Therapeutic opportunities of the IL-22–IL-22R1 system

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Abstract | Interleukin-22 (IL-22) is a key effector molecule that is produced by activated T cells, including T helper 22 (T_H22) cells, T_H17 cells and T_H1 cells, as well as subsets of innate lymphoid cells. Although IL-22 can act synergistically with IL-17 or tumour necrosis factor, some important functions of IL-22 are unique to this cytokine. Data obtained over the past few years indicate that the IL-22–IL-22 receptor subunit 1 (IL-22R1) system has a high potential clinical relevance in psoriasis, ulcerative colitis, graft-versus-host disease, certain infections and tumours, as well as in liver and pancreas damage. This Review highlights current knowledge of the biology of the IL-22–IL-22R1 system, its role in inflammation, tissue protection, regeneration and antimicrobial defence, as well as the positive and potentially negative consequences of its therapeutic modulation.

IL-10 cytokine family
A group of cytokines that, in humans, comprises interleukin-10 (IL-10), IL-19, IL-20, IL-22, IL-24, IL-26 and the interferon-λ (IFNλ) species (IL-28α, IL-28β and IL-29).

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Cytokines have essential roles in cell proliferation, differentiation and mobility, as well as in defence against pathogens and tumours. Consequently, dysregulated cytokine activity leads to disorders such as chronic inflammatory diseases, disturbed wound healing, infections and cancers, and so modulating the cytokine network using either biological or small chemical agents offers therapeutic potential. One novel cytokine–cytokine receptor system that has high potential clinical relevance is the interleukin-22 (IL-22)–IL-22 receptor (IL-22R) system.

IL-22, which was discovered in 2000, is part of the IL-10 cytokine family[1–3]. Like all members of this family, IL-22 acts via a transmembrane receptor complex that consists of two different subunits: IL-22R1 and IL-10R2. Of note, IL-22R1 is also used as a receptor subunit by two further members of the IL-10 cytokine family: IL-20 and IL-24. The binding of IL-10 family members to their respective receptor complexes activates signal transduction pathways that mainly result in gene expression or repression[4,5]. A secreted single-chain receptor for IL-22 — called IL-22-binding protein (IL-22BP) — also exits, which binds to this cytokine with strong affinity and prevents its cellular effects[4,5].

IL-22 is unusual among most interleukins because it does not directly regulate the function of immune cells[6]. Rather, IL-22 targets cells at outer-body barriers, such as the skin and tissues of the digestive and respiratory systems, as well as cells of the pancreas, liver, kidney and joints. As described below, in many of these cells IL-22 induces the production of antibacterial proteins and selected chemokines. These effects of IL-22 are often amplified by cytokines such as IL-17, tumour necrosis factor (TNF) or IL-1β. In addition, IL-22 protects its target cells against damage, inhibits their differentiation and/or increases their proliferation. These effects are not shared by other cytokines. Interestingly, IL-22 also induces the expression of molecules that allow a positive feedback loop to further amplify its actions.

Knowledge of the pathogenesis of several human diseases indicates that increased antimicrobial defence, resistance against damage as well as tissue regeneration might be beneficial in some disorders. Accordantly, as discussed below, studies using mouse models have suggested that strengthening of the IL-22–IL-22R system, — for example, through the application of IL-22 — might have a beneficial impact in inflammatory bowel disease, alcoholic liver and pancreas damage, graft-versus-host disease (GvHD) and transplantation of selected organs. Conversely, the influence of IL-22R1 on differentiation and/or proliferation and inflammation might have a pathogenetic role in some disorders, such as psoriasis and selected cancers. In such situations, attenuation of the IL-22–IL-22R system might have a beneficial effect. To achieve this, targeting IL-22R1 may produce better clinical effects than IL-22 neutralization. This is because, in addition to lymphoid cell-derived IL-22, cytokines that are related to IL-22 (such as IL-20 and IL-24) are often produced in parallel by tissue and myeloid cells and mediate IL-22-like effects in an IL-22R1-dependent manner.

As IL-22 does not affect immune cells, modulation of the IL-22–IL-22R1 system might not result in some of the immune-related side effects that occur when the

activity of classical cytokines such as TNF or type I interferons (IFNs) is modulated. For example, administration of IL-22 to patients with GvHD or pancreas damage might support the protection and regeneration of tissue cells without inducing inflammation, which would otherwise aggravate the disease state. In addition, blockade of IL-22R1 in cancer could combat tumour cells without having a negative influence on the immune system, which is needed for anticancer defence.

In this Review, we first describe key features of the structure and biology of the IL-22–IL-22R1 system and then present clinical situations in which modulating its activity has potential therapeutic relevance.

IL-22

Structure of the IL-22 protein. The human *IL22* gene encodes a protein that is 179 amino acids in length. After removal of the predicted 33-amino-acid signal peptide, the cytokine is secreted as a protein that is 146 amino acids long[3,7]. The ternary structure of IL-22 (expressed in *Escherichia coli* and *Drosophila melanogaster*) was solved using crystallization and X-ray diffraction[7,8]. IL-22 has a bundle-like structure that is composed of α-helices (helices pre-A and helices A to F) and connecting loops. This structure is stabilized by two intramolecular disulphide bridge bonds. IL-22 has three potential *N*-linked glycosylation sites, two of which were glycosylated in the crystallized IL-22 expressed in insect cells[8]. Although glycosylation is associated with only minor changes in the IL-22 tertiary structure[8], the glycosylated form of the protein should be considered when generating therapeutically usable neutralizing IL-22-specific monoclonal antibodies. The biologically active form of IL-22 seems to be a monomer[7,9,10]. However, non-covalent and non-intertwining dimers and — at high concentrations of IL-22 — tetramers have also been observed[7,9].

Cellular sources of IL-22. The exact cellular sources of IL-22 in human diseases are often unknown and probably vary depending on the nature of the disease. In general, T cells and innate lymphoid cells (ILCs) are considered to be major producers of IL-22 in humans (TABLE 1). It has been known for over a decade that T helper 1 (T_H1) cells produce IL-22 (REF. 11), which is driven by IL-12. IL-22 is also secreted by T_H17 cells[12–14]. This is important because IL-17 and IL-22 have some synergistic actions, which can lead to massive amplification of their effects. Among the cytokines that promote T_H17 cell development and IL-17 expression, IL-6 and IL-23 drive IL-22 production by these cells, whereas transforming growth factor-β (TGFβ) inhibits it[15]. T cells that produce IL-22 in the absence of IFNγ, IL-17 or IL-4 secretion have also been discovered and are referred as T_H22 cells[16,17]. Additional T cells such as $CD8^+$ T cells, γδ T cells and natural killer T (NKT) cells are able to produce IL-22 upon activation, especially in the presence of IL-23 (REF. 18).

IL-22-producing ILCs in humans include NK cells[11] and subsets of novel ILCs (that is, lymphoid tissue inducer (LTi) cells and natural cytotoxicity triggering receptor (NCR)-positive ILCs)[19–26], which have recently been classified as group 3 ILCs[27] (TABLE 1). It should be noted that in mouse models of infection, group 3 ILCs are the main producers of IL-22 at early stages of inflammation, whereas T_H22 cells seem to take over this function at later stages[28,29]. In humans, IL-22 is not produced by monocytes, macrophages, dendritic cells or non-haematopoietic tissue cells[6,11,30].

Targeting IL-22. Promising approaches to inhibit the IL-22–IL-22R1 system include agents that block those chemokines that attract IL-22-producing cells into the tissue (for example, CC-chemokine ligand 20 (CCL20)) or antibodies that neutralize the mediators that support the stability and IL-22 production of these cells (such as IL-23 or TNF). Conversely, small molecules (for example, agonists of the aryl hydrocarbon receptor, such as 6-formylindolo(3,2-b)carbazole) that are able to activate the transcription factors that promote T_H22 cell and group 3 ILC differentiation or that induce IL-22 production from these cells could be used to increase the presence of IL-22, as discussed below[31].

IL-22 receptor complex

Protein structure of IL-22R subunits. IL-22R is a heterodimeric complex composed of IL-22R1 and IL-10R2 subunits[2,3,32] (FIG. 1), both of which contain an intracellular moiety, a transmembrane moiety and an extracellular moiety. The intracellular moiety of IL-22R1 is much longer than that of IL-10R2 and contains four Tyr-X-X-Gln motifs, which represent putative STAT (signal transducer and activator of transcription) recruitment sites[32]. As is typical for members of the class 2 cytokine receptor family, the extracellular moieties of IL-22R1 and IL-10R2 form two tandem domains: the amino-terminal D1 domain and the D2 domain that is positioned close to the cell membrane[33–35]. There are three putative *N*-linked glycosylation sites in the extracellular domains of IL-22R1 and four in the extracellular domains of IL-10R2.

IL-22 has a high affinity for the extracellular moiety of IL-22R1 (with a K_d (dissociation constant) value of 1–20 nM) but no affinity for the extracellular moiety of IL-10R2 (REFS 10,33,36). However, IL-10R2 has a measurable affinity for the IL-22–IL-22R1 complex (with a K_d value of 7–45 μM)[33,35,10] and for defined peptides derived from the IL-22 amino acid sequence[37]. These data suggest that the IL-22–IL-22R interaction is a multistep process, in which cytokine binding initially occurs on the IL-22R1 subunit, leading to a conformational change in the cytokine, which in turn favours the secondary binding of the IL-22–IL-22R1 complex to the IL-10R2 chain (FIG. 1). The crystal structure of the extracellular moiety of IL-22R1 bound to IL-22 showed that both partners form a complex with 1:1 stoichiometry[33,34]. The D1 and D2 domains of IL-22R1 both contain two antiparallel β-sheets comprising a total of seven β-strands that are connected by loops (including small α-helices) and adopt an interdomain angle of about 100 degrees. There are two stabilizing disulphide bonds in IL-22R1: one in the D1 domain and the other in the D2 domain. The contact site between IL-22 and IL-22R1 mainly involves

Antibacterial proteins
Small proteins that are mainly produced by epithelial cells and phagocytes; these proteins kill or inhibit the growth of bacteria using different mechanisms, including pore formation in the bacterial membrane and sequestration of metal ions that are essential for bacterial growth.

