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REVIEW

IL-22 in tissue-protective therapy

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IL-22, a member of the IL-10 cytokine family, has recently gained significant attention as a protective agent in murine models of diseases driven by epithelial injury. Like its biochemical and functional sibling IL-10, IL-22 elicits cellular activation primarily by engaging the STAT3 signalling pathway. Exclusively produced by leukocytes, but targeting mostly cells of epithelial origin, IL-22 has been proposed as a specialized cytokine messenger acting between leukocytic and non-leukocytic cell compartments. A lack of response in leukocytes to IL-22 mirrors tightly controlled IL-22 receptor expression and probably explains the apparent lack of instant adverse effects after systemic IL-22 administration to mice. Anti-apoptotic, pro-proliferative and pro-regenerative characteristics the major biological properties of this cytokine. Specifically, application of IL-22 is associated with tissue protection and/or regeneration in murine models of infection/microbe-driven inflammation at host/environment interfaces, ventilator-induced lung injury, pancreatitis and liver damage. Overall, preclinical studies would support therapeutic administration of seemingly well-tolerated recombinant IL-22 for treatment of an array of acute diseases manifested in epithelial tissues. However, the feasibility of prolonged administration of this cytokine is expected to be restricted by the tumourigenic potential of the IL-22/STAT3 axis. IL-22, moreover, apparently displays an inherent context-specific capacity to amplify distinct aspects of autoimmune inflammation. Here, the prospects, expectations and restrictions of IL-22 administration in tissue-protective therapy are discussed.

Abbreviations

DAMPs, danger-associated molecular patterns; IL-22BP, IL-22 binding protein

Introduction

Cell death and loss of tissue integrity is regarded a major pillar of pathophysiology determining the course of disease in acute and chronic inflammation. As a result of direct infection, infection-related collateral tissue damage, sterile inflammation or drug-induced toxicity, danger-associated molecular patterns (DAMPs or alarmins), normally located in the intracellular compartment or fixed in the extracellular matrix, are released from dying cells into the extracellular space. Among others, DAMPs include heat shock proteins, hyaluronic acid fragments, biglycan, high mobility group box-1, uric acid and nucleic acids. Once released, these molecules serve as ligands for Toll-like receptors thereby initiating or enhancing inflammatory mechanisms usually associated with activation of innate immunity. This concept of DAMP release and recognition is essential to the perpetuation and amplification of inflammatory pathogenesis (Gallucci and Matzinger, 2001; Rock and Kono, 2008; Goh and Midwood, 2012; Lukens *et al.*, 2012; Pradeu and Cooper, 2012) and has been proposed as a promising target for pharmacological intervention and drug development. In this context, therapeutic approaches using tissue-preserving biological agents, including recombinant IL-22, may have the ability to break cell death-driven vicious cycles that would otherwise perpetuate pathological inflammation.

IL-22 is a member of the IL-10 cytokine family with pronounced tissue-protective properties that recently became a major focus of cytokine biology and related translational research (Wolk *et al.*, 2010; Sonnenberg *et al.*, 2011; Gao, 2012; Kronenberger *et al.*, 2012). Because of its ability to strengthen homeostatic epithelial barrier functions as well as

overall tissue robustness and stress resistance, therapeutic administration of IL-22 may open the way to novel strategies for the treatment of injury-driven pathogenic inflammation. In the present review, prospects, expectations and limitations related to use of IL-22 as a tissue-protective biological treatment are assessed in the context of pulmonary, intestinal, pancreatic and hepatic inflammatory disorders.

Biochemical properties of IL-22

IL-22, formerly known as IL-10-related T–cell-derived inducible factor (Dumoutier *et al.*, 2000; Xie *et al.*, 2000), displays crucial properties that define this cytokine as a member of the IL-10 family. Those characteristics include structural features such as bundle-forming clustering of α-helices as well as activation of the transcription factor STAT3 as dominant means of signal transduction and coincide with a 25% overall amino acid identity between IL-22 and its cytokine sibling IL-10. Interestingly, both cytokines share the IL-10 receptor chain-2 as one of two receptor chains, which combines with either IL-10 receptor chain-1 or IL-22 receptor chain-1, to generate functional heterodimeric receptors for IL-10 or IL-22, respectively (Aujla and Kolls, 2009; Wolk *et al.*, 2010; Ouyang *et al.*, 2011). Subsequent to receptor ligation and activation of the JAK1/Tyk2/STAT3 pathway, IL-22 acts primarily by modulating gene expression profiles in target cells. Accordingly, prototypic STAT3-inducible genes such as LPS-binding protein (Wolk *et al.*, 2007) or suppressor of cytokine signalling-3 are up-regulated under the influence of IL-22 (Nagalakshmi *et al.*, 2004; Brand *et al.*, 2006; Hoegl *et al.*, 2011).

