor (ROR)-γt, and B-cell-activating transcription factor (BATF)/junB transcription factors enforce whereas c-musculoaponeurotic fibrosarcoma (c-Maf) restrains IL-22 expression [87]. Our laboratory performed promoter analysis in phorbolester/calcium ionophore-stimulated human Jurkat T cells and identified by chromatin immunoprecipitation (ChIP) and luciferase reporter assays functional binding of nuclear factor of activated T cells (NF-AT)-c2 to the *IL22* promoter. This observation should be clinically relevant since NF-AT inhibition not only suppresses IL-22 production by Jurkat T cells and PBMC (use of cyclosporin A (CsA)) [88–90] but likewise curbs IL-22 in mice enduring experimental psoriasis upon tacrolimus [91] or CsA administration [92]. Moreover, IL-22 is suppressed in patients treated with CsA [93,94]. We also identified functional docking of cAMP response element-binding protein (CREB) to the *IL22* promoter of activated Jurkat T cells [88] which concurs with induction of IL-22 by the prostaglandin E_2/$EP_{2,4}$/cAMP-axis in primary murine $CD4^+$ T cells [95]. Interestingly, IL-21 was shown to direct differentiation of murine $CD4^+$ T cells into cells that produce IL-22, but not IL-17. Activation of the *il22* promoter by IL-21 was dependent on STAT3 and involved epigenetic changes [96]. IL-21 also supports IL-22 production by ILC3 [97]. Accordingly, IL-21 must be regarded as one major determinant of IL-22 biology with the potential to shape course of disease – as shown for dextran sulfate sodium (DSS)-induced colitis [96,97].

Besides transcriptional regulation, IL-22 mRNA is post-transcriptionally destabilized by direct action of tristetraprolin (TTP) on its 3′-untranslated region. Specifically, TTP-deficient mice display enhanced serum IL-22 which associates with an increased mRNA half-life as detected in activated murine primary T cells [98]. Beyond direct control by innate and/or adaptive immune pathways, IL-22 is subject to regulation by age (inversely) [99] and by environmental stress such as hypoxia [100] or hypothermia [89]. Those latter two observations may relate to stress-induced release of danger-associated molecular patterns, PAMPs, and/or IL-1 [101,102]. Molecular mechanisms driving these responses deserve further elucidation.

After secretion via the Golgi pathway, IL-22 activates a heterodimeric receptor consisting of IL-22R1 and IL-10R2 [71]. Expression profiles of these receptor chains are key to IL-22 biology. Whereas IL-10R2 is ubiquitous, IL-22R1 confines, with few exceptions, to the epithelial (-like) cell compartment, among others renal tubular epithelial cells, keratinocytes, lung alveolar epithelial cells, colon epithelial cells, and hepatocytes [72,103–108]. Thus, IL-22 is regarded a messenger between the body's lymphocyte and epithelial cell compartment [105]. IL-22 receptor binding initiates classical Janus kinase (Jak)-1/Tyk2 signaling characterized by strong STAT3 activation [71,103,109]. Besides that, more moderate/transient activation of STAT1 is detectable in diverse cell types such as human hepatoma [109] and colon carcinoma cells [107,110,111] as well as keratinocytes [112]. Moreover, activation of MAP kinases, typically extracellular signal-regulated kinases 1 and 2 (ERK1,2) [108,111,113], and of protein kinase B (PKB) [111,114,115] is consistently observed (albeit to variable degree) in IL-22-responsive cells (Fig. 1, right panel) and may contribute to this cytokine's characteristics. It is noteworthy that activation of STAT1 by IL-22 is potentiated under the influence of interferons [112,116]. This regulatory path is detectable in cell culture [112,117,118] and *in vivo* [117,118] and may relate to the fact that *STAT1* gene expression is inducible by activated pSTAT1 [112,116,119,120].

Janus-faced properties of IL-22 are determined by the given (patho)-physiological and tissue context. Generally speaking, IL-22 functions are, to a large part, directed by strong activation of STAT3 which results in gene induction mediating proliferation (e.g. via cyclin D1 and/or c-myc) and anti-apoptosis (e.g. via B-cell lymphoma (Bcl)-2 and/or Bcl-X_L) [103,104,108,121]. Those pro-proliferative/-survival activities should be further supported by concurrent stimulation of PKB and

ERK1/2 [122]. Besides regulation of proliferation, IL-22 activates DNA repair mechanisms which has been demonstrated for murine intestinal stem cells [123]. This biochemical profile hints to a key role of endogenous IL-22 in tissue protection, repair, and regeneration which has been documented, among others, for concanavalin A (ConA)-induced ALI [108,124], intestinal (during DSS-colitis) [125,126] and cutaneous [127] wounding, kidney regeneration after acute renal injury [128], as well as for collateral tissue damage during influenza A virus (IVA) infection [129–131]. Consequently, a related therapeutic potential of recombinant IL-22 [103] has been proven early on in rodent models of e.g. inflammatory liver [108], kidney [104], intestine [132], and lung [133] injury. Early studies on murine pneumonia also exposed substantial anti-bacterial properties of endogenously produced and administered recombinant IL-22 [134]. Those latter preclinical data emphasize a crucial role for the STAT3 axis in pulmonary host defense/repair that translates to human disease. Patients with the rare STAT3 hyper-IgE syndrome (HIES) are a remarkable example in this context. HIES is caused by heterozygous dominant-negative STAT3 mutations. Of note, patients frequently develop infectious pneumonia, a manifestation that associates with pneumatoceles and abscess formation and requires rigorous therapy [135].