Psoriasis
A chronic disease that is characterized by red, raised, sharply demarcated, scaling skin lesions that frequently occur on the scalp, the back and the extension side of the limbs. Lesions have infiltration of immune cells in the dermis and epidermis, and a massively altered epidermis structure.

Innate lymphoid cells
(ILCs). Immune cells that are characterized by lymphoid morphology, the absence of T cell and B cell receptors and a lack of myeloid cell surface markers. Based on their cytokine production profile, they are divided into three groups: group 1 cells (which have a profile similar to T helper 1 (T_H1) cells), group 2 cells (which have a profile similar to T_H2 cells) and group 3 cells (which have a profile similar to T_H17 and T_H22 cells).

Class 2 cytokine receptor family
A group of transmembrane receptor chains with extracellular domains composed of two tandem fibronectin type III domains that have conserved cysteine residues but that do not contain the Trp-Ser-X-Trp-Ser motif that is typical of the class 1 cytokine receptor family.

Table 1 | **Major cellular sources of IL-22 in humans**

Cell type	Cell-specific surface markers	Cell-specific transcription factors	Cell-specific cytokine production	Cytokines that promote IL-22 production	Transcription factors that promote IL-22 production
T_H1 cells	$CD3^+CD4^+$	TBX21	IFNγ	IL-12	STAT4
T_H17 cells	$CD3^+CD4^+$	RORγt	IL-17, IL-26	IL-6, IL-23, IL-21, IL-1β or TNF	STAT3, RORγt, Notch, AHR
T_H22 cells	$CD3^+CD4^+$	Not determined	IL-22	IL-6, TNF	STAT3, AHR
$CD8^+$ T cells	$CD3^+CD8^+$	TBX21, STAT4, STAT5	IFNγ	IL-23	STAT3
γδ T cells	$CD3^+$γδ TCR^+	Not determined	IGF1, IL-17	IL-23	STAT3
Natural killer cells	$CD3^-CD56^+CD16^{+*}$ $CD117^-NKp46^+$	TBX21	IFNγ, (TNF, GM-CSF)‡	IL-12 (IL-2, IL-18)§	STAT4
Lymphoid tissue inducer cells	Lin^-CD117^+NKp46-	RORγt, AHR	IL-17, IL-22	IL-23	STAT3
NCR^+ $ILC3^-$ cells	$Lin^-CD117^+NKp46^+$	RORγt, TBX21, AHR, Notch	IL-22	IL-23	STAT3, TBX21, Notch

AHR, aryl hydrocarbon receptor; GM-CSF, granulocyte–macrophage colony-stimulating factor; IFNγ, interferon-γ; IGF1, insulin-like growth factor 1; IL-22, interleukin-22; IL-22R1, IL-22 receptor subunit 1; ILC3, innate lymphoid cell group 3; NCR, natural cytotoxicity triggering receptor; NKp46, natural killer cell p46-related protein; ROR, retinoic acid-related orphan receptor; STAT, signal transducer and activator of transcription; TBX21, T-box transcription factor TBX21 (also known as T-bet); TCR, T cell receptor; T_H, T helper; TNF; tumour necrosis factor. *Not on all cells. ‡Not by all cells. §Less potent than IL-12.

the AB loop and helix F of IL-22 as well as the loops L2 to L4 in D1 domain of IL-22R1. The amino acid residues Thr70, Arg73 and Lys162 of IL-22 are critical for this interaction[38]. Compared to the structure of free IL-22, deviations in the IL-22R1-bound IL-22 structure are mainly found for the helices pre-A and A as well as for the AB loop[34].

The crystal structure of the extracellular IL-10R2 moiety is similar to that of IL-22R1 (REF. 35). However, the L2 loop of the D1 domain is much shorter, which may explain why IL-22 does not directly bind to IL-10R2. Moreover, compared to IL-22R1, the L5 loop of the D2 domain forms a protruding structure in IL-10R2. Both differences give rise to pronounced clefts in IL-10R2. It was proposed that helix A (which contains a binding hotspot lying adjacent to the main IL-22R1-binding site) and helix D of IL-22 are involved in the interaction with IL-10R2. Moreover, it was determined which amino acids of IL-22 and IL-10R2 are essential for this interaction[35–38]. Interestingly, although glycosylation of IL-22 at the Asn54 residue is not important for its interaction with IL-22R1, it is important for the interaction of IL-22 with IL-10R2 (REF. 36). Based on the crystallization and mutation data, a computational model of the IL-22–IL-22R1–IL-10R2 ternary complex was generated[35]. This model also proposed a contact site between the D2 domains of IL-22R1 and IL-10R2.

Although the combination of IL-22R1 and IL-10R2 specifically mediates signalling by IL-22, both of the receptor subunits can be used by other cytokines of the IL-10 family. The IL-10R2 subunit is also part of the receptor complexes for IL-10, IL-26, IL-28 and IL-29 (REFS 4,5). However, based on the high cellular expression and low cytokine binding affinity to this receptor chain, there is no competition among these mediators for IL-10R2. Importantly, IL-22R1 is also used by IL-20 and IL-24 in a complex composed of the IL-22R1 and IL-20R2 subunits[39,40] (FIG. 1). Despite the different nature of the R2 subunit and different receptor binding kinetics, the IL-22R1–IL-20R2 complex seems to mediate signalling events and effects that are very similar to those mediated by the IL-22R complex. It should be noted that IL-20 and IL-24 can use a second receptor complex (FIG. 1), which is likely to mediate distinct effects. Therefore, blocking IL-22R1 would presumably only partially block the functions of IL-20 and IL-24.

Intracellular signals downstream of IL-22R. IL-22 primarily signals through Janus kinases (which are associated with IL-22R subunits) and STAT molecules[41] (FIG. 1). The formation of the IL-22–IL-22R1–IL-10R2 complex induces the phosphorylation and thereby activation of these tyrosine kinases, which in turn phosphorylate specific tyrosine residues in the cytoplasmic domain of IL-22R1. STAT molecules bind to the phosphorylated IL-22R1 tyrosine residues through their SRC homology 2 (SH2) domain or constitutively interact with the carboxyl terminus of IL-22R1 via their coiled-coil domains[42]. The activated Janus kinases then phosphorylate the IL-22R1-associated STAT molecules. Phosphorylation of STAT3 at the Tyr705 residue is the main event observed in IL-22-exposed primary cells, although weak activation of STAT1 and/or STAT5 has also been observed[6]. Interestingly, acetylation of Lys686 of STAT3 is required for its phosphorylation at Tyr705, and the deacetylase sirtuin 1 (which counteracts this acetylation) inhibits IL-22-induced STAT3 activation and cellular effects[43–45]. These modifications to the STAT molecules enable their dimerization and translocation into the nucleus, where they regulate the expression of their target genes. In addition, the activation of one or more major mitogen-activated protein kinase (MAPK) pathways and the phosphoinositide 3-kinase (PI3K)–AKT–mammalian target of rapamycin (mTOR) pathway has been observed after cellular IL-22 stimulation[41,46–50] (FIG. 1).

Janus kinases
A group of tyrosine kinases (JAK1, JAK2, JAK3 and TYK2) that are associated with the intracellular domains of the class I and class II family of cytokine receptors. By initiating phosphorylation steps, they transduce the signal that is generated from a receptor complex (following the binding of the cytokine to the receptor) to intracellular signal transducer and activator of transcription (STAT) molecules.