Although the STAT3 pathway must be regarded as the principal and dominant mechanism of cellular activation by IL-22, this cytokine is able to engage additional means of signal transduction. The capacity of IL-22 to mediate some moderate activation of STAT1, in addition to STAT3, has been appreciated early on (Dumoutier *et al.*, 2000; Nagalakshmi *et al.*, 2004; Ziesche *et al.*, 2007). This feature of IL-22 biology is greatly enhanced under the influence of type I IFN (Bachmann *et al.*, 2013). Given the pro-inflammatory characteristics of STAT1 (Paludan, 2000), this interaction with type I IFN probably underlies some specific pro-inflammatory functions of IL-22 (Mühl, 2013). IL-22 likewise activates, albeit to a rather variable degree, pro-proliferative MAPK pathways (Eyerich *et al.*, 2010), mostly ERK 1/2, in a range of cell types, among others, rat and human hepatoma cells (Lejeune *et al.*, 2002; Radaeva *et al.*, 2004; Brand *et al.*, 2007), human colon carcinoma cells (Brand *et al.*, 2006; Fukui *et al.*, 2011), myofibroblasts (Andoh *et al.*, 2005), hepatic stellate cells (Kong *et al.*, 2012) as well as primary keratinocytes (Sestito *et al.*, 2011) and immortalized human keratinocytes (HaCaT cells; Zhang *et al.*, 2012). Besides that, activation of pro-survival Akt (PKB) by IL-22 has been reported for human colon carcinoma cells (Brand *et al.*, 2006; Fukui *et al.*, 2011), primary hepatocytes (Brand *et al.*, 2007) as well as for primary keratinocytes and synovial fibroblasts (Mitra *et al.*, 2012). Notably, activation of the key pro-inflammatory transcription factor NF-κB is generally not associated with IL-22 biological activity (Eyerich *et al.*, 2010), with a few exceptions. For example, in contrast to reports on human primary keratinocytes (Wolk *et al.*, 2006) and DLD1 colon carcinoma cells (Ziesche *et al.*, 2007), IL-22 activates the NF-κB pathway in human SW404 colon carcinoma cells (Fukui *et al.*, 2011) and myofibroblasts (Andoh *et al.*, 2005).

IL-22 in health and disease

The biological activity of IL-22 is largely determined by two principal features that in combination set the basis for quite unique properties of this cytokine in physiology and pathophysiology. First, IL-22 acts primarily on non-leukocytic cells and characteristically not on leukocytes. This property is based on selective expression of the IL-22 receptor chain-1 on non-leukocytic cells, in particular on cells of epithelial origin such as keratinocytes, intestinal or lung epithelial cells, and hepatocytes (Wolk *et al.*, 2004; 2010; Aujla and Kolls, 2009; Sonnenberg *et al.*, 2011). In addition, the IL-22 receptor chain-1 is expressed on hepatic stellate cells (Kong *et al.*, 2012) and on synovial fibroblasts (Ikeuchi *et al.*, 2005) and intestinal sub-epithelial myofibroblasts (Andoh *et al.*, 2005). With regard to the pancreas, IL-22 receptor chain-1 has been detected on human insulin-expressing beta-cells and glucagon-expressing alpha-cells, but not on acinar cells (Shioya *et al.*, 2008). In contrast, pancreatic acinar cells of murine origin respond to stimulation with IL-22 (Aggarwal *et al.*, 2001). In contrast to the IL-22 receptor chain-1, IL-10 receptor chain-2, the second component of the heterodimeric IL-22 receptor, is ubiquitous (Ouyang *et al.*, 2011). Secondly, IL-22 is exclusively produced by leukocytes, primarily activated Th1, Th17, Th22 and $CD8^+$ T cells, γδ T-cells, dendritic cells, NK cells (Colonna, 2009; Duhen *et al.*, 2009; Eyerich *et al.*, 2009; Pickert *et al.*, 2009; Bachmann *et al.*, 2010; Wolk *et al.*, 2010; Ouyang *et al.*, 2011), invariant NK T-cells (Paget *et al.*, 2012) and a range of NK-like cells recently named as innate lymphoid cells (Colonna, 2009; Koyasu and Moro, 2012). This spectrum of producer and target cells suggests that IL-22 is a specific messenger between leukocytic and non-leukocytic cell compartments. Despite this rather diverse pattern of leukocyte subsets capable of producing IL-22, some common parameters determining production of this cytokine have emerged. These are chiefly IL-1 (Dinarello, 2011) and IL-23, which in some cases synergize to induce IL-22 (Bachmann *et al.*, 2010; Hughes *et al.*, 2010; Marijnissen *et al.*, 2011; Paget *et al.*, 2012; Shaw *et al.*, 2012). As expected, in light of IL-22 being exclusively produced by leukocytes, increased levels of local or systemic IL-22 have been consistently detected in numerous human diseases associated with overt immunoactivation. Such conditions may be infection- or microbe-driven, as seen in *Mycobacterium tuberculosis* infection (Matthews *et al.*, 2011), sepsis (Bingold *et al.*, 2010) and inflammatory bowel diseases (Andoh *et al.*, 2005; Brand *et al.*, 2006; Schmechel *et al.*, 2008) or be unrelated to obvious infections, as in autoimmune inflammation, including rheumatoid arthritis (Ikeuchi *et al.*, 2005; Leipe *et al.*, 2011) and psoriasis (Wolk *et al.*, 2006; Boniface *et al.*, 2007; Nakajima *et al.*, 2011). In addition, production of IL-22 is enhanced in patients with chronic hepatitis and liver cirrhosis of diverse aetiology (Jiang *et al.*, 2011; Kang *et al.*, 2012; Kronenberger *et al.*, 2012).