Strengthening of host defense by IL-22 connects to induction of antimicrobial proteins such as regenerating islet-derived protein (Reg)-3 proteins [136,137], lipocalin [134,138], or β-defensins [105,111,134]. Moreover, IL-22 can amplify expression of anti-microbial inducible nitric oxide synthase (iNOS) as detected in cultured human colon DLD1, Caco2 [110,112] and LS174T cancer cells [139] or murine primary vaginal epithelial cells [140]. Interestingly, IL-22 was sufficient to strongly induce iNOS in human colonic LS174T cells as a single stimulus, likely because IL-22 is capable of activating STAT1 in this cell type with relatively high efficiency [139]. IL-22-dependend iNOS in the inflamed intestinal epithelium has been confirmed *in vivo* in murine colitis-induced cancer [141].

It is noteworthy that infection-driven IL-22 production is impaired in obese mice. Moreover, lack of IL-22 biological activity actually supports development of murine metabolic disorders. *Vice versa*, administration of recombinant IL-22-Fc corrects a disturbed host defense in obese mice and betters metabolic disease in murine type 2 diabetes [142].

Interestingly, IL-22 mostly fails to effectively activate nuclear factor-κB (NF-κB) or activator protein (AP)-1 and thus is not provoking acute inflammatory responses after administration to healthy mice. Moreover, as leukocytes are not targeted by IL-22, the recombinant cytokine (in contrast to IL-10) fails to mediate immunomodulation as detected by cytokine analysis during murine endotoxemia [105,143]. Data concur with phase I clinical trials demonstrating that F-652 (IL-22 dimer fused to IgG_2-Fc) and UTR1147A (IL-22/IgG_4-Fc fusion protein), are biologically active as determined by systemic induction of serum amyloid A (SAA) or Reg-3α but also display an acceptable safety profile when administered to healthy volunteers [144,145].

Though preclinical research suggests a therapeutic potential of recombinant IL-22 for short-term treatment of acute diseases driven by tissue damage and/or infection, IL-22's Janus-faced characteristics are evident [103,146]. In fact, IL-22 can promote chronic inflammation. In that context, experimental psoriasis and arthritis are exemplarily outlined. In psoriasis IL-22 was found to drive a long-term proliferative capacity in keratinocytes [147] and inhibits their terminal differentiation [148,149]. Moreover, IL-22 activates pathogenic genes in keratinocytes, among others CXCL5, MMP-3 [149], Th17-promoting CCL20 [150], and CXCL8 [151]. It is noteworthy that Bcl-3, inducible by IL-22 in various cell types [151,152], fine-tunes activation of keratinocytes by the STAT3 pathway [151]. In fact, *il22*$^{-/-}$ mice display reduced [153] and IL-22-Fc-treated wiltyp mice enhanced imiquimod-induced psoriasis [154]. In agreement with that, IL-22-overexpressing mice develop a psoriasis-like phenotype [148]. Pathogenic IL-22 action was also repeatedly reported for collagen-induced arthritis [155,156]. Here, synoviocytes are established non-epithelial IL-22 targets which, in response to IL-22, proliferate and produce pro-arthritic factors such as CCL2 and receptor activator of NF-κB ligand (RANK-L) [157,158].

While STAT3 is pivotal for tissue repair and regeneration in acute disease [6,8] its unleashed activity is linked to carcinogenesis [159]. Accordingly, overt IL-22 is supposed to promote cancer which has been well-documented e.g. for hepatocellular carcinoma (HCC). Notably, IL-22 is upregulated in liver cirrhosis (particularly in patients with cirrhosis-related complications) and HCC patients and its serum levels predict patients' prognosis [160–163]. Clinical data are supported by murine HCC models which display enhanced tumorigenesis in IL-22 overexpressing mice [164] and reduced carcinogenesis upon IL-22 deficiency [160]. The complex nature of IL-22 in inflammatory carcinogenesis is, however, illustrated in murine models of colitis-induced colon cancer [82]. Initial IL-22-dependent tissue repair and anti-microbial action is, on the whole, anti-inflammatory and protective thus counteracting colitis-induced cancer. Later in pathogenesis, the oncogenic capacity of the IL-22/STAT3-axis prevails thereby supporting cancer growth at this stage [82,165,166]. Interestingly, IL-22-dependent iNOS supports colitis-induced cancer via inducing DNA mutations [141].

4. IL-18/IL-22 interactions

IL-18 and IL-22 serve crucial functions in the delicate cytokine balance that determines host defense and inflammation particularly at biological barriers. Accordingly, interactions between these two cytokines should be highly relevant. Being pivotal for maintaining Th1 responses [31,32] – and to some degree supporting Th17 responses [61] – IL-18 must be regarded as a significant determinant of T cell-derived IL-22. Interestingly, IL-18 likewise amplifies expression of IL-22 by ILC3 [50]. Moreover, IL-18 has the capability to downregulate IL-22BP expression [165]. Current data thus suggest that IL-18 enhances IL-22 biological activity. At this point it is worth mentioning that some members of the IL-1 family have the capability to directly activate STAT3 which includes IL-18 [167] and IL-37 [168]. As STAT3 promotes IL-22 transcription [87], it is tempting to speculate that this ability contributes to IL-18-induced IL-22.

Vice versa, upregulation of IL-18 by IL-22 is also evident. Although proIL-18 is, to a large degree, a constitutively expressed protein, it is also a target of transcriptional regulation, especially in epithelial cells. In fact, IL-22 enhances proIL-18 expression in human keratinocytes [169] and murine intestinal epithelial cells [170].

As already alluded to, IL-18 is a cytokine primarily communicating from the mononuclear phagocyte- and epithelial cell-compartment to lymphocytes. In contrast, IL-22 appears to operate in the opposite direction, predominantly signaling from lymphocytes to epithelial cells (Fig. 2A). Accordingly, a positive feedback loop appears to determine interactions between IL-18 and IL-22 and their respective expression levels (Fig. 2B). To control such (potentially hazardous) regulatory paths is a major task of reparative inflammation and the sphere of cytokine opponents such as binding proteins.