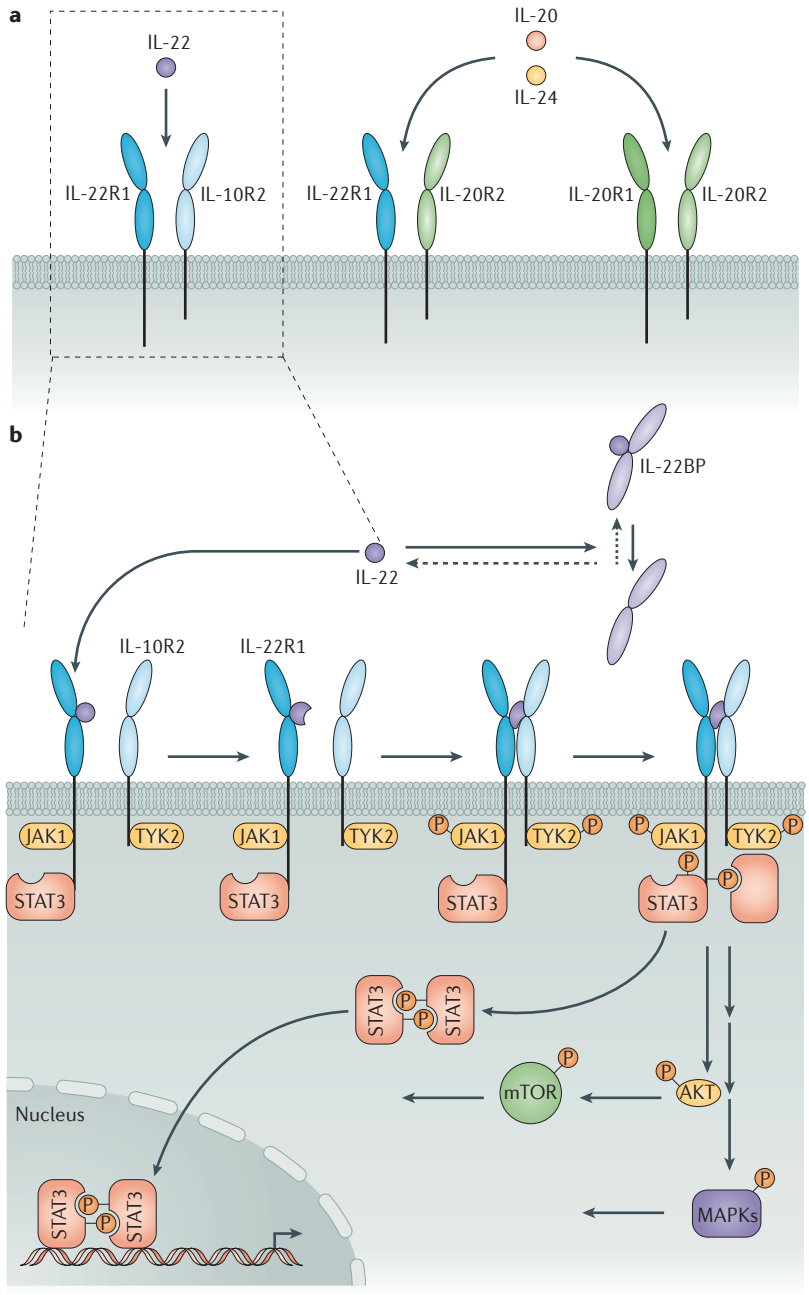

Figure 1 | **IL-22–IL-22R1 system and downstream signalling events. a** | Interleukin-22 (IL-22) mediates its cellular effects via a heterodimeric receptor complex composed of IL-22 receptor subunit 1 (IL-22R1) and IL-10R2. The components of the heterodimeric IL-22R complex are also used by other cytokines of the IL-10 family. IL-10R2 also mediates the effects of IL-10 (in a complex with IL-10R1) and IL-26 (in a complex with IL-20R1), as well as IL-28A, IL-28B and IL-29 (in a complex with IL-28R1; not shown). IL-22R1, which is only expressed by specific cell types, can also associate with IL-20R2 to form one of the receptor complexes for IL-20 and IL-24. IL-20 and IL-24 use a second receptor complex that is composed of IL-20R1 and IL-20R2. **b** | The binding of IL-22 to its receptor complex takes place in two steps. First, IL-22 binds to its high-affinity receptor subunit, IL-22R1. This induces a conformational change in the IL-22 protein that confers enough affinity to allow the protein to bind secondarily to the IL-10R2 subunit. IL-10R2 then stabilizes the association of IL-22 with IL-22R1. The cytoplasmic parts of IL-22R1 and IL-10R2 are associated with the kinases Janus kinase 1 (JAK1) and tyrosine kinase 2 (TYK2), respectively. The formation of the IL-22–IL22R1–IL-10R complex induces the phosphorylation of JAK1 and TYK2, which in turn phosphorylate four specific tyrosine residues in the cytoplasmic domain of IL-22R1. These residues become binding sites for the SRC homology 2 (SH2) domains of signal transducer and activator of transcription (STAT) molecules. Furthermore, IL-22R1 can be pre-associated with STAT3 as a result of a tyrosine-independent recruitment. Receptor-bound STAT molecules are then phosphorylated by the JAKs. This enables the dimerization and translocation of STATs into the nucleus, where they bind to responsive elements and regulate the expression of their target genes. STAT3 has a major role in these events; STAT1 and STAT5 can be involved but this is cell-type dependent. In addition to the JAK–STAT pathway, the activation of mitogen-activated protein kinase (MAPK) pathways (which leads to phosphorylation of extracellular signal-regulated kinase 1 (ERK1), ERK2, JUN N-terminal kinase (JNK) and p38 MAPK) can occur, as well as pathways including the activation of phosphoinositide 3-kinase (PI3K), AKT and mammalian target of rapamycin (mTOR). IL-22 can also bind to a secreted, single-chain receptor — IL-22 binding protein (IL-22BP) — which acts as a natural inhibitor of IL-22 activity.

IL-22R-bearing cells. As the R2 subunit of the IL-22R complex (IL-10R2) is ubiquitously expressed in the human body[6], the expression of IL-22R1 determines cellular sensitivity towards IL-22. Unexpectedly, monocytes, B cells, T cells, NK cells, monocyte-derived macrophages as well as immature and mature dendritic cells do not express IL-22R1 (REFS 6,11,30). It is now well established that immune cells are not the target cells of IL-22. Instead, IL-22R1 is expressed by a few types of tissue cells in organs that mainly build up the outer-body barriers: that is, the respiratory system (for example, the trachea and lungs), the gastrointestinal system (for example, the stomach, small intestines and colon) and the skin. IL-22 is also expressed by tissue cells in the liver, the pancreas and the kidney[6].

IL-22 acts on bronchial epithelial cells in the lung[51,52], whereas both epithelial cells[53] and subepithelial myofibroblasts[46] respond to IL-22 stimulation in the intestines. In the skin, keratinocytes are the main IL-22-responsive cells, although dermal fibroblasts also express limited levels of IL-22R1 (REF. 54). Melanocytes, dermal endothelial cells and subcutaneous adipocytes do not express IL-22 and are not responsive to this cytokine[54]. Interestingly, IFNγ and TNF were able to upregulate IL-22R1 expression in both keratinocytes and dermal fibroblasts, which suggests that the presence of these cytokines during inflammation may amplify the actions of IL-22 (REFS 6,54). In the pancreas, IL-22 acts on acinar cells[55] and possibly islet β-cells[56]. Further target cells include hepatocytes[2],

thymic epithelial cells[57] and specific tissue-resident stem cells[58,59]; tissue-resident stem cells probably contribute to the strong protective properties of IL-22 against damage in selected tissues (see below).

Targeting IL-22R. Options for targeting IL-22R activity first include monoclonal antibodies against the high-affinity subunit IL-22R1 or antagonistic recombinant mutant proteins that bind to IL-22R1 but not to IL-10R2 or IL-20R2. Such IL-22R1-blocking strategies would prevent not only the effects of IL-22 but also the IL-22R1-dependent (that is, IL-22-like) effects of IL-20 and IL-24 (see below). Additionally, therapeutic inhibition of IL-22R downstream signalling is feasible using small molecules that directly or indirectly block the activity of STAT3, albeit this is a less specific approach.

IL-22 binding protein

IL-22BP is a 210-amino-acid-long, secreted (that is, soluble), single-chain IL-22R that is encoded by an IL-22R1-independent gene[60–65]. The binding of IL-22 to IL-22BP prevents the interaction of IL-22 with its transmembrane receptor complex and so inhibits its effects. The affinity between IL-22 and IL-22BP is 20- to 1,000-fold higher than that between IL-22 and IL-22R1 (REFS 10,66). The low dissociation rate indicates that IL-22–IL-22BP complexes are highly stable. The three-dimensional structure of IL-22BP bound to IL-22 shows that the surfaces involved in the binding of IL-22 to IL-22BP overlap with those involved in the binding of IL-22 to IL-22R1 (REFS 38,67), which is consistent with the inhibitory action of IL-22BP.

IL-22BP is expressed on immature dendritic cells, and its level of expression decreases as the cells mature[68–70]. Normal tissues from the lymphatic organs (that is, the thymus, spleen and lymph nodes) as well as the gastrointestinal system (that is, the stomach and intestines), lungs, skin and female reproductive system (that is, the placenta and breast) express IL-22BP[60–62,65]. During acute inflammation, which is usually associated with increased IL-22 levels, tissue IL-22BP expression is downregulated[53,66,68]. However, IL-22BP expression is increased in the liver of mice at later time points after infection with *Toxoplasma gondii*, *Schistosoma mansoni* and *Mycobacterium avium*[71]. These changes in IL-22BP expression are consistent with the biology of dendritic cells. Immature dendritic cells reside in undisturbed tissues. During acute inflammation, these cells become activated, mature and leave the tissue. By contrast, there are increased levels of dysregulated dendritic cells in chronically inflamed tissues[173].

The fact that IL-22 is the only member of the IL-10 family that has an extra binding protein underpins the need to fine-tune IL-22 activity. In addition to inhibiting local actions of IL-22, IL-22BP might — to some extent — support the stabilization and systemic dissemination of this cytokine. This hypothesis is supported by the observation that IL-22 is one of the very few cytokines that are clearly detectable in the plasma following local tissue inflammation[48,66].

Effects of IL-22

IL-22 has important effects on epithelial cells, pancreatic cells and hepatocytes. Moreover, IL-22-mediated effects have been described for specific types of fibroblasts and stem cells (FIG. 2).

Epithelial cells. IL-22 regulates the expression of several genes in epithelial cells of the skin, gut and respiratory tract[28,48,52]. The effects of IL-22 on these cells can be arranged into five functional groups: IL-22 increases the innate defence mechanisms; it inhibits cellular differentiation or increases proliferation; it induces the production of specific chemokines; it promotes cellular mobility; and it induces the expression of extracellular and intracellular molecules that amplify the actions of IL-22.

The human skin, gut and respiratory tract are colonized by 1×10^{14} bacteria. Different innate mechanisms such as antibacterial proteins and mucus have an essential role in preventing and limiting the propagation of these bacteria[72]. The spectrum of antibacterial proteins differs according to the complexity of respective microbiota in different areas of the body. IL-22 induces the expression of β-defensin 2 (BD2) in keratinocytes, intestinal epithelial cells and bronchial epithelial cells; BD3 in keratinocytes; S100A7 in keratinocytes and bronchial epithelial cells; S100A8 and S100A9 in keratinocytes and intestinal epithelial cells; S100A12 in bronchial epithelial cells; regenerating islet-derived protein (REG) family members (including REG3β, REG3γ and REG1α) in intestinal epithelial cells; and lipocalin 2 in keratinocytes and tracheal epithelial cells[6,28,48,52,73,74]. IL-22 also induces the production of several mucus-associated proteins, such as mucin 1 (MUC1) in colonic epithelial cells and tracheal epithelial cells, and MUC3, MUC10 and MUC13 in colonic epithelial cells[52,53].

The differentiation of epithelial cells, particularly in the skin, is necessary for the formation of a functional barrier against the external environment[75] (BOX 1). IL-22 strongly reduces the expression of proteins that are crucial for the different steps of keratinocyte differentiation, such as keratin 1 (KRT1), KRT10, profilaggrin, involucrin, loricrin, kallikrein 7, desmocollin 1 and the late cornified envelope protein 1B[48,54,76]. In line with these molecular changes, IL-22 induces acanthosis, parakeratosis and hypogranularity in three-dimensional epidermis models[54,77]. These same features were found in newborn transgenic mice overexpressing IL-22 (REF. 54). Interestingly, whereas other T cell cytokines such as IFNγ and IL-17 also induce the expression of antibacterial proteins, only IL-22 impairs keratinocyte differentiation[54]. However, IL-22-mediated impairment of differentiation is further diminished by TNF, which may be mediated indirectly via TNF-induced enhancement of IL-22R subunit and STAT3 expression[54]. In addition, IL-22 inhibits the differentiation of epithelial cells from the respiratory tract and the gut[78], and enhances their proliferation — an effect that was not seen in keratinocytes.