Of particular interest are the interactions between IL-22 and other inflammatory cytokines including Th17-/Th22-

related cytokines, especially IL-17 and TNFα (Lowes *et al.*, 2008; Eyerich *et al.*, 2009; Korn *et al.*, 2009). In fact, IL-22 cooperates with IL-17 or TNFα for efficient induction of antimicrobial peptides and chemokines (Liang *et al.*, 2006; Aujla *et al.*, 2008; Eyerich *et al.*, 2011) as well as IL-36γ, IL-6 and granulocyte colony-stimulating factor (Aujla *et al.*, 2008). This may not only be relevant for effective initiation of host defence. Notably, because of this IL-17A/IL-22 synergism, the presence or absence of IL-17A can determine the net pro- or anti-inflammatory and protective functions of IL-22 in lethal airway inflammation induced by high-dose bleomycin (Sonnenberg *et al.*, 2010b). If also applicable to other pathological conditions, this observation should be highly relevant when considering IL-22 for use as a tissue-protective therapy.

The functions of IL-22 *in vivo* mirror elemental roles of STAT3 in cell physiology. Among the cellular tasks connected with STAT3, anti-apoptosis and proliferation are particularly crucial (Jarnicki *et al.*, 2010; Wang *et al.*, 2011). IL-22 up-regulates STAT3-inducible Bcl-2 and/or Bcl-X_L (Radaeva *et al.*, 2004; Zhang *et al.*, 2008; Sonnenberg *et al.*, 2010a; Curd *et al.*, 2012; Kong *et al.*, 2012) as well as cyclin D1 and/or c-Myc (Radaeva *et al.*, 2004; Kong *et al.*, 2012), all of which are prototypic parameters relating to anti-apoptosis and proliferation. These pro-survival proteins, along with the activation of ERK 1/2 (Wortzel and Seger, 2011) and Akt (X Zhang *et al.*, 2011), are likely to form the cellular basis for tissue protective properties of IL-22, as observed in pathophysiological situations, driven by epithelial cell death. Figure 1 summarizes the cellular signalling engaged by IL-22 in relation to the specific functional properties of this cytokine.

The biological activity of IL-22 is controlled by its specific endogenous antagonist, IL-22 binding protein (IL-22BP). This protein is encoded by a unique gene locus and displays 34% amino acid identity compared with the extracellular domain of IL-22 receptor chain-1, but lacks its transmembrane and intracellular domains. In fact, IL-22BP is functionally regarded as a soluble, neutralizing decoy receptor for IL-22. As IL-22BP displays higher affinity towards IL-22 as compared with the IL-22 receptor complex, it is supposed to control IL-22 biological activity *in vivo* (Dumoutier *et al.*, 2001; Kotenko *et al.*, 2001; Xu *et al.*, 2001; Huber *et al.*, 2012). Notably, in terms of the clinical IL-22 administration, individual IL-22BP levels may affect the therapeutic efficacy of this cytokine in patients.

Modulation of IL-22 bioactivity, achieved either by application of neutralizing antibodies or by using knockout mice, exacerbates symptoms in a range of disease models. This is well-documented for liver injury induced by concanavalin A (Radaeva *et al.*, 2004; Zenewicz *et al.*, 2007) or by the combination of LPS plus D-galactosamine (Radaeva *et al.*, 2004; Marks *et al.*, 2009). IL-22 neutralization likewise impairs proliferation and recovery in experimental hepatectomy (Ren *et al.*, 2010) and aggravates cerulein-induced pancreatitis in the context of enhanced IL-22 biological activity under the influence of aryl hydrocarbon receptor ligands (Xue *et al.*, 2012). Using knockout mice, tissue-protective effects of endogenous IL-22 were also identified in influenza A virus infections in mice. In this model, sufficient production of IL-22 early during infection stabilized lung epithelial integrity (Kumar *et al.*, 2013; Paget *et al.*, 2012). Actually, IL–22-knockout mice displayed a more severe course of disease