5. Blockage of IL-18 biological activity by IL-18 binding protein

In 1999 two research groups reported on the discovery of murine and human soluble neutralizing IL-18 'receptors' that are different from IL-18Rα or IL-18Rβ and encoded by separate gene loci [20,171]. Later on, the rat [172] and macaque [173] genes were cloned. This glycosylated protein was coined IL-18BP, is secreted via the Golgi pathway, and comes in humans as one of 4 major splice variants (IL-18BPa,b,c,d). The most widely expressed and highly antagonistic human variant is IL-18BPa which binds mature (but not pro-) IL-18 with an affinity substantially higher than IL-18Rα. Accordingly, IL-18BPa is a genuine decoy receptor that blocks IL-18 signaling with outstanding efficiency. The murine splice variants IL-18BPc and IL-18BPd suppress murine IL-

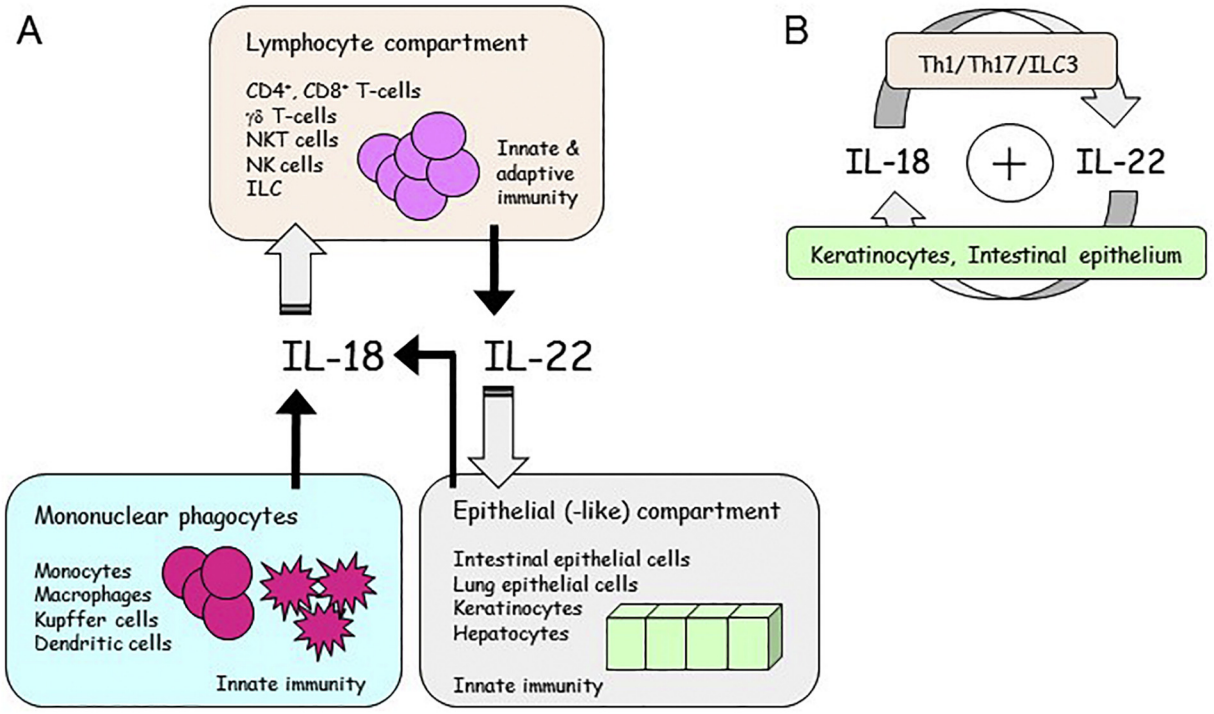

Fig. 2. IL-18 and IL-22: sources and cellular targets. (A) IL-18 is a messenger mainly produced by mononuclear phagocytes/epithelial cells and is acting foremost on lymphocytes. On the contrary, IL-22 generally signals in opposite direction, from the lymphocyte to the epithelial cell compartment. (B) Since both cytokines have been reported to mutually enhance production of each other, a positive (potentially hazardous) feedback loop appears to be in place.

18 activity. The affinity of human IL-18BPc to IL-18 is ten-fold lower compared to IL-18BPa whereas human variants b and d do not exhibit neutralizing capacity [20,174,175]. Unless specified otherwise, herein human IL-18BP refers to IL-18BPa. Of note, increased levels of free (unbound) IL-18 [175] are regarded as clinical indicators of pathologically enhanced IL-18 biological activity which is detectable in marked manifestation e.g. in AOSD [176,177] and HPS [62].

IL-18BP is well-detectable in sera of healthy humans (at approx. 2 ng/ml) and likely serves as 'buffer' for bioactive IL-18. Cellular mechanisms driving 'physiological' IL-18BP demand further investigation. Yet, constitutive expression of the gene is detectable e.g. in human (and murine) spleen, human PBMC, monocytes [20,178,179], and umbilical vein endothelial cells [180]. Of note, IL-18BP is robustly upregulated during inflammatory conditions which might be viewed as part of (or attempt to implement) inflammation resolution. Prominent examples are human sepsis [175] and rodent systemic inflammation in the context of endotoxemia [181] or TLR9-stimulating CpG oligonucleotides [182] as well as clinical [183,184] and experimental inflammatory bowel disease (IBD) [185]. Interestingly, IL-18BP is upregulated in various human malignancies, among others breast [186], pancreas [187], prostate [188], and ovarian [189] cancer. It is tempting to speculate that induction of IL-18BP during carcinogenesis may contribute to immunosuppressive characteristics of the tumor microenvironment [190]. However, functions of IL-18 in cancer are complex and likewise comprise the potential to promote progression e.g. by enhancing metastasis [190,191].