IL-22 also influences the production of specific chemokines in epithelial cells. In keratinocytes it increases the expression of neutrophilic granulocyte-attracting chemokines (that is, CXC-chemokine ligand 1

Mucus-associated proteins
A family of macromolecules composed of a central protein that is highly glycosylated. Glycosylation is associated with a very high water-binding capacity and protection from proteolysis. These molecules are produced by cells of the respiratory and intestinal tracts, where they form the mucus that protects the epithelial layer.

Acanthosis
Thickening of the stratum spinosum layer of the epidermis.

Parakeratosis
The presence of remnants of the cell nucleus in the epidermal stratum corneum, caused by dysfunction of the keratinocyte cornification process.

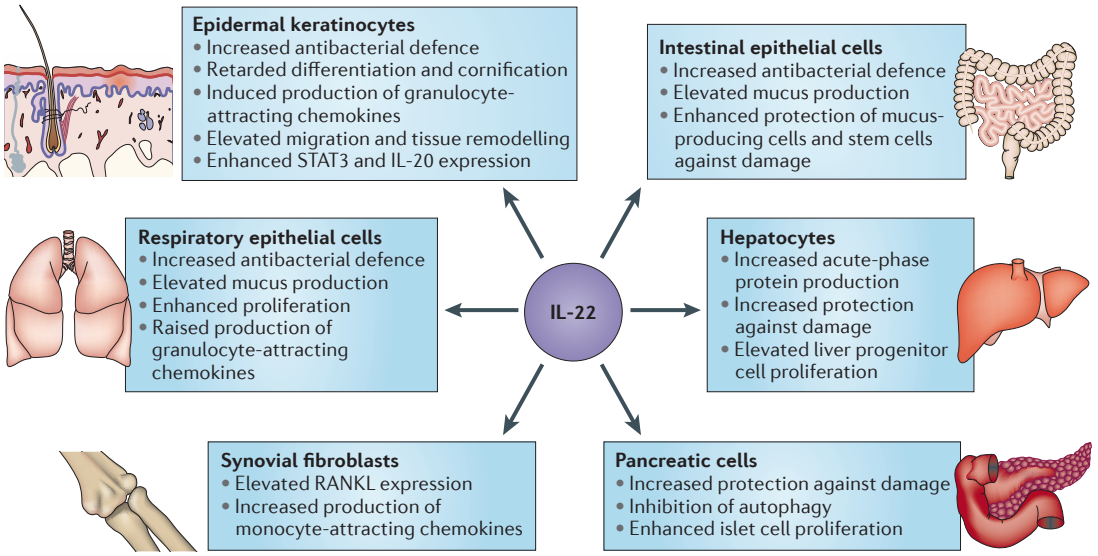

Figure 2 | **Key effects of IL-22.** Interleukin-22 (IL-22) mainly acts on epithelial cells of various organs, pancreatic cells and liver cells, as well as some fibroblast populations. This leads to changes in the expression of a few — albeit highly disease-relevant — genes. In epithelial cells, IL-22 increases the production of antibacterial binding proteins (such as β-defensin 2 (BD2), BD3, S100A7, S100A8, S100A9 and lipocalin 2 (LCN2)), matrix metalloproteinases (such as matrix metalloproteinase 1 (MMP1) and MMP3) and granulocyte-attracting chemokines (such as CXC-chemokine ligand 1 (CXCL1), CXCL5 and CXCL8). In epithelial cells of the skin, IL-22 also retards the expression of proteins that are necessary for epithelial cell differentiation, such as keratin 1 (KRT1), KRT10, profilaggrin, involucrin and desmocollin 1. In colonic and respiratory epithelial cells, IL-22 further enhances the production of mucus-associated proteins (for example, mucin 1 (MUC1)). In hepatocytes and pancreatic cells, IL-22 increases the expression of anti-apoptotic proteins (such as B cell lymphoma 2 (BCL-2), BCL-X_L and myeloid cell leukaemia sequence 1 (MCL1)), mitogenic proteins (such as retinoblastoma-like protein 2, cyclin D1, p21 and cyclin-dependent kinase 4), as well as regenerative and antibacterial proteins (such as regenerating islet-derived protein 3β (REG3β)). Furthermore, in hepatocytes IL-22 induces the production of acute-phase proteins (such as haptoglobin, lipopolysaccharide-binding protein and serum amyloid A). In synovial fibroblasts from patients with rheumatoid arthritis, IL-22 elevates the production of monocyte-attracting chemokines such as CC-chemokine ligand 2 (CCL2) and the expression of receptor activator of NF-κB ligand (RANKL), which favours the differentiation of monocytes into osteoclasts. Of note, IL-22 does not influence the function of resting or activated immune cells. STAT3, signal transducer and activator of transcription 3.

(CXCL1), CXCL2, CXCL5 and CXCL8), whereas it decreases the expression of the T_H17 cell- and T_H2 cell-attracting chemokine CCL22 (REF. 54). CXCL5 was also induced by IL-22 in tracheal epithelial cells[52], and IL-22 prevented CCL17 production induced by inflammatory stimuli in murine Clara cells of the bronchioles[79].

The enhanced migratory capacity of epithelial cells is especially important for epithelial repair and is facilitated by IL-22 through increased expression of the extracellular matrix (ECM)-degrading enzymes matrix metalloproteinase 1 (MMP1) and MMP3 (REFS 48,76).

Finally, the effects of IL-22 on epithelial cells include an increase in the expression of STAT3 and IL-20, which amplify the actions of IL-22 through a positive feedback loop[54,80]. The effects observed so far of IL-20 on keratinocytes are similar to those of IL-22 and are probably also mediated by IL-22R1. Neutralization of endogenous IL-20 production following IL-22 stimulation partially diminished some of the IL-22-mediated effects at a later time point[80]. This indicates the existence of a cascade, in which a T cell or ILC cytokine (that is, IL-22) induces a second mediator (that is, IL-20) in tissue cells, which then strengthens and/or prolongs the action of the initiating mediator; this could have an important role in the maintenance of chronic inflammatory diseases.

As well as affecting epithelial cells of the outer-body barriers, IL-22 acts on thymic epithelial cells. In these cells, IL-22 promotes survival and proliferation[57], which is important for T cell renewal after stress and infection.

Pancreatic cells. The pancreas has the highest levels of IL-22R1 expression among human tissues, which suggests that IL-22 has important actions in this organ; however, only a few of the IL-22-mediated effects on the pancreas are known and these mainly relate to the acinar cells. In these cells, IL-22 induces the production of the antimicrobial and regenerative proteins REG3β and REG3γ as well as osteopontin[55,81]. Furthermore, in these cells IL-22 directly upregulates the expression of B cell lymphoma 2 (BCL-2) and BCL-X_L — two proteins that bind to beclin 1 to inhibit autophagy and also have anti-apoptotic functions[82]. IL-22R1 might also be expressed by pancreatic islet cells[56]. It has recently been proposed that IL-22 induces REG1 and REG2 expression and proliferation in these cells[83].

Box 1 | **Skin structure and keratinocyte differentiation**

The skin is composed of the constantly renewing epidermis, which forms a direct barrier to the environment, and the dermis, which is responsible for the nutrition of the epidermis and lies on the subcutaneous adipose layer (FIG. 3). In the epidermis of healthy skin, the proliferation of epidermal stem cells is limited to those in the lowest layer — the stratum basale. Stem cell mitosis generates one further proliferating cell and one cell that loses its ability to adhere to the basement membrane and finally becomes a corneocyte as part of the upper stratum corneum. In this way, keratinocytes undergo a differentiation process that begins in the stratum spinosum with the inhibition of the expression of basal cell keratins (that is, KRT5, KRT14 and KRT15) and the production of the keratins KRT1 and KRT10. Subsequently, the cell starts synthesizing several additional proteins, including profilaggrin. Profilaggrin is first stored in cellular granules (which are characteristic for the stratum granulare) before being proteolytically processed. This process provides the amino-terminal peptide and several copies of filaggrin, which bundles KRT1 and KRT10 filaments into macrofibrils, leading to a flattened cell shape. Further proteins (including involucrin and loricrin) are synthesized and use transglutaminase 3 to covalently and irreversibly associate with the keratin–filaggrin aggregations. The resulting cornified envelope replaces the cytoplasmic membrane. Furthermore, lipids are synthesized and extruded into the extracellular space, where they are processed. After the dissolution of the cell nuclei — a process that is supported by the profilaggrin-derived N-terminal peptide — the final corneocytes lie in a lipid matrix and are tightly attached to each other by corneodesmosomes. In the uppermost stratum corneum, corneodesmosomal proteins are cleaved again by proteases of the kallikrein and cathepsin families to allow physiological desquamation.

Acute-phase proteins
Plasma proteins, levels of which increase (positive acute-phase proteins) or decrease (negative acute-phase proteins) during infection or inflammation owing to altered secretion — mostly by hepatocytes — in response to circulating cytokines.

Rheumatoid arthritis
A systemic autoimmune disease with a relapsing progressive course that begins with synovitis and leads to arthritis, tendovaginitis and substantial loss of function of affected joints.

Hepatitis
A group of liver disorders characterized by inflammation and the presence of immune cells within the organ. The persistent inflammation and immune cell attack on hepatocytes leads to hepatocyte injury, fibrosis and consequent loss of liver function.

Pancreatitis
A disorder of the pancreas that is characterized by intrapancreatic activation of digestive enzymes, immune cell infiltration and progressive destruction of the exocrine — and eventually also endocrine — tissue of this organ.

Hepatocytes. Hepatocytes are important target cells of the actions of IL-22 on the liver. Some of the effects mediated by IL-22 on these cells have been described in detail. The first type is the IL-22-induced production of acute-phase proteins, including serum amyloid A, α1-antichymotrypsin, haptoglobin and lipopolysaccharide (LPS)-binding protein[2,6,66,84,85]. Accordingly, administration of IL-22 to mice elevates levels of acute-phase proteins in the blood within a few hours[2,6,85]. IL-22 also further enhances the production of acute-phase proteins that are induced by inflammatory stimuli such as IL-6, TNF or LPS[6,66]. The second type of IL-22-mediated effects leads to cell protection against damage. IL-22 induces the expression of several anti-apoptotic proteins (such as BCL-2, BCL-X_L and myeloid cell leukaemia sequence 1 (MCL1)) and mitogenic proteins (such as retinoblastoma-like protein 2, cyclin D1, p21 and cyclin-dependent kinase 4 (CDK4)) and enhances cellular proliferation during serum starvation[86,87] (which is an *in vitro* model of cell stress) but not under normal growth conditions[66,88]. Furthermore, IL-22 elevates the hepatic expression of the antioxidants metallothionein 1 and metallothionein 2 (REFS 87,89). IL-22 also acts on liver stem/progenitor cells, which are especially important for regeneration in chronic or severe liver injury and are able to generate hepatocytes and biliary epithelial cells. In liver stem/progenitor cells, IL-22 induces the expression of BCL-2, BCL-X_L and cyclin D, and it increases their proliferation in a STAT3-dependent manner[59].