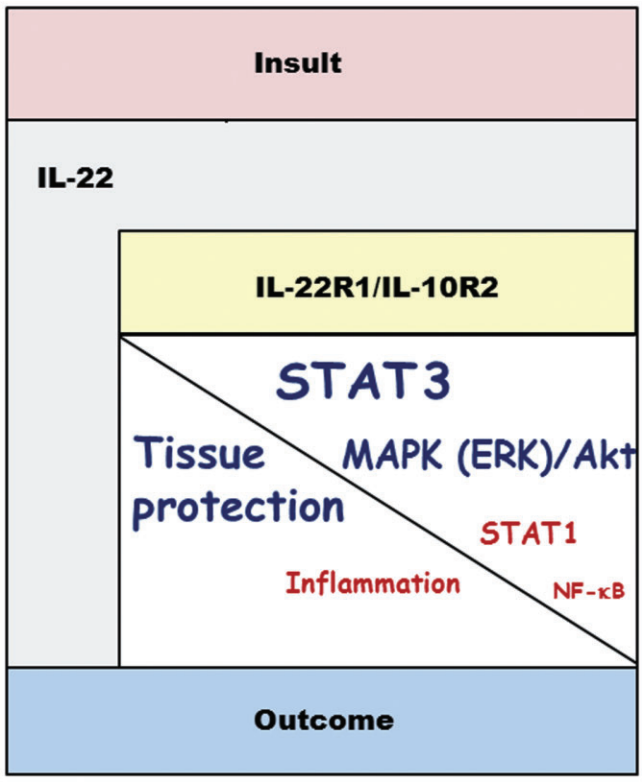

Figure 1

Structure chart-like illustration of IL-22 signalling related to cytokine function. Regardless of whether endogenously produced in response to an epithelial insult or provided in the course of tissue-protective therapy, IL-22 will activate its heterodimeric IL-22R1/IL-10R2 receptor, which is predominantly expressed at the liver and host/environment interfaces. Subsequent to receptor activation, signal transduction mechanisms are engaged that are greatly dominated by STAT3 along with activation of MAPK and Akt pathways. This specific profile of cellular activation mediates proliferation and anti-apoptosis, finally increasing tissue robustness and stress resistance. Through these pathways, IL-22 is capable of mediating tissue protection in the context of various pathogenic conditions. However, a latent pro-inflammatory role of IL-22 related to activation of STAT1 and NF-κB may counteract the therapeutic potential of this cytokine in a context-specific manner. IL-10R2, IL-10 receptor chain-2; IL-22R1, IL-22 receptor chain-1.

(Kumar *et al.*, 2013). The notion that endogenous IL-22 acts protectively in the lung extends to murine allergic asthma, where application of neutralizing antibodies worsens established disease (Besnard *et al.*, 2011). A further study on experimental allergy likewise documents exacerbation of airway constriction and inflammation in IL–22-knockout mice (Taube *et al.*, 2011). Finally, IL–22-deficient mice display increased pathology in experimental graft versus host disease (Hanash *et al.*, 2012) and murine heart transplant rejection (Kapessidou *et al.*, 2008) and likewise show impaired thymic regeneration in response to total body irradiation. In accord with a tissue-protective activity of IL-22, authors of the latter study demonstrated that the cytokine was pivotal for thymic epithelial proliferation and survival, subsequent to the thymic insult (Dudakov *et al.*, 2012).

In addition to these anti-apoptotic and pro-proliferative mechanisms, IL-22 mediates further protection at host/environment interfaces by enhancing mucus production and, moreover, by activating more specific means of antibacterial host defence. IL-22 may, thus, also have an anti-infective indication. Of note, killing by antibacterial peptides such as β-defensins, lipocalin and RegIIIβ/γ or by inducible NO synthase-derived NO are candidate effector mechanisms likely to be utilised by IL–22-dependent control of infection- or microbe-associated tissue injury and inflammation (Aujla and Kolls, 2009; Blaschitz and Raffatellu, 2010; Mühl *et al.*, 2011; Sonnenberg *et al.*, 2011; Eddens and Kolls, 2012). However, it should be noted that inducible NO synthase (Mühl *et al.*, 2000) and β-defensins (Niyonsaba *et al.*, 2007) also have an inherent potential to serve pro-inflammatory functions. Therefore, overt induction of both these systems may, under some conditions, interfere with the protective potential of IL-22.

Specifically, neutralization of IL-22 increases mortality in murine *Klebsiella pneumonia* infection (Aujla *et al.*, 2008). Moreover, deficiency of IL-22 bioactivity correlates with increased disease severity in murine intestinal *Citrobacter rodentium* infection (Zheng *et al.*, 2008) and experimental colitis subsequent to dextran sulfate sodium-associated epithelial injury (Sugimoto *et al.*, 2008; Pickert *et al.*, 2009). The role of endogenous IL-22 in promoting intestinal healing has been recently confirmed in mice deficient for IL-22BP, who displayed enhanced tissue regeneration in response to mechanical intestinal injury (Huber *et al.*, 2012). Most recently, the ability of IL-22 to mediate epithelial healing has been extended from intestinal to cutaneous wound healing. In experimental full-thickness wounding, IL-22-deficient mice indeed exhibited defective skin repair (McGee *et al.*, 2013).