Interestingly, host IL-18BP is augmented by some viral infections which has been documented for Chikungunya [192], Dengue [193], and hepatitis C (HCV) [194,195] virus. This response should partly be mediated by infection-driven type I IFN (see below) and may actually favor viral spread. The latter assumption is supported by the fact that pox viruses [20,196], specifically *Molluscum contagiosum* [196], *Vaccinia*, *Ectromelia*, *Cowpox* [197], and *Yaba* monkey tumor virus [198], acquired during evolution the capability to express active viral forms of IL-18BP. Accordingly, viral IL-18BP has been linked to suppression of cutaneous inflammation in patients after infection with *Molluscum cantagiosum* virus [196]. Notably, by investigating a viral vIL-18BP-deletion mutant in mice, augmented *Vaccinia* virus virulence attributable to vIL-18BP biological activity has been verified experimentally [199].

Cellular signaling and molecular mechanisms driving *IL18BP* gene induction have been investigated in detail. We identified IFNγ as a key cytokine strongly inducing IL-18BP mRNA and protein release. Initial studies were performed on human colon carcinoma cells, HaCaT keratinocytes, and primary renal mesangial cells [200,201]. Subsequently, IFNγ-induced IL-18BP has been confirmed in various cell types (Table 1). Because IL-18 is pivotal for IFNγ production which in turn upregulates IL-18BP, we proposed a negative feedback loop that

Table 1
IFNγ-induced (single stimulus) IL-18BP gene induction as detected in diverse human cellular systems (selection).

Cells	Reference
Cervix carcinoma cells (WISH)	[202]
Colon carcinoma cells (Caco2, DLD1, HCT116, LoVo)	[200,201]
Colonic biopsy specimens, organ culture	[201]
Endometrial epithelial and stromal cells, primary	[203]
Endothelial cells, primary retinal microvascular	[204]
Fibroblasts, primary skin/muscle	[204,205]
Hepatoma cells (HepG2)	[206,207]
Mesangial cells, renal primary	[200]
Monocytes/macrophages, primary	[179,180]
Monocytic cell lines (THP1, TPA-differentiated U937)	[180,206,208]
Keratinocytes, immortalized (HaCaT)	[200,208]
Keratinocytes, primary	[205,209–211]
Ovarian carcinoma cells (A2774, A2780, OVCAR5, SKOV3)	[189]
Peripheral blood mononuclear cells (PBMC)	[178,180,204,206,208]
Prostate carcinoma cells (DU145, PC3)	[188,212]
Synoviocytes, primary fibroblast-like	[213]
Umbilical vein endothelial cells	[207]
Whole blood	[214]

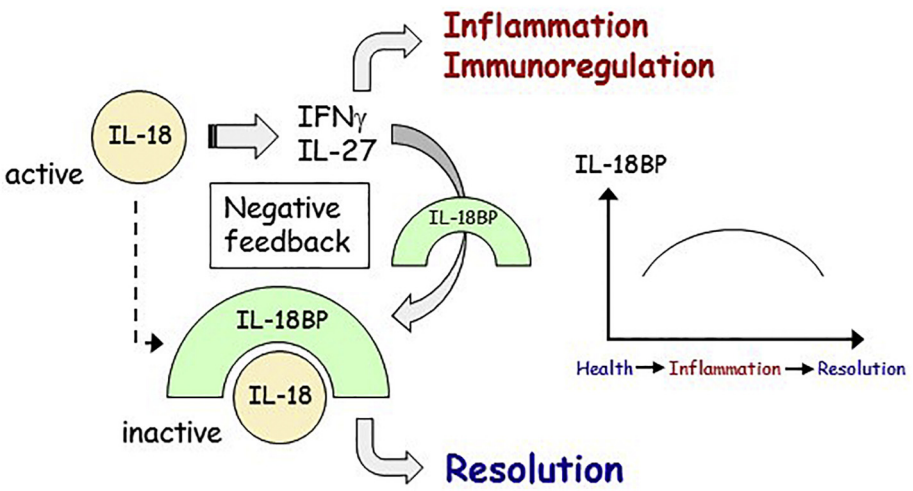

Fig. 3. Control of IL-18 by IFNγ-driven IL-18BP dependent negative feedback. IL-18 mediates innate and adaptive IFNγ and, as consequence of Th1-like inflammation, IL-27 production. Both, IFNγ and IL-27, efficiently upregulate IL-18BP expression which counteracts overt biologically active IL-18 by its decoy function. Since IL-18 is a key driver of pathological inflammation, negative feedback regulation by IFNγ-induced IL-18BP is regarded a pivotal mechanism contributing to inflammation resolution. Expression of IL-18BP during the course inflammation is supposed to be bell-shaped which has been shown for murine DSS-colitis [220].