Fibroblasts. A few reports have also documented the effects of IL-22 on fibroblasts or their derivatives from the skin, colon and arthritic joints. In synovial fibroblasts from patients with rheumatoid arthritis, high concentrations of IL-22 increased proliferation and elevated the production of the monocyte-attracting chemokine CCL2 (REF. 47). Furthermore, IL-22 induced the expression of receptor activator of NF-κB ligand (RANKL; also known as CD254), which binds to RANK on monocytes and leads to their differentiation into bone-degrading osteoclasts[90].

In contrast to synovial fibroblasts, IL-22 did not influence the proliferation of human colonic subepithelial myofibroblasts[46] or mouse lung fibroblasts[91]. In human colonic subepithelial myofibroblasts, high concentrations of IL-22 alter the expression of several genes involved in cellular mobility (upregulation of MMP1, MMP3 and MMP9), signal transduction (downregulation of peroxisome proliferator-activated receptor-γ (PPARγ) and interferon regulatory factor 1 (IRF1)), metabolism (upregulation of stanniocalcin), growth (by upregulating amphiregulin and leukaemia inhibitory factor) and inflammation. Interestingly, it has been shown that IL-22 simultaneously upregulates the expression of anti-inflammatory or protective mediators (such as follistatin and IL-11) as well as inflammatory mediators (such as IL-6, CCL7, CXCL1, CXCL2, CXCL3, CXCL6 and CXCL8) in human colonic subepithelial myofibroblasts[46]. Furthermore, IL-22 has been described to enhance the expression of ECM proteins in some studies (carried out on murine dermal fibroblasts)[92] but not in others (carried out on human colonic myofibroblasts)[46].

Role of the IL-22–IL-22R1 system in diseases

Disorders in which the IL-22–IL-22R1 system appears to be important include chronic inflammatory diseases of the skin, intestines, lungs and joints as well as chronic infections, hepatitis, pancreatitis and cancer.

Inflammatory skin disorders

Psoriasis. Psoriasis was the first disorder that was associated with dysregulated IL-22 production[6], showing that the primarily regenerative role of IL-22 can become pathogenetic. The skin alterations observed in psoriasis are caused by the inflammation-induced hyperproliferation and impaired differentiation of keratinocytes. Although psoriasis results in a disturbed epidermal barrier, lesional psoriatic skin remains highly resistant to bacterial and viral keratinocytes[93,94].

IL-22 is highly expressed in lesional skin but not in non-lesional psoriatic skin or in the skin of healthy individuals[6]. In lesions, IL-22 is mainly produced by dermal $CD4^+$ cells and here in roughly equal amounts by T_H22 cells, T_H1 cells and $T_H17$cells[95]. In contrast to other T_H cell cytokines that are overexpressed in lesional skin (including IFNγ and IL-17A), IL-22 is increased in the blood of patients with psoriasis, and its levels strongly correlate with disease severity[48].

The IL-22-induced alterations to normal keratinocytes (as discussed above) are very similar to the alterations seen in keratinocytes from psoriatic lesions (FIG. 3). For example, IL-22-induced inhibition of the terminal differentiation of keratinocytes is in line with the strongly

altered epidermis structure observed in psoriasis[54,76,77]. The IL-22-induced production of granulocyte-attracting chemokines by keratinocytes may contribute to the accumulation of neutrophilic granulocytes observed in psoriatic lesions[54]. Moreover, the strong potential of IL-22 to induce the production of several antibacterial proteins in keratinocytes mirrors the large antibacterial competence observed in psoriasis[6,48,76,96]. Finally, IL-20 and STAT3, which mediate the positive feedback loop that amplifies the actions of IL-22, are highly expressed in lesional psoriatic skin[54,97,98]. Accordingly, there was a positive correlation between IL-22 levels and IL-20 levels in psoriatic lesions[80].

Although IL-17 does not share or amplify the effects of IL-22 on keratinocyte differentiation, it cooperates with IL-22 to induce the production of soluble molecules such as chemokines, antibacterial proteins and cytokines[12,54]. As mentioned above, the effects of IL-22 on keratinocytes can also be strengthened by TNF[54].

Several studies in mice further emphasize the pathogenetic role of IL-22 in the skin alterations that are seen in psoriasis[14,54,99–101]. In IL-22-transgenic mice that overproduce this cytokine, the epidermis exhibits acanthosis, loss of granularity and parakeratosis[54]. In addition, studies of IL-22-deficient mice have shown that IL-22 is an essential mediator of epidermal acanthosis and skin infiltration of neutrophilic granulocytes induced by the repeated intradermal application of IL-23 (REF. 14). In another mouse model of psoriasis (induced by the adoptive transfer of $CD4^+$ naive T cells into pathogen-free severe combined immunodeficient (*scid*/*scid*) mice), neutralization of endogenous IL-22 led to reduced skin alterations[99]. Last, in mice receiving daily applications of the Toll-like receptor 7 (TLR7) and TLR8 antagonist imiquimod, skin alterations — including macroscopic changes, the expression of chemokines and S100 protein as well as neutrophil infiltration — were strongly reduced in IL-22-deficient mice or in mice treated with neutralizing IL-22-specific antibodies[100].

TNF-neutralizing biologics (such as adalimumab (Humira; AbbVie) and etanercept (Enbrel; Amgen/Pfizer)) have led to an immense improvement in psoriasis therapy. Interestingly, TNF blockers are associated with an early reduction in the expression of IL-22 and its target molecules — such as IL-20 and BD2 — in psoriatic lesions[102]. TNF seems to be important for the differentiation of T_H17 cells and T_H22 cells, for the infiltration of IL-22-producing T_H1 cells, T_H17 cells and T_H22 cells into the skin and, as mentioned above, for the extent of the IL-22-mediated effects on keratinocytes[16,54]. However, targeting the IL-22–IL-22R system itself would be a more specific therapeutic intervention, as it is not anticipated to induce major side effects, especially because immune cells are not responsive to IL-22.

The targeting of IL-22R1 in psoriasis appears to be, by far, more promising than the targeting of IL-22, because blocking IL-22R1 would be expected to simultaneously block the actions of IL-20 and IL-24, both of which are strongly expressed in psoriatic lesions[97,98]. These cytokines induce IL-22-like effects on keratinocytes *in vitro* and in respective transgenic mice, and IL-20 was demonstrated to have a crucial role in the induction and maintenance of disease in the human skin xenograft model of psoriasis[54,77,103–105].

Atopic dermatitis. IL-22 is also highly expressed in the affected skin of patients suffering from atopic dermatitis[6]. Chronic forms of the disease are characterized by a conversion of the immune response from one that is initially T_H2 cell-dominated to one that is T_H1 cell-, T_H22 cell- and T_H2 cell-dominated. In contrast to psoriasis, the expression of IL-22 in atopic dermatitis is mainly derived from T_H22 cells and from IL-22-producing $CD8^+$ cells[95]. A high percentage of circulating T_H22 cells and IL-22-producing $CD8^+$ T cells from patients with atopic dermatitis can co-express IL-13 (REF. 106). The absence of mediators (particularly IL-17) that would otherwise cooperate with IL-22 to produce antibacterial proteins leads to frequent cutaneous infections in patients with atopic dermatitis[96,107]. Although the role of IL-22 in the development and maintenance of atopic dermatitis has not been specifically explored, it probably contributes to the epidermal acanthosis that is observed in the chronic stage of the disease. In line with this assumption, a randomized, double-blind, placebo-controlled study was initiated in October 2013 to investigate the safety, tolerability and clinical efficacy of an IL-22-specific antibody administered intravenously to patients with atopic dermatitis (ClinicalTrials.gov identifier: NCT01941537).

Acne inversa. IL-22 expression is rather low in acne inversa (also known as hidradenitis suppurativa)[96], which — like atopic dermatitis — is associated with bacterial skin infections that significantly contribute to disease pathogenesis[108]. The deficiency in IL-22 upregulation in acne inversa lesions (compared to other inflammatory disorders) was associated with insufficient upregulation of several antibacterial proteins, even in the presence of high cutaneous levels of other inducers of antibacterial proteins, including IL-17 (REF. 96). Given the synergistic action of IL-22 and IL-17 in inducing the production of antibacterial proteins by keratinocytes, it seems that a deficiency in either IL-22 (in acne inversa) or IL-17 (in atopic dermatitis) leads to substantially reduced protection of the disturbed skin against infections. In acne inversa, local delivery of IL-22 could be a promising approach to increase the antibacterial defence and to prevent tissue destruction in the affected skin of patients.

Inflammatory bowel disease

Inflammatory bowel disease is a chronic, relapsing, immune-mediated disorder of the intestines that is subdivided into two major forms: Crohn's disease and ulcerative colitis. In both forms of inflammatory bowel disease, the number of IL-22-producing cells is increased in the inflamed intestine, although patients with Crohn's disease show higher numbers of IL-22-producing cells[46]. Most IL-22-producing cells are T_H cells that are located throughout the intestinal wall (in patients with Crohn's disease) or located preferentially within the lamina propria (in patients with ulcerative colitis)[46]. In contrast to respective mouse models, the contribution of other cell

Atopic dermatitis
A chronic skin disease that is characterized by itchy, red and flaky lesions that often occur on bending sides of the limbs. The lesions have infiltration of immune cells in the dermis and epidermis as well as acanthosis, fibrosis and collagen deposition in the chronic stage.

Acne inversa
A chronic inflammatory disease that affects axillary, inguinal and perianal skin areas, leads to the development of inflamed nodules, abscesses and fistula, and is associated with painful tissue destruction, malodorous purulence and extensive scarring.