Altogether, thedata indicate the inherent potential of endogenously produced IL-22 to serve protective functions in a diverse array of disease conditions involving deleterious insults at tissues of epithelial origin. As already alluded to, those pathogenic processes are linked to release of DAMPs from dying cells that perpetuate and amplify the inflammatory state of the affected organ. Specifically, DAMPs such as extracellular DNA, high-mobility group box-1, heat shock proteins, hyaluronan or uric acid may significantly contribute to diverse manifestations of pathogenic inflammation ranging from acetaminophen (paracetamol)-induced liver injury to ventilator-induced lung injury (Imaeda *et al.*, 2009; Maher, 2009; Kuipers *et al.*, 2011) and asthma bronchiale (Shim *et al.*, 2012). IL-22 could have the potential to interfere with the injury-driven vicious cycle, present in these conditions.

Interestingly, recent studies also indicate that endogenous IL-22 not only provides essential protection during pathophysiological processes, but may play a pivotal role in preserving intestinal homeostasis under steady-state conditions. Specifically, it has been demonstrated that innate lymphoid cells/lymphoid tissue inducer-like cells located in the intestinal mucosa are able to produce ample amounts of IL-22. Either commensal microbes (Sanos *et al.*, 2009) or ligands of the aryl hydrocarbon receptor have been implicated in this process (Lee *et al.*, 2012). Neutralization experiments revealed that this homeostatic IL-22 activity at the intestinal host/environment interface serves pivotal antibacterial functions that avoid potentially hazardous systemic bacterial translocation (Sonnenberg *et al.*, 2012).

Tissue-protective therapy by IL-22 administration in rodent disease

Various preclinical studies have been conducted in recent years that emphasize the broad therapeutic potential of recombinant IL-22 in liver, pancreatic, intestinal and lung pathophysiology associated with epithelial injury (Table 1). Although produced as an endogenous protective factor in most of such conditions, the data, on the whole, indicate that the modulatory potential of the IL-22/STAT3 axis is not saturated by endogenous IL-22, which consequently raises expectations for use of this cytokine in novel therapeutic strategies. Effects of IL-22 on liver pathology are particularly well characterized. Specifically, administration of recombinant IL-22 significantly alleviates murine hepatic injury in response to concanavalin A (Radaeva *et al.*, 2004), alcohol (Ki *et al.*, 2010; Xing *et al.*, 2011b), LPS plus D-galactosamine (Xing *et al.*, 2011a), acetaminophen (Scheiermann *et al.*, 2013) or ischaemia-reperfusion (Chestovich *et al.*, 2012). Overexpression of IL-22 by *in vivo* cDNA delivery likewise attenuates experimental concanavalin A-, carbon tetrachloride- or Fas-mediated liver damage (Pan *et al.*, 2004). Protective properties of recombinant IL-22 also extended to murine high fat diet-induced steatosis. In this model, amelioration of hepatic disease by IL-22 correlates with rapid down-regulation of lipogenesis-related genes (Yang *et al.*, 2010). In addition, using IL-22 transgenic mice, *in vivo* adenoviral gene provision or application of recombinant cytokine, an anti-fibrotic role of IL-22 in the liver compartment was recently demonstrated. Notably, hepatic stellate cells are regarded to be the crucial target of IL-22 in this pathophysiological context (Kong *et al.*, 2012; Meng *et al.*, 2012).

Several studies testify to the benefit of IL-22 application in disease models relating to tissues other than the liver. Specifically, provision of IL-22 as recombinant protein attenuated pancreatitis induced by a cerulein- or choline-deficient diet supplemented with DL-ethionine (Feng *et al.*, 2012; Xue *et al.*, 2012), probably by up-regulation of anti-apoptotic Bcl-2 and/or Bcl-X_L and by modulating acinar cell autophagy (Feng *et al.*, 2012). With regard to pulmonary insults, recombinant IL-22 once more displays the capability to ameliorate disease in the context of most diverse pathogenic entities. Local application of recombinant IL-22 was protective in murine models of allergic airway inflammation (Besnard *et al.*, 2011; Takahashi *et al.*, 2011; Taube *et al.*, 2011) and lung fibrosis. In the latter pathogenic condition, IL-22 clearly reduced pulmonary collagen deposition, a hallmark of established disease (Simonian *et al.*, 2010). Moreover, IL-22 attenuated damage in rat baro-/biotrauma initiated by ventilator-induced lung injury. Notably, in that study, recombinant rat IL-22 was applied by inhalation (Hoegl *et al.*, 2011). In accord with the corresponding data on IL-22 blockade in intestinal disease, provision of IL-22 by *in vivo* delivery of IL-22-expressing plasmids ameliorated murine disease in severe infection by *Citrobacter rodentium* (Tumanov *et al.*, 2011; Qiu *et al.*, 2012) and in Th2-driven colitis observed in T-cell