controls IL-18 activity in biological systems (Fig. 3) [200,215]. Administration of recombinant IFNγ in fact increases serum IL-18BP levels in mice [202,206] and IFNγ-receptor deficient mice display enhanced IFNγ production upon inflammatory challenges [216,217]. Recently, by analysis of colitis-associated IL-18BP expression, this regulatory path has been proven to operate *in vivo* in murine intestinal epithelial cells [218]. Data concur with the capability of IFNγ to strongly upregulate IL-18BP in the murine rectal carcinoma cell line CMT-93 [218]. Kinetic analysis of IL-18BP expression during murine DSS-induced (Th1-like [219]) colitis furthermore underscored the role of local inflammation for securing IL-18BP expression. Whereas colonic IL-18BP expression is barely detectable in healthy mice, the gene is strongly upregulated during colitis (in agreement with data on IBD patients [183,184]) and promptly returns to basal levels after inflammation resolution [220]. Finally, a phase I clinical trial revealed that administration of recombinant IL-18 to humans results in augmented systemic IFNγ and IL-18BP [221]. On a molecular level, a specific γ-activated site (GAS) near the transcriptional start site within the human *IL18BP* promoter was identified to be essential for increasing transcription by IFNγ. Further analysis suggested that complexes comprising either of – interferon regulatory factor-1 (IRF1) plus CCAAT/enhancer-binding-protein-β (C/EBPβ) [206] – or of STAT1 [208] dock to this promoter site and mediate gene induction in cell-type dependent mode. Notably, as detected by analysis of serum IL-18BP, IRF1-deficient mice show inhibition of IFNγ-induced (IFNγ administration *in vivo*) but interestingly also of constitutive/basal IL-18BP production [206]. In keeping with viral infections enhancing IL-18BP it was recently shown that papillomavirus oncoprotein E7 augments IFNγ-induced IL-18BP in human keratinocytes [210]. Interestingly, compared to whole blood cultures (WBC) from healthy volunteers, WBC from HPS patients are characterized by diminished IFNγ-induced IL-18BP which may contribute to HPS pathogenesis [214]. Subsequent to that initial observation, it was shown that PBMC from HPS patients, having high plasma IL-18 and IFNγ, actually display IFNγ hypo-responsiveness [204] which should cause a drop in IL-18BP along with increased systemic free IL-18 [62].

Comparative analysis of IFNγ-induced IL-18BP indicated early on that gene induction is diminished in monocytes or PBMC but pronounced in non-leukocytic cells [200,206,208]. Subsequent analysis revealed that the methylation status of a single CpG near the human *IL18BP* transcriptional start site discriminates efficient expression in epithelial cells from a reduced one in monocytic cells [179]. Thus, in addition to e.g. human *ZFP36* (coding for TTP) [222] and *TNFSF11* (coding for RANK-L) [223], the human *IL18BP* promoter adds to the list of currently only few genes whose expression is diminished by single site CpG methylation. Accordingly, treatment with the demethylating agent 5-aza-2′-deoxycytidine amplified IL-18BP expression in monocytic cells but decisively not in epithelial cells [179]. This epigenetic layer controlling IL-18BP is likely to support specific tasks of IL-18. Curbing IL-18BP production in monocytes may allow for efficient generation of IL-18 activity in the blood compartment which is pivotal for infection control and preventing septic conditions. On the other hand, efficient production of IL-18BP by epithelial cells should avoid pathologically increased IL-18 activity at host/environment interfaces which already ‘in health’ are in states of immunological alertness.

Besides IFNγ, type I IFN can stimulate IL-18BP production which has been observed in IFNα-treated HCV patients [194]. Finally, immunoregulatory IL-27 [224] was identified as consistent inducer of IL-18BP in human primary and immortalized HaCaT keratinocytes, dermal fibroblasts [205], and epithelial ovarian cancer cells [225]. Aforementioned proximal GAS element in the human IL-18BP promoter [206,208] also is pivotal for IL-18BP induction by IL-27/STAT1 signaling [205]. In accord with a key role in pathophysiology and the necessity to stringently fine-tune its production, regulatory mechanisms controlling IL-18BP likewise intervene on the post-transcriptional level. For example, IL-18BP mRNA is directly targeted by miR-134, the expression of which correlates with disease activity in AOSD patients [226].

Biological functions of IL-18BP largely connect to IL-18 supporting Th1-like inflammation. In fact, IL-18BP-overexpressing (IL-18BP-Tg) mice, apparently normal if unchallenged, display a marked reduction in IFNγ and inflammatory cytokines when investigated in murine systemic inflammation [227]. IL-18BP-Tg mice, moreover, are protected in models of acute tissue injury such as ConA-induced ALI [227] or ischemic kidney injury [228], in streptozotocin-induced diabetes [229], and in experimental myocardial hypertrophy [230]. Notably, a protective role of IL-18BP as detected previously in the murine liver [227] has recently been confirmed in a human patient displaying an *IL18BP* loss-of-function mutation [207]. Specifically, under the influence of this *IL18BP* loss-of-function mutation, a hepatitis A virus infection associated with IL-18 hyperactivity and resulted in fatal progression of the patient towards fulminant hepatitis [207]. This key clinical observation thus emphasizes the relevance of endogenous IL-18BP for control of hepatic inflammation in humans and moreover suggests pivotal functions of the protein for control of pathogenic immune-mediated processes affecting other human tissues. So far, only few studies investigated IL-18BP deficient mice. Available data demonstrate that endogenous IL-18BP restrains IFNγ production during murine endotoxemia [231]. Moreover, in experimental HPS, IL-18BP deficiency potentiates systemic levels of free IL-18 and downstream IFNγ which is paralleled by disease exacerbation [182]. Finally, *il18bp*$^{-/-}$ mice display aggravated DSS-induced colitis [220] which is likely based on enhanced IL-18-induced IFNγ/TNFα-driven inflammation [219,232] and

Table 2
Amelioration of rodent experimental diseases by application of recombinant IL-18BP (partly Fc-coupled) (selection).