Crohn's disease
A chronic bowel disease — often located in the terminal ileum and proximal colon — that is characterized by an inflammation of all layers of the intestinal wall. Typical characteristics include ulcerations, crypt abscesses that have neutrophilic granulocytes, granuloma-containing macrophages and subserous lymphocyte aggregates.

Ulcerative colitis
A chronic bowel disease that mostly begins from the rectum and continuously spreads proximally. It usually affects the mucosa, which is infiltrated with lymphocytes and macrophages.

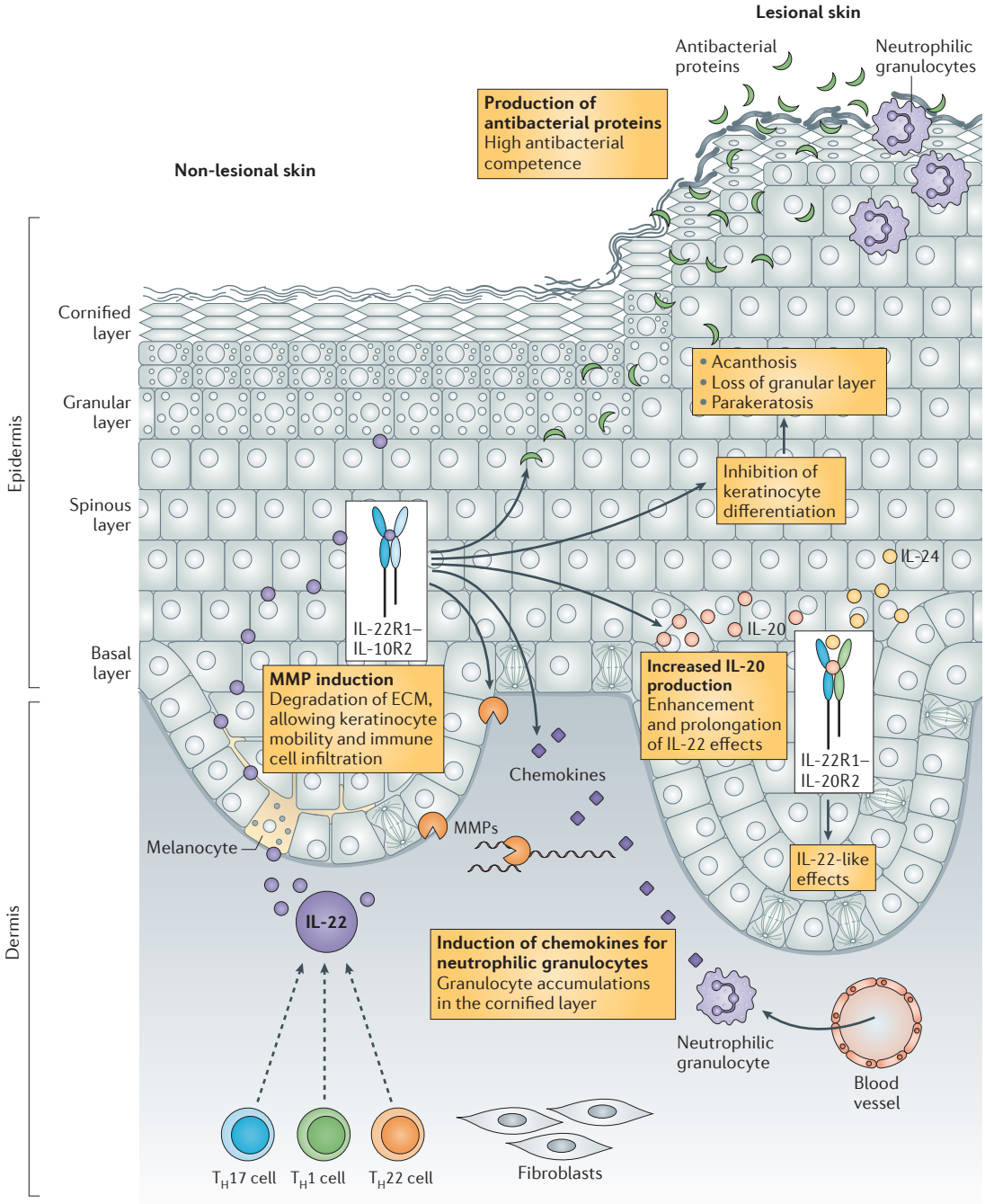

Figure 3 | **Role of the IL-22–IL-22R1 system in psoriasis.** In non-lesional and lesional skin of patients with psoriasis, keratinocytes are the major target cells of interleukin-22 (IL-22). By influencing their biology, IL-22 induces five features of psoriatic lesions. First, it inhibits the differentiation and cornification of keratinocytes. This leads to epidermal thickening (acanthosis), loss of the granular epidermis layer and cell nuclei remnants in the cornified epidermis layer (parakeratosis). Second, IL-22 induces the production of antibacterial binding proteins. These natural antibiotics prevent skin infections of the psoriatic lesions, the latter being characterized by a highly disturbed barrier function. Third, IL-22 induces the production of matrix metalloproteinase 1 (MMP1) and MMP3 in keratinocytes. These extracellular matrix (ECM)-degrading enzymes facilitate immune cell infiltration and the restructuring of the epidermis. Fourth, IL-22 induces keratinocytes to produce chemokines that attract neutrophilic granulocytes, and it thereby contributes to the accumulation of these cells in the upper corneal layer of the epidermis (known as Munro's abscesses). Fifth, IL-22 uses mechanisms that enhance or prolong its own action. These include the induction of signal transducer and activator of transcription 3 (STAT3; not shown) and IL-20. Like IL-22, IL-20 (as well as IL-24) uses an IL-22 receptor subunit 1 (IL-22R1)-containing receptor complex and mediates IL-22-like effects on keratinocytes. The effects of IL-22 can be strengthened by tumour necrosis factor (TNF). Moreover, IL-17 acts synergistically with IL-22 to boost the production of antibacterial proteins and granulocyte-attracting chemokines (not shown). T_H, T helper.

subsets to the presence of intestinal IL-22 in inflammatory bowel disease seems to be limited[46,74], although $CD3^-$ IL-22-producing cells have been detected[109].

Besides IL-22, levels of IL-20 and IL-24 are also increased in the intestine of patients with inflammatory bowel disease[110,111]. Whereas IL-20 production is mainly localized to mucosal epithelial cells and macrophages, IL-24 is expressed by myofibroblasts. In addition to local expression, levels of IL-22 are increased in the blood of patients with Crohn's disease and correlate with disease severity[66]. Furthermore, the number of IL-22-producing memory $CD4^+$ T_H cells in the blood is elevated in Crohn's disease and correlates inversely with the extent of mucosal inflammation[112].

Studies in mice have demonstrated a protective effect of increased levels of IL-22 in T_H2 cell-mediated ulcerative colitis-like intestinal inflammation[53]. In addition, inhibition of IL-22 activity increased tissue damage in a mouse model of acute intestinal injury (dextran sodium sulphate (DSS)-induced colitis). A similar conclusion was drawn from a mouse model of colitis that is induced by the transfer of naive $CD4^+$ T cells into mice that are deficient in recombination activating gene 1 (*Rag1*), which lack both B and T cells. When IL-22-deficient naive $CD4^+$ T cells were transferred into *Il22*$^{-/-}$*Rag1*$^{-/-}$ mice, the colitis was worsened[113].

The protective effect of IL-22 in inflammatory bowel disease has been linked to the increased expression of mucus-associated molecules and the restitution of mucus-producing goblet cells[53] (see the section on IL-22 effects for details). Furthermore, the elevation of antibacterial protein production (which leads to modulation of the colonic microbiota)[114] and the increased proliferation of epithelial cells (which leads to the repair of the epithelial barrier)[68,115] might have a role. It should be noted, however, that in selected mouse models the IL-22-mediated epithelial cell proliferation and induction of MMPs was associated with mucosal hyperplasia and a worsened intestinal state[116,117].

The elevated systemic IL-22 levels also seem to have a protective effect. IL-22 induces the hepatic production of LPS-binding protein; at higher levels, LPS-binding protein may prevent systemic inflammation provoked by systemic LPS. LPS levels are indeed increased in the blood of patients with Crohn's disease, and this elevation is probably due to the translocation of LPS through the impaired intestinal barrier[66].

Importantly, a case study report suggests that IL-22 has a protective role in inflammatory bowel disease; a patient with ulcerative colitis, who infected himself with the nematode *Trichuris trichiura* to treat his symptoms, had an accumulation of IL-22-producing $CD4^+$ cells in the intestinal mucosa, goblet cell hyperplasia, increased mucus production and disease remission[118].

In summary, local availability of IL-22 in the intestines might promote recovery from inflammatory bowel disease. Based on the insufficient expression of IL-22 and the nature of intestinal alterations in ulcerative colitis, increasing IL-22 levels could be expected to have therapeutic benefit in this condition. This might be associated with a lower rate of adverse effects than observed with current therapy options for severe ulcerative colitis, such as corticosteroids and immunosuppressants (for example, cyclosporine A and azathioprine), which often cause altered glucose metabolism and infections.

An excellent approach to enhance the activity of the IL-22–IL-22R1 system might involve the oral application of IL-22 in a protease-resistant form or the application of small chemical molecules that induce the differentiation of T_H22 cells or increase their stability and/or IL-22 production. Agonists of aryl hydrocarbon receptor may be an option as they have been shown to induce IL-22 production and to inhibit inflammation in the gastrointestinal tract in mice[31].

Lung inflammation

The important pathogenetic role of T_H2 cells in asthma has been recognized for around 20 years. Recently, however, it has been proposed that T_H17 cells exacerbate disease severity, especially in patients who have neutrophil infiltration in their lungs. IL-22 protein and mRNA levels are elevated in serum and peripheral blood cells, respectively, of patients with asthma, and in the lungs in mouse models of asthma[119,120]. Several studies using the mouse model of ovalbumin-induced asthma have suggested that IL-22 might have a protective role in asthma-associated lung inflammation. Indeed, IL-22 application during the effector phase reduced pulmonary eosinophil infiltration, the expression of chemokines as well as T_H2 cell cytokines and airway constriction[79,119]. Accordingly, neutralization of IL-22 during the effector phase exacerbated lung inflammation and enhanced goblet cell hyperplasia and hyperresponsiveness[119,121]. Interestingly, the role of IL-22 during the sensitization phase in this mouse model seems to be dependent on the route of sensitization: IL-22 has a pathogenic role during subcutaneous sensitization[119] but not during intraperitoneal sensitization[79,121,122].