Table 1

Tissue-protective therapy by provision of IL-22, in rodent disease models

Organ	IL-22 treatment	Observed effect	Reference
Lung	Single inhalation of recombinant IL-22 (10 μg·kg^{-1})	Attenuation of ventilator-induced lung injury	Hoegl *et al.*, 2011
Lung	3 intranasal doses of recombinant IL-22 (1 μg per mouse on days 14, 15, and 16 during antigen challenge)	Protection from lung inflammation in the OVA model	Besnard *et al.*, 2011
Lung	2 intranasal doses of recombinant IL-22 (0.1 μg per mouse, 48 and 2 h before OVA challenge)	Amelioration of allergic airway inflammation in the OVA model	Takahashi *et al.*, 2011
Lung	Single intranasal dose of recombinant IL-22 (0.1, 1 or 10 μg per mouse, 1 h before OVA challenge)	Amelioration of allergic airway inflammation in the OVA model	Taube *et al.*, 2011
Lung	Intratracheal treatment with recombinant IL-22 (100 pg and 100 ng per mouse, 3×/week for 4 weeks)	Protection from lung fibrosis in the *Bacillus subtilis* model	Simonian *et al.*, 2010
Liver	Single i.v. dose of recombinant IL-22 (3.5 μg per mouse)	Attenuation of acetaminophen (paracetamol)-induced liver damage	Scheiermann *et al.*, 2013
Liver	IL-22 transgenic mice; administration of Ad-IL-22	Anti-fibrotic role of IL-22 in the liver	Kong *et al.*, 2012
Liver	Single i.v. dose of recombinant IL-22 (5 μg per mouse)	Protection from hepatic ischaemia-reperfusion injury	Chestovich *et al.*, 2012
Liver	Daily doses of recombinant IL-22 (0.5 μg per mouse) for 7 days	Anti-fibrotic role of IL-22 in the liver	Meng *et al.*, 2012
Liver	Single i.v. dose of recombinant IL-22 (0.5 μg·g^{-1})	Protection from hepatic injury induced by LPS plus D-galactosamine	Xing *et al.*, 2011a
Liver	Daily i.v. dose of recombinant IL-22 (0.5 mg·kg^{-1})	Protection from liver injury after acute alcohol intoxication	Xing *et al.*, 2011b
Liver	IL-22 transgenic mice	Enhanced tumour formation; protection from ConA-induced liver damage; accelerated liver regeneration after partial hepatectomy	Park *et al.*, 2011
Liver	Single i.p. dose of recombinant IL-22 (1 μg·g^{-1})	Protection from liver injury after chronic alcohol feeding	Ki *et al.*, 2010
Liver	Daily i.p. doses of recombinant IL-22 (300 μg·kg^{-1}) for 36 days; in *ob/ob* mice daily s.c. doses of recombinant IL-22 (500 μg·kg^{-1}) for 14–40 days	Protection from high fat diet-induced steatosis	Yang *et al.*, 2010
Liver	*In vivo* IL-22 cDNA delivery	Protection from ConA-, carbon tetrachloride-, and Fas-induced liver damage	Pan *et al.*, 2004
Liver	Single i.v. dose of recombinant IL-22 (0.25 μg·g^{-1})	Protection from ConA-induced liver damage	Radaeva *et al.*, 2004
Intestinal tract, liver, spleen	Repeated i.p. doses of recombinant IL-22 (25 μg per mouse, every other day starting on day 0)	Protection from systemic translocation of commensal intestinal bacteria in the context of impaired innate lymphoid cell function	Sonnenberg *et al.*, 2012
Intestinal tract	Repeated i.p. doses of recombinant IL-22-Fc fusion protein (0.05 mg per mouse) on days 0, 3, and 6	Protection from severe DSS-induced colitis	Cox *et al.*, 2012
Intestinal tract	*In vivo* delivery of an IL-22-expressing plasmid	Protection from severe infection by *Citrobacter rodentium*	Qiu *et al.*, 2012
Intestinal tract	*In vivo* delivery of an IL-22-expressing plasmid	Protection from severe infection by *Citrobacter rodentium*	Tumanov *et al.*, 2011
Intestinal tract	*In vivo* delivery of an IL-22-expressing plasmid	Protection from Th2-mediated colitis in the TCRα-KO model	Sugimoto *et al.*, 2008
Pancreas	*In vivo* delivery of adenovirus-IL-22; single i.p. dose of recombinant IL-22 (1 μg·g^{-1}); IL-22 transgenic mice	Attenuation of cerulein-induced pancreatitis	Feng *et al.*, 2012
Pancreas	Single i.p. dose of recombinant IL-22 (200 ng per mouse) 24 h after onset of pancreatitis	Protection from pancreatitis induced by either cerulein or choline-deficient diet supplemented with DL-ethionine	Xue *et al.*, 2012

ConA, concanavalin A; DSS, dextran sulfate sodium; OVA, ovalbumin; TCRα; T-cell receptor α-chain.

receptor α-chain knockout mice (Sugimoto *et al.*, 2008). Moreover, a recombinant IL-22-Fc fusion protein was protective in experimental colitis provoked by dextran sulphate sodium-induced epithelial injury (Cox *et al.*, 2012). Finally, administration of IL-22 protected mice from systemic translocation of intestinal commensal bacteria in the context of an impaired innate lymphoid cell function (Sonnenberg *et al.*, 2012). Those latter data indicate the potential of IL-22 administration as a prophylactic strategy to strengthen the intestinal barrier in patients at risk for developing microbial translocation, among others HIV-infected patients (Brenchley *et al.*, 2006). In fact, mucosal IL-22 production is impaired upon HIV infection and recombinant IL-22 can counteract gut epithelial damage induced by the virus in an *in vitro* model (Kim *et al.*, 2012).