Experimental disease model	Strain	Outcome compared to treatment without IL-18BP	Ref.
ConA-induced ALI	C57BL/6	Liver damage ↓, (IFNγ, Fas-L) ↓	[235]
P. acnes + LPS/Anti-Fas-induced ALI	BALB/c	Liver damage ↓, (IFNγ, Fas-L) ↓ / Liver damage ↓	[235]
Endotoxemia	BALB/c	Lethality ↓, IFNγ ↓	[235]
Experimental colitis (DSS- or TNBS-induced)	C57BL/6	Colitis ↓, (IFNγ, IL-1, TNFα) ↓ / Colitis↓	[219/237]
Collagen-induced arthritis	DBA/1	Arthritis ↓, IL-6 ↓ / Arthritis ↓, (IFNγ, IL-1β, TNFα) ↓	[240]/[241]
Traumatic brain injury	Sabra	Improved outcome	[239]
B16M melanoma hepatic metastasis	C57BL/6J	Liver metastasis ↓, VCAM-1 ↓	[242]
Contact hypersensitivity	C57BL/6	Disease severity ↓, T cell infiltration↓, IFNγ ↓	[243]
Non-obese diabetic-Typ I Diabetes	NOD mice	Cumulative diabetes incidence ↓	[244]
Lung metastasis	BALB/c	Lung metastasis ↓	[245]
T. gondii-induced small intestine pathology	C57BL/6	Small intestinal inflammation ↓	[246]
Renal ischemia-reperfusion injury (IRI)	Dawley / Wistar	IRI↓, Mϕ ↓,(MCP-1, IL-1, TNFα) ↓ / IRI↓, (IFNγ, IL-6, TNFα)↓	[247]/[248]
Adriamycin-induced nephropathy	BALB/c	Disease severity ↓, (iNOS, IFNγ, TNFα, IL-17, CCL2, CCL5) ↓	[249]
Irinotecan-induced intestinal mucositis	C57BL/6	Diarrhea, duodenal morphometric alteration ↓, iNOS ↓	[250]
Heart failure	C57BL/6	Left ventricular systolic dysfunction↓	[251]
Pulmonary disease - Alveolar hypoxia	C57BL/6	Left ventricular diastolic function ↑	[252]
Cardiac IRI	C57BL/6	Cardiac IRI ↓, leukocytic infiltration ↓, (IL-1β, IL-23, IL-17) ↓	[253]
Hepatic IRI	C57BL/6 / Wistar	IRI ↓, TNFα ↓/ IRI ↓, (TNFα, IL-6) ↓	[254]/[255]
HPS (CMV infection upon perforin-1$^{-/-}$)	C57BL/6	Disease severity ↓, (IFNγ, TNFα, Fas-L)↓	[238]
APAP-induced ALI	C57BL/6	ALI ↓, (IFNγ, Fas-L) ↓	[236]
LPS/Bleomycin (BLM)-induced lung injury	C57BL/6	LPS-induced injury ↓, Nrf2 ↑ / BML-induced injury ↓, survival ↑	[256]/[257]

hampered development of mucin-producing globlet cells [220] due to overt colonic IL-18 activity. The function of IL-18 in experimental IBD is, however, complex because complete lack of IL-18 in *il18*$^{-/-}$ mice likewise exaggerates colitis [233]. Of note, a protective function of IL-18 in experimental IBD should be based on IL-18 strengthening the intestinal barrier. This property relates to the capability of IL-18 to enforce anti-microbial host defense by inducing anti-microbial peptides [234]. Moreover, IL-18 may amplify IL-22 biological activity by suppressing IL-22BP which has been shown in acute DSS-induced murine colitis [165].

Protective properties of recombinant IL-18BP as detected in preclinical research suggest this protein as anti-inflammatory therapeutic applicable as (modified) 'biologic' in diverse settings of pathological inflammation. Experimental disease models with recombinant IL-18BP (partly Fc-coupled) being protective range from experimental ALI [235,236] to DSS- or trinitrobenzene sulphonic acid (TNBS)-induced colitis [219,237] and from HPS [238] to traumatic brain injury [239] (see Table 2). In addition to administrating the recombinant protein, IL-18BP gene therapy was applied in rodents. Interestingly, adenoviral overexpression of murine IL-18BPc in the central nervous system of mice undergoing experimental encephalomyelitis not only results in reduced disease incidence and severity but also in a drop of Th17 responses [258] thus corroborating aforementioned capability of IL-18 to support Th17 [61]. Besides that, it is pointed out exemplarily that adenoviral delivery of IL-18BP prolongs allograft survival in a rat model of orthotopic liver transplantation [259] and that *in vivo* transfection with an IL-18BPd expression plasmid ameliorates murine atherosclerosis [260]. Taken together, current studies on rodent disease models suggest IL-18BP as potent anti-inflammatory agent and support its further development for the treatment of inflammatory syndromes.

While investigating IL-18BP's anti-inflammatory properties in human WBC, it was observed early on that in some donors lower concentrations of recombinant IL-18BPa:Fc display a better inhibitory capacity as compared to higher ones [261]. It is tempting to speculate that this observation connects to the biochemical property of IL-18BP to physically bind anti-inflammatory IL-37 [262]. Since IL-37 is lacking in mice, this proposed interaction is irrelevant in murine models but might, to some degree, defuse anti-inflammatory characteristics of IL-18BP in the human system, particularly if used at higher concentrations [263]. However, a missing 'dose-response-relationship' with lower dosages slightly tending to be more potent in reducing clinical scores could also be seen in arthritic mice (lacking IL-37) where IL-18BP alleviates disease severity [240]. Most importantly, in a recent phase II clinical trial, IL-18BP (tadekinig-alfa) showed efficacy along with reduction of C-reactive protein in AOSD patients which clearly emphasizes the therapeutic potential of IL-18BP for the treatment of human inflammatory diseases [63].

6. Blockage of IL-22 biological activity by IL-22 binding protein

In 2001 three research groups reported on the discovery of human IL-22BP (*IL22RA2*), a soluble neutralizing IL-22 'receptor' that is different from IL-22R1 or IL-10R2 and encoded by a separate genus locus. Similar to IL-18BP blocking IL-18, IL-22BP acts as a glycosylated decoy secreted via the Golgi apparatus. Extracellular IL-22BP targets IL-22 with outstanding affinity thereby suppressing receptor activation and biological functions of the cytokine [22,264–266]. Later on, murine [267,268] and rat IL-22BP [268,269] were characterized. Three splice variants exist in humans which are entitled IL-22BPi1, IL-22BPi2, and IL-22BPi3. Further analysis revealed that IL-22BPi2 and IL-22BPi3 are capable of neutralizing IL-22, albeit the latter shortest variant (without exons 3 and 5) displays reduced efficacy [270]. In contrast, long IL-22BPi1, retaining exon 3, is not secreted [270,271] and biochemically unable to neutralize IL-22 [271]. Interestingly, IL-22BPi1 is connected to the unfolded protein response (UPR) [271] and may thus be involved in cellular control of environmental stress. In mice only a single type of IL-22BP molecule exists which is similar to IL-22BPi2 [22].