The exact molecular mechanism that underlies the positive effects of IL-22 on allergic lung inflammation has not yet been conclusively explained. It might involve the inhibition of CCL17 and IL-25 production by airway epithelial cells[79,121] and the minimization of lung epithelial damage[123], and it seems to be an IL-10-dependent mechanism[122]. In contrast to IL-17A, IL-22 does not regulate allergen-induced airway hyperresponsiveness through a direct effect on the airway smooth muscle[124].

IL-22 also limits lung fibrosis. Indeed, blocking IL-22 enhanced collagen deposition in the lungs of mice that were repeatedly exposed to the ubiquitous microorganism *Bacillus subtilis*. Accordingly, exogenous IL-22 repressed lung fibrosis in this model of inflammation-induced pulmonary fibrosis[125]. The protective role of IL-22 was also observed in a rat model of barotrauma, in which IL-22 decreased pulmonary disintegration and oedema[126]. Interestingly, the impact of IL-22 activity may be influenced by cytokines that are also present in inflamed airways. Although IL-22 alone has a protective effect in the model of bleomycin-induced fibrosis, it can synergize with IL-17 to exacerbate lung inflammation and fibrosis[127].

Asthma
The most common form of chronic inflammatory airway disease that is characterized by bronchial hyperresponsiveness and variable, recurring and reversible airflow obstructions.

Ovalbumin-induced asthma
A mouse model of human asthma. The repeated application of ovalbumin during the sensitization phase leads to the generation of ovalbumin-specific T helper cells. Lung inflammation is induced by subsequent intranasal application of ovalbumin (effector phase).

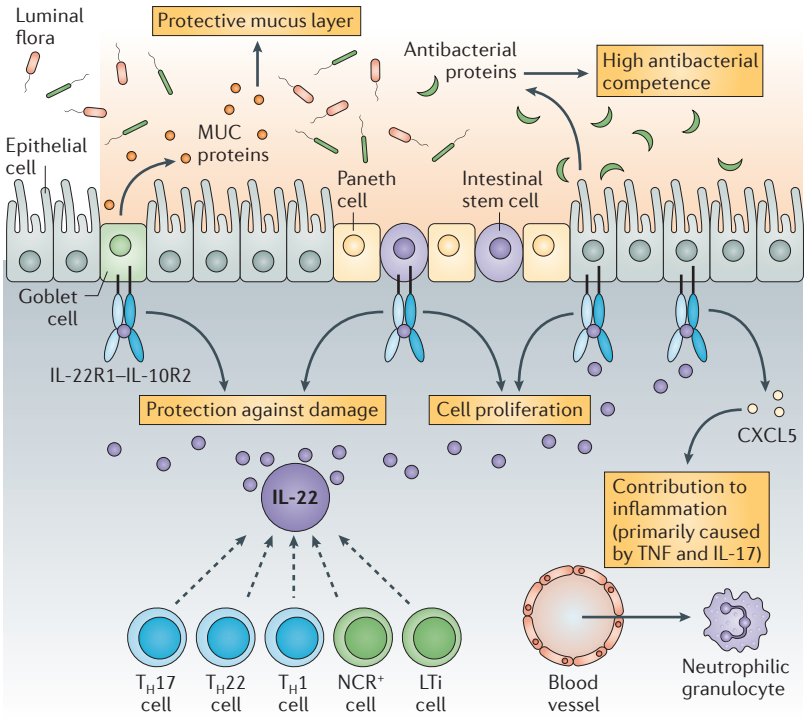

Figure 4 | **Role of the IL-22–IL-22R1 system in the defence against intestinal infections.** Interleukin-22 (IL-22) enhances the antibacterial defence of mucosal epithelial cells through different mechanisms. First, IL-22 helps to maintain the epithelial barrier. It prevents epithelial damage induced by bacteria and inflammation. Additionally, IL-22 promotes the production of mucus-associated proteins (mucins (MUCs)), which are necessary for the formation of the protecting mucus layer, and helps to restore the epithelial layer by directly acting on epithelial stem cells to promote their protection and proliferation. Second, IL-22 induces the secretion of antibacterial proteins. Finally, IL-22 — by itself or by synergizing with other cytokines — can trigger the expression of chemokines that can recruit and activate leukocytes for controlling invading pathogens. CXCL5, CXC-chemokine ligand 5; IL-22R1, IL-22 receptor subunit 1; LTi, lymphoid tissue inducer; NCR, natural cytotoxicity triggering receptor; T_H, T helper; TNF, tumour necrosis factor.

In summary, increased levels of IL-22 in the lungs might be helpful in some lung disorders, particularly those that are associated with damage to the airway epithelia and with a risk of bacterial infection, such as lung transplantation and GvHD. There are two worthwhile therapeutic options: IL-22 application in the form of an aerosol, and oral application of small IL-22-inducing molecules (such as aryl hydrocarbon receptor agonists).

Host defence against infections

Bacterial infections. The profound role of IL-22 in the prevention of — and defence against — infections with extracellular bacteria of the respiratory and intestinal tracts has been repeatedly demonstrated. For example, IL-22 — together with IL-17 — has a crucial defensive role in pulmonary infection with the Gram-negative bacterium *Klebsiella pneumoniae*[52]. In addition, IL-22 is indispensable for host defence against enteric infection with the Gram-negative bacterium *Citrobacter rodentium*[28] in mice, as animals that are deficient in the IL-22 pathway succumb in the second week after oral inoculation of the bacteria[28,29]. Conversely, IL-22 is dispensable for host defence in mice that are intravenously infected with intracellular bacteria such as *M. avium* or *Listeria monocytogenes*[71,128], as well as in mice that are intraperitoneally infected with *Salmonella enterica* serovar Enteritidis[129]. IL-22 is also negligible for host defence after intratracheal routes of infection with *Francisella tularensis*, which is a facultative intracellular bacterium[130].

In addition to its involvement in defence against invading pathogenic bacteria, IL-22 controls commensal bacteria in lymphoid tissues of the intestinal tract[131] and regulates the composition of the intestinal microbiota[114]. In fact, there is a decreased abundance of *Lactobacillus* spp. in the colonic microbiota of IL-22-deficient mice, which makes these mice susceptible to colitis. Recent studies have suggested that the intestinal microbiota affects the development of many autoimmune diseases[132,133], so it is possible that the occurrence of these diseases might be influenced by the intestinal activity of the IL-22–IL-22R1 system.

We now have a good understanding of the mechanisms by which IL-22 enhances the antibacterial defence of epithelial cells in the respiratory and intestinal tracts (FIG. 4). First, IL-22 helps to maintain the epithelial barrier. Moreover, IL-22 induces various innate defence mechanisms in the epithelia (see above) and supports the recruitment and activation of leukocytes. With the exception of the induction of epithelial cell proliferation and mucus production, the mechanisms by which IL-22 prevents bacterial infection might be similar in the skin. Unfortunately, studies regarding the role of IL-22 in skin infections are still limited[96].

Yeast infections. IL-22 contributes to protective immunity against yeast infection, and this was first shown through studies in mice. IL-22 controls the fungal burden during lung infection with *Aspergillus fumigatus*[134]. Furthermore, IL-22 is required to sequester the dissemination of intragastrically applied *Candida albicans* to other organs including the kidney and stomach[135]. By contrast, IL-22 has a minor role in the defence against *C. albicans* skin infection in mice[136].

Importantly, studies in patients with thymoma or autoimmune polyendocrine syndrome type I (who are known to have a high rate of chronic mucocutaneous candidiasis) strongly suggest that IL-17 and/or IL-22 have essential roles in mucocutaneous defences against *C. albicans*. Indeed, chronic mucocutaneous candidiasis in these patients is associated with high levels of neutralizing IL-17- and IL-22-specific autoantibodies[137].

Viral infections. Although IL-22 does not induce direct antiviral responses in epithelial cells as do IFNα and IL-29 (REF. 94), several recent studies have suggested that IL-22 is required for limiting tissue damage caused by viral infection. For example, IL-22 not only contributed to the protection and regeneration of tracheal and pulmonary epithelial cells upon infection with influenza virus but it also limited secondary bacterial infection[78,123,138,139]. During HIV infection, the reduction in the numbers of T_H22 cells correlated with disturbed epithelial integrity and increased microbial translocation

Citrobacter rodentium
A bacterium that induces acute colitis in mice. This infectious colitis is used as a murine model of human infection produced by attaching and effacing bacterial pathogens such as enterohaemorrhagic *Escherichia coli* and enteropathogenic *E. coli*, which cause diarrhoea, morbidity and mortality, especially among infants and children.

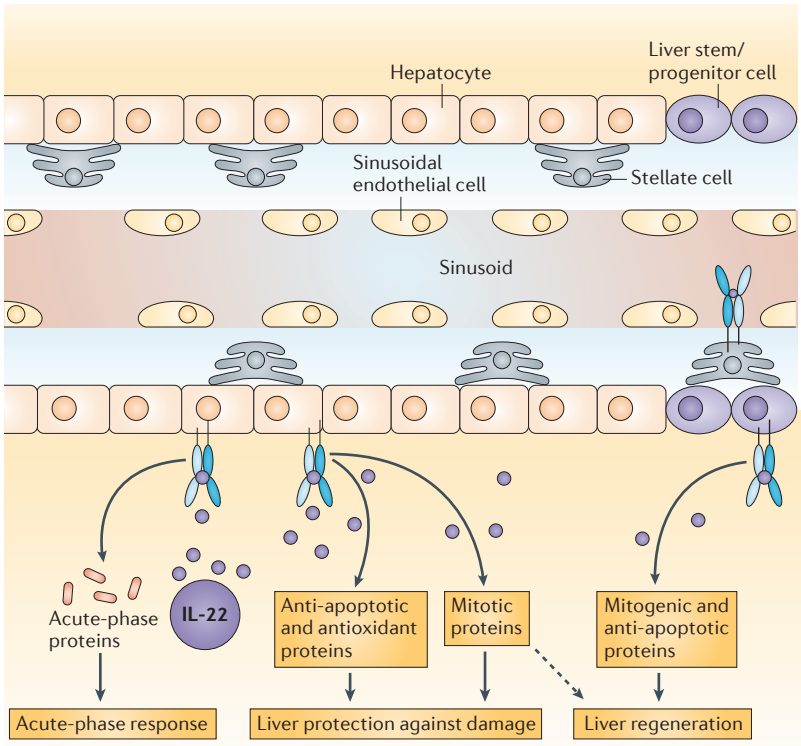

Figure 5 | **Roles of the IL-22–IL-22R1 system in liver damage.** Interleukin-22 (IL-22) strongly protects the liver against damage and favours its regeneration by acting mainly on hepatocytes and liver stem cells. By inducing the expression of mitogenic and anti-apoptotic proteins, IL-22 promotes cellular proliferation and protection against apoptosis, respectively. Moreover, the induction of antioxidant proteins may protect hepatocytes against oxidative stress. IL-22 also induces acute-phase proteins that exert anti-inflammatory, antibacterial and regenerative effects. IL-22R1, IL-22 receptor subunit 1.

in the gut[140,141]. A protective role of IL-22 was also reported in hepatic hepatitis B virus infection in mice and humans (see below)[59].