Restrictions of IL-22 usage for tissue-protective therapy

Besides activation of the hepatic acute phase response, administration of recombinant IL-22 to healthy mice, either of BALB/c or C57Bl/6 background, in doses of up to 8 μg per animal did not evoke signs of acute systemic immunoactivation as determined by analysis of serum IL-1β, TNF-α and IL-6 (Wolk *et al.*, 2004; Scheiermann *et al.*, 2013). Moreover, IL-22 treatment of mice undergoing fulminant endotoxaemia failed to reduce production of these inflammatory cytokines. This observation would exclude the possibility of rapid immunosuppression by IL-22 (Scheiermann *et al.*, 2013), a regulatory function supposed to be characteristic for the related anti-inflammatory cytokine IL-10 (Ouyang *et al.*, 2011). Data concur with the notion that IL-22, in contrast to the related cytokines IL-10 and IL-6, does not directly affect leukocyte biology. Taken together, current preclinical observations would suggest the up-regulation of IL-22 bioactivity, for example, by administration of recombinant protein, as a promising, acutely well-tolerated and innovative pharmacological approach targeting pathogenic processes driven by epithelial injury and/or fibrosis. However, there are specific drawbacks that may rule out the long-term application of IL-22.

One particular concern is the inherent capacity of IL-22 to amplify specific aspects of ongoing autoimmune inflammation. This latent pro-inflammatory property of IL-22 is actually considered to contribute to the pathogenesis of rheumatoid arthritis and psoriasis (Pan *et al.*, 2013), two prototypic chronic inflammatory diseases. Not only is production of IL-22 increased in rheumatoid arthritis and psoriasis patients, but it also correlates with disease severity (Boniface *et al.*, 2007; Leipe *et al.*, 2011; Nakajima *et al.*, 2011). Notably, IL-22-knockout mice exhibit striking attenuation of collagen-induced arthritis (Geboes *et al.*, 2009). Synovial fibroblasts in the arthritic joint are regarded as crucial cellular targets of IL-22, which, probably via STAT3, drives proliferation of this cell type (Ikeuchi *et al.*, 2005). Thus, the IL-22/STAT3 pathway may contribute to the transformed-like character of synovial fibroblasts, which has been proposed to drive disease progression in rheumatoid arthritis. (Muller-Ladner *et al.*, 1995; Aidinis *et al.*, 2003). Besides that, activation of synovial fibroblasts by IL-22 up-regulates expression of the chemokine CCL2 (Ikeuchi *et al.*, 2005) and of receptor activator of NF-κB ligand (KW Kim *et al.*, 2012), which serve pro-inflammatory and joint destructive functions, respectively. Reduction of IL-22 bioactivity likewise reduces severity in experimental psoriasis (Van Belle *et al.*, 2012), an observation that also agrees with psoriasis-like symptoms evolving in IL-22 transgenic mice (Wolk *et al.*, 2009; Park *et al.*, 2011). Keratinocytes are obvious targets of IL-22 in psoriasis. IL-22 modulated differentiation of keratinocytes and mediated keratinocyte expression of key inflammatory parameters, among others CXCL5, IL-20 and matrix metalloproteinases-1 and -3 (Boniface *et al.*, 2005; Nograles *et al.*, 2008; Sabat and Wolk, 2011). As already alluded to, under the influence of type I IFN, IL-22 significantly activates the pro-inflammatory transcription factor STAT1 (Bachmann *et al.*, 2013), which obviously should amplify its pro-inflammatory potential (Paludan, 2000). Notably, there is up-regulation of IFN-β in the inflamed synovium of patients with rheumatoid arthritis (van Holten *et al.*, 2005). Altogether, it is tempting to speculate that reduction of IL-22 biological activity by neutralizing antibodies, IL-22BP or antagonistic IL-22 muteins (Niv-Spector *et al.*, 2012) would reduce signs of inflammation and disease severity in psoriasis and rheumatoid arthritis patients. The development of antagonistic IL-22 muteins (Niv-Spector *et al.*, 2012) is particularly promising, for instance, in psoriasis. These artificial analogues of IL-22, generated by introduction of mutations, are able to bind to IL-22 receptor chain-1 with high affinity, but because they do not also recruit the IL-10 receptor chain-2, are unable to initiate IL-22 signal transduction. Because IL-20 and IL-24, at least partly, signal likewise via the IL-22 receptor chain-1 (Commins *et al.*, 2008), those IL-22 muteins should inhibit not only IL-22, but also the biological activity of IL-20 and IL-24. Notably, along with IL-22, IL-20 and IL-24 may play a key role in the pathogenesis of psoriasis (Sa *et al.*, 2007; Sabat and Wolk, 2011; Wang *et al.*, 2012a).