Steady-state expression of IL-22BP is detectable in various human tissues, predominantly in lymph nodes, spleen, thymus, the female reproductive system (mammary gland, endometrium, and breast), and the digestive system (stomach, small intestine, esophagus, gastroesophageal, pancreas, duodenum, ileum, colon, and small bowel) as well as in lung, placenta, and skin [22,265,268]. In fact, serum levels of IL-22BP in healthy volunteers are in the remarkable range of 30 to 80 ng/ml [272,273].

It was observed early on that human pre-mature monocyte-derived dendritic cells (MDDC) constitutively express IL-22BP which upon further activation (by LPS) is downregulated [269,274]. In contrast, cultivation of MDDC under the influence of retinoic acid amplifies IL-22BP [269,270] which can be viewed as a safeguard mechanism to avoid pathologically increased IL-22 activity. In fact, retinoic acid potentiates γδT cell-derived IL-22 and downstream gene induction in the context of intestinal inflammation [275]. Notably, IL-22BP has been studied foremost in the intestine. By using rodent models, DC-like cells/

conventional (c)DC in intestinal secondary lymphoid organs were established to express IL-22BP in health [165,269].

Although basal production of IL-22BP by cDC/mononuclear phagocytes in fact translates to the human gut [276], intestinal eosinophils have recently been identified as a major producer of 'physiological' IL-22BP in humans [277]. IL-22BP expression is likewise evident in murine and human healthy skin. In mice, skin-draining lymph nodes and keratinocytes were reported to be major sources of cutaneous IL-22BP [154,278].

Increased levels of IL-22BP mRNA and protein are detectable in human chronic inflammation. This specifically applies to inflamed lesions of Crohn's disease and colitis ulcerosa patients [277,279]. Although the cDC-pool probably contributes to enhanced IL-22BP production in these patients, current knowledge suggests that, in addition to their function in the steady state, eosinophils [277] but also $CD4^+$ T cells [279] are likely responsible for IL-22BP upregulation aiming to counteract overt and potentially hazardous IL-22 during chronic intestinal inflammation. Compared to chronic IBD entities, IL-22BP is differentially regulated in human diverticulitis. During this condition of acute inflammation, IL-22BP is suppressed [279] which actually reflects IL-22BP regulation in the model of murine acute DSS-induced colitis [165,280,281]. Notably, compared to mice, DSS-induced colitis in rats displays a delayed onset of IL-22BP downregulation [277]. Interestingly, increased serum levels of IL-22BP are detectable in psoriasis patients [272] and patients diagnosed with acute-on-chronic liver failure (ACLF) [273] – both chronic inflammatory syndromes. This latter study confirms and extends previous observations on pathogenic functions of IL-22 in the context of chronic liver diseases [160–163].

With the use of suitable knockout models, knowledge on the role of IL-22BP in health and disease is evolving. *il22ra2*$^{-/-}$ animals are generally regarded healthy [154]. However, because IL-22 and IL-22BP are produced in the steady state and thus are supposed to serve specific lifelong functions in health, the possibility of subtle changes affecting immunophysiology upon IL-22BP deficiency exist. In that context Peyer's patches (PP) are exemplarily outlined. This specialized gut-associated lymphoid tissue is pivotal for the generation of adaptive immunity and gut homeostasis. Not only is IL-22BP highly expressed in steady state murine PP, recent data moreover show that unleashed IL-22 activity in the PP microenvironment (as in *il22ra2*$^{-/-}$ mice) impairs normal antigen uptake by the PP follicular associated-epithelium thereby likely affecting tissue function [282].

Data obtained from *il22ra2*$^{-/-}$ rodents widely reflect already outlined biological functions of IL-22 in disease. By investigating rat DSS-induced colitis [277] or the murine $CD45RB^{high}$ transfer colitis model [279] a pathogenic role of IL-22BP in promoting intestinal inflammation was proven. Those results from *il22ra2*$^{-/-}$ rodents concur with early data on IL-22BP gene delivery demonstrating aggravation of murine DSS-induced colitis by IL-22BP provision [281]. Of note, IL-22BP-deficient mice likewise revealed that endogenous IL-22BP has the clear capability to curb colon carcinogenesis which is likely due to its potential to block IL-22-driven proliferation in the epithelial compartment [165]. Data thus altogether emphasize aforementioned Janus-faced properties of IL-22 in inflammation-associated tumorigenesis in the intestine. Whereas IL-22BP is largely pathogenic in intestinal inflammation [277,279], its role in experimental psoriasis is contrariwise (Fig. 4). Specifically, by analyzing the model of imiquimod-induced psoriasis in the context of *il22ra2*$^{-/-}$ rats [272] and mice [154] endogenous expression of IL-22BP (limiting IL-22 activity) has been linked to amelioration of disease. Importantly, those result were pharmacologically confirmed by administering recombinant IL-22-Fc [154] or a neutralizing IL-22BP antibody [272] to wildtype mice and rats, respectively. In fact, treatment with these biologics exacerbated experimental psoriasis [154,272]. Recent data, moreover, indicate that IL-22BP supports bacterial superinfection in murine influenza [283] and also plays a pathogenic role in rodent experimental multiple sclerosis [284].