It should also be mentioned at this point that IL-22 may aggravate tissue inflammation in some types of viral infections. Specifically, IL-22 has been shown to serve pathogenic functions in experimental hepatitis B virus infection (Y Zhang *et al.*, 2011b) and murine West Nile virus encephalitis (P Wang *et al.*, 2012b). In both viral infections, IL-22 increases expression of local chemokines such as CXCL1, CXCL9 and CXCL10, which, via recruitment of leukocytes into liver or CNS, may potentiate collateral tissue damage and associated pathogenic inflammation. Notably, these observations contrast with the role of IL-22 in influenza A virus infection where tissue protection at the lung epithelium is the predominant effect (Kumar *et al.*, 2013; Paget *et al.*, 2012). On the whole, it must be concluded that in some pathogenic conditions, the latent pro-inflammatory potential of IL-22 conflicts with its tissue protective potential. The actual outcome, in such conditions, of IL-22 treatment might then be determined by context-specific parameters.

Further reservation against provision of IL-22 over the longer term as a viable pharmacological strategy lies in the pronounced and well established pro-tumourigenic role of STAT3. A variety of studies have demonstrated overt activation of STAT3 in a range of human solid tumours (Yu *et al.*, 2009; Jarnicki *et al.*, 2010; Johnston and Grandis, 2011). Like-

wise, enhanced levels of IL-22 are detectable in human cancer, including non-small cell lung (Zhang *et al.*, 2008) and hepatocellular (Jiang *et al.*, 2011) carcinoma as well as gastric cancer (Zhuang *et al.*, 2012). The functional relevance of IL-22 in this context has been adequately demonstrated in experimental hepatocellular carcinoma, where IL–22-knockout mice display decreased (Jiang *et al.*, 2011) and IL-22 transgenic mice enhanced tumour formation in the diethylnitrosamine model of liver carcinogenesis (Park *et al.*, 2011). A most recent study furthermore clearly demonstrates that IL-22 promotes experimental tumourigenesis in the colon (Huber *et al.*, 2012). Taken together, the bulk of experimental and clinical data strongly suggest a pathogenic role of the IL-22/STAT3 axis in carcinogenesis.

Conclusion

To develop novel therapeutic strategies for the treatment of diseases driven by epithelial injury is a vital challenge of current pharmacological and translational research. Preclinical data suggest augmentation of IL-22 bioactivity, for example, by administration of the recombinant protein, as a promising and entirely novel therapeutic approach for the treatment of diverse pathogenic conditions ranging from toxic liver injury and ventilator-induced lung injury to severe infections at host/environment interfaces. It can be assumed that IL-22 is characterized by a rather short half-life in circulation. Therefore, PEGylation or ligation of IL-22 to an Fc fragment will probably be necessary for efficient use of the cytokine in clinical practice (Jazayeri and Carroll, 2008; Veronese and Mero, 2008). In fact, a phase I clinical trial aiming to assess the safety profile of an IL-22-like biopharmaceutical agent (F-652) in healthy humans has recently been initiated [Generon (Shanghai) Corporation Ltd.] 12 years after introduction of the cytokine as IL–10-related T–cell-derived factor. However, potential applications of IL-22 in clinical therapy must be carefully selected (Figure 2). Whereas

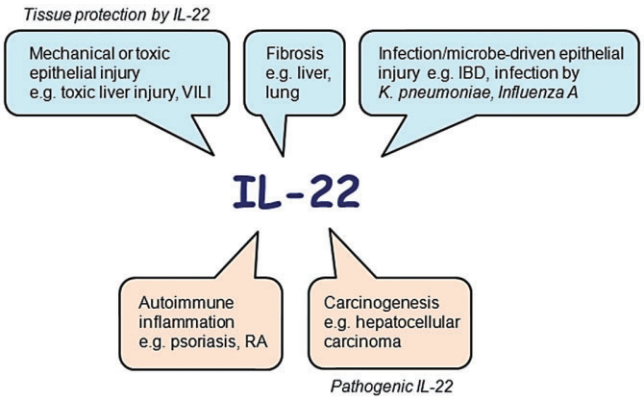

Figure 2
Summary scheme and contraposition of the protective and pathogenic properties of IL-22, expressed in a range of conditions. IBD, inflammatory bowel disease; RA, rheumatoid arthritis; VILI, ventilator-induced lung injury.

IL-22 appears highly suitable for tissue-protective therapy in acute disease, chronic application of the cytokine may pose a threat through its inherent potential to promote carcinogenesis and specific aspects of autoimmune inflammation.

Conflicts of interest

There are no conflicts of interest to declare.

Note added in proof

Most recently Sarkar *et al.* (2013) documented the capability of systemically applied recombinant IL-22 to ameliorate collagen-induced arthritis in mice. Data, at first sight, do not concur with reduced disease severity observed in the same model using IL-22 deficient mice (Geboes *et al.*, 2009) and may indicate the exciting possibility that therapeutically administered IL-22 can serve different functions as compared with the endogenously produced cytokine.

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