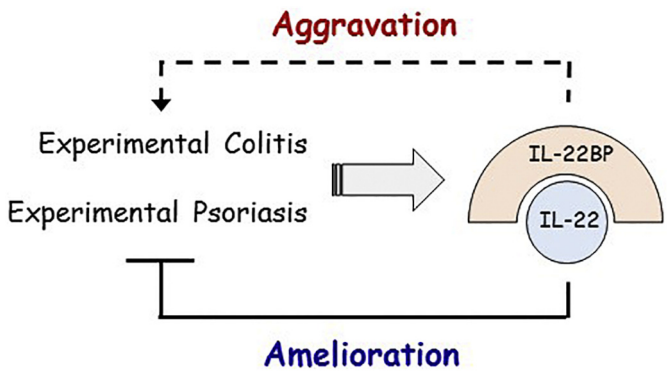

Fig. 4. Differential pathophysiological functions of IL-22BP detected in experimental psoriasis and colitis. By using *il22ra2*$^{-/-}$ animals, the pathophysiological role of IL-22BP was analyzed in rat models of chronic inflammation, namely experimental psoriasis and colitis [272,277]. Interestingly, *il22ra2*$^{-/-}$ rats display aggravated disease in imiquimod-induced psoriasis but ameliorated DSS-colitis. In other words, IL-22 neutralization by IL-22BP ameliorates disease in experimental psoriasis but aggravates disease in colitis. Both observations agree with well-described functions of IL-22 in the respective inflammatory syndromes. Data from these models altogether suggest that endogenous production of IL-22BP and associated neutralization of IL-22 is a decisive determinant of disease severity in intestinal and cutaneous inflammation.

IL-22 serum levels are increased in human and rodent sepsis [285,286]. Despite IL-22 being an established anti-bacterial mediator strengthening host environment interfaces, application of IL-22BP-Fc surprisingly enhanced anti-bacterial host defense in murine sepsis [287]. Those data might connect to a pathogenic effect of IL-22 observed by analysis of *il22*$^{-/-}$ mice in endotoxemia [288]. In contrast, application of recombinant IL-22 protects from intestinal leakiness and reduces systemic inflammation in murine experimental ethanol/burn-injury [289]. Altogether, the role of the IL-22/IL-22BP system in systemic inflammation and sepsis is not fully understood and requires further investigation.

il22ra2$^{-/-}$ mice display aggravated hepatic ischemia/reperfusion injury and acetaminophen (APAP)-induced ALI. In APAP-induced ALI of the same study, *il22*$^{-/-}$ mice surprisingly did show a very similar degree of increased liver injury as compared to *il22ra2*$^{-/-}$ mice (detected by serum alanine aminotransferase) suggesting a complex mode of endogenous IL-22 action [290]. Notably, only a single administration of recombinant IL-22 [143,291,292] or IL-22 application by liver-targeted gene therapy [293] results in alleviation of murine APAP intoxication emphasizing the potential of short-term use of IL-22-based biologics in the pharmacotherapy of drug-induced ALI.

7. Clinical significance and concluding remarks

Present knowledge identifies IL-18 and IL-22 as pivotal determinants of innate and adaptive immunity. In fact, information from basic research is beginning to translate to the clinical setting which opens the avenue towards novel therapeutic approaches addressing some difficult-to-treat human diseases.

As already alluded to, clinical trials revealed that recombinant IL-18 and IL-22 can be administered safely to humans with side effects typically in the acceptable range. Most importantly, when administered to human volunteers these cytokines are active which has been confirmed in phase I clinical trials by proof of upregulation of IFNγ and IL-18BP by IL-18 (iboctadekin) [221] or of hepatic e.g. SAA by IL-22 (F-652, UTR1147A) [144,145]. Further clinical trials must reveal whether use of IL-18 as immunostimulant/adjuvant will prevail in pharmacotherapy. Interestingly, recent preclinical research suggests application of IL-18 along with chimeric antigen receptor (CAR) T cell approaches as promising strategy for therapy of solid tumors [294,295].

Concerning IL-22, clinical trials on F-652 are underway assessing its prospect for the treatment of alcoholic hepatitis (https://clinicaltrials.gov/ct2/show/NCT02655510) or lower gastrointestinal acute Graft-versus-host (GvH) disease (https://clinicaltrials.gov/ct2/show/NCT02406651). Previous preclinical data proved the therapeutic potential of IL-22 in the context of these pathological conditions [296–299].

Basic research demonstrates the significance of endogenous IL-18BP and IL-22BP for implementing regulatory circuits that control IL-18 [182,220,231] and IL-22 activity [154,165,272,277,279] particularly at biological barriers. In the steady state and during disease IL-18BP and IL-22BP are thus supposed to contribute to maintenance of or to return to homeostasis. If applicable in a given disease context, blockage of pathogenic agonists (like IL-18 and IL-22) by using decoy receptors is a most attractive strategy in terms of drug development. In fact, a phase II clinical trial showed efficacy of IL-18BP (tadekinig-alfa) in AOSD patients [63]. IL-18BP, moreover, was successfully applied in an emergency case of autoinflammatory HPS/macrophage activation syndrome [64]. Concerning IL-22BP, patient data on clinical trials are currently lacking. However, encouraging results of a phase II clinical trial on fezakinumab (an IL-22 neutralizing antibody) in atopic dermatitis patients [300] suggests a similar therapeutic potential of IL-22BP.

Taken together, IL-18/IL-18BP and IL-22/IL-22BP are two highly interesting agonist/opponent couples not only serving pivotal functions in (patho)-physiology when expressed endogenously. Beyond that, both agonists (IL-18 and IL-22) and their opponents (IL-18BP and IL-22BP) are promising candidates for development as biological drugs addressing diverse medical conditions from acute and chronic inflammation through to cancer.

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