To summarize, in contrast to other T_H cell cytokines such as IFNγ and IL-4, IL-22 is more effectively involved in controlling infections caused by extracellular bacteria and yeast, especially those that directly attack epithelial cells. Bearing in mind the regenerative properties of IL-22 as well, increasing levels of IL-22 appear to be especially useful for conditions in which there is damage to the respiratory or intestinal tract that is associated with an increased rate of infection, such as GvHD, major injury or the initial period after transplantation. In these situations, the administration of IL-22-inducing small molecules may be a useful basic therapy. However, as observed in patients suffering from autoimmune polyendocrine syndrome type I, inhibition of the IL-22–IL-22R1 system — especially if IL-17 is simultaneously inhibited — might be associated with mucocutaneous infection.

Pancreatitis

Pancreatitis can be triggered by excessive alcohol consumption or the presence of a gallstone. Apart from the elimination of the triggers, at present there is no curative therapy for pancreatitis. Three recent reports suggest the high therapeutic potential of IL-22 for treating pancreatitis. The application of IL-22 or liver-specific transgenic overexpression of this cytokine reduced the severity of acute and chronic pancreatitis in mouse models, as deduced from reduced serum levels of digestive enzymes and reduced inflammatory cell infiltration and necrosis in the pancreas[82]. Further confirmation came from the protective effect of aryl hydrocarbon receptor activation using small molecules[81]. The protective effect of IL-22 was linked to its direct effect on pancreatic acinar cells, in which IL-22 induces the expression of the proteins REG3β and REG3γ as well as BCL-2 and BCL-X_L, which inhibit autophagosome formation by binding to beclin 1 (see above). In addition to its effects on acinar cells, IL-22 was proposed to increase the proliferation of pancreatic islet cells[83] — an effect that may also contribute to the protective effect of IL-22 in pancreatitis.

All of these results from studies in mice suggest that the application of either IL-22 or inducers of IL-22 may have high potential in the treatment of pancreatitis and during the first period after pancreas transplantation.

Hepatitis

The most common causes of hepatitis are viral infections and alcohol abuse. In humans, IL-22 levels and the number of IL-22-producing cells are elevated in the liver of patients suffering from chronic hepatitis B virus or hepatitis C virus infection[87,142].

Numerous *in vitro* and mouse studies have shown that IL-22 has a strong protective effect against hepatocyte damage. In a murine model of T cell-mediated hepatitis induced by concanavalin A, neutralization of IL-22 worsened liver damage, whereas pretreatment with IL-22 prevented damage[86]. In addition, delivery of an IL-22 expression vector under the control of the liver-specific albumin promoter protected mice from CCL4- and FAS ligand (FASL)-induced hepatic injury[143]. The protective role of IL-22 in acute hepatitis was confirmed using IL-22-deficient mice, which are highly susceptible to concanavalin A-mediated liver injury, and IL-22-overexpressing mice, which are highly resistant to concanavalin A-mediated liver injury[87,144]. Furthermore, IL-22 application ameliorated liver injury, fatty liver and hepatic oxidative stress in mouse models of acute and chronic alcohol-induced liver damage[89,145]. Hepatoprotection was also achieved by IL-22 pretreatment in a model of liver ischaemia–reperfusion injury[146] as well as during systemic bacterial and parasitic infection[129,147]. In addition, IL-22 enhanced the liver regeneration that is seen in mice after partial hepatectomy and that leads to the rebuilding of this organ[87,148].

Although IL-22 itself does not influence hepatitis B virus replication, there was a positive correlation between the numbers of IL-22-producing cells and the number of stem/progenitor cells in the liver of patients with chronic hepatitis B virus. In line with this, IL-22 increased the proliferation of liver stem/progenitor cells in mice[59].

The mechanisms that underlie the actions of IL-22 might include the STAT3-dependent induction of anti-apoptotic, mitogenic and antioxidant molecules in damaged hepatocytes and hepatic stem cells (FIG. 5).

Table 2 | **Clinical conditions that could benefit from the targeting of the IL-22–IL-22R1 system**

Disease	Disease frequency*	Medical need‡	Required therapeutic modulation	Supporting evidence§	Suggested therapeutic approach
Psoriasis	2–3%‖	High	Reduction	High	• Parenteral application of IL-22R1-targeting monoclonal antibodies • Topical application of small molecules inhibiting IL-22R1-mediated signalling
Colorectal carcinoma	20–80¶	Very high	Reduction	Moderate	• Small molecules that inhibit IL-22R1-mediated signalling • Parenteral application of IL-22R1-targeted monoclonal antibody (this would be the preferred strategy to prevent metastasis)
Ulcerative colitis	0.1–0.2%‖	High	Enhancement	High	• Oral application of protease-stable IL-22 • Small molecules that induce IL-22 production (given as interval therapy)
Asthma	5%‖	Moderate	Enhancement	Low	• Inhalation of small molecules that induce IL-22 production
Pancreatitis	20–70¶	Very high	Enhancement	High	• Parenteral application of IL-22 (at acute stage of disease) • Application of small molecules that induce IL-22 production (given at chronic stage of disease as interval therapy)
Acute liver damage	-	High	Enhancement	Very high	• Parenteral application of IL-22
GvHD	1.6–3.2¶	Very high	Enhancement	Moderate	• Parenteral application of IL-22 (for acute GvHD) • Application of small molecules that induce IL-22 production (given as basic therapy)
Lung transplantation	0.3–0.5¶	Very high	Enhancement	Moderate	• Parenteral application of IL-22 (given for short-term use after transplantation) • Application of small molecules that induce IL-22 production (given as a basic therapy)
Pancreas and pancreas-kidney transplantation	0.2–0.4¶	High	Enhancement	Moderate	• Parenteral application of IL-22 (given for short-term use after transplantation) • Application of small molecules that induce IL-22 production (given as a basic therapy)

GvHD, graft-versus-host disease; IL-22, interleukin-22; IL-22R1, IL-22 receptor subunit 1. *Frequency of disorders or organ transplantations based on specifications from the United States and Europe. ‡Medical need was defined by taking into consideration the impact of the disease on the quality of life and mortality of affected patients, as well as the existence of effective and safe therapies. §The strength of supporting evidence is based on the amount and persuasiveness of published data, mostly from basic and preclinical research that is described in the respective sections of this Review. ‖Prevalence: the proportion of a population suffering from a disease at a specific time. ¶Incidence: the number of individuals per 100,000 people who were recently diagnosed with a disease or underwent organ transplantation during 1 year.

Therefore, IL-22 application could be a promising hepatoprotective approach in liver transplantation, acute viral hepatitis and alcoholic liver disease. The upregulation of hepatic IL-22R1 expression demonstrated in some models of liver injury[87,89,146] may further support the therapeutic effect of IL-22 in this organ.

Arthritis and enthesitis

High levels of *IL22* mRNA are found both in synovial tissues and mononuclear cells in the synovial fluid of patients suffering from rheumatoid arthritis[47]. Furthermore, the percentage of IL-22-expressing $CD4^+$ T cells is increased in the blood of patients with rheumatoid arthritis and correlate with increases in blood plasma IL-22 levels[149–152]. In addition, elevated plasma IL-22 levels positively correlate with levels of rheumatoid factor, disease severity and the progression of erosive rheumatoid arthritis[151–153].

However, it seems that endogenous IL-22 has a very weak — if any — pathogenic contribution to experimental rheumatoid arthritis, as measured using three different mouse models: collagen-induced arthritis; spontaneously developed arthritis in IL-1RA-deficient mice; and arthritis induced by the application of methylated bovine serum albumin[154–157]. By contrast, the application of recombinant IL-22 alleviated inflammation in an IL-10-dependent manner in the collagen-induced model of arthritis[157]. Interestingly, IL-20 and IL-24 are also present in the synovial fluid of patients with rheumatoid arthritis[158]. Inhibition of IL-20 activity seems to be associated with reduced disease severity in experimental rheumatoid arthritis[159] and protection against osteoporotic bone loss[160]. In summary, there is currently insufficient evidence to demonstrate whether modulating the activity of the IL-22–IL-22R1 system represents an effective therapeutic strategy for rheumatoid arthritis.

By contrast, IL-22 was recently suggested to be a driver of enthesitis pathogenesis[161]. Systemic IL-22 overexpression was sufficient to induce enthesitis *in vivo*. Moreover, hepatic overexpression of IL-23 provoked enthesitis, which was associated with IL-22 production induced in a previously unknown subset of $CD4^-CD8^-$ T cells and was inhibited following IL-22 neutralization. Interestingly, IL-22 was more efficient than IL-23 in regulating the

Rheumatoid factor
Autoantibodies against the Fc portion of an organism's own immunoglobulin G. Around 80% of patients suffering from rheumatoid arthritis have high levels of rheumatoid factor, whereas only 5% of healthy people have rheumatoid factor, and mostly at a low level.

Enthesitis
Inflammation at the sites where tendons or ligaments insert into the bone. Enthesitis is often associated with ankylosing spondylitis and psoriatic arthritis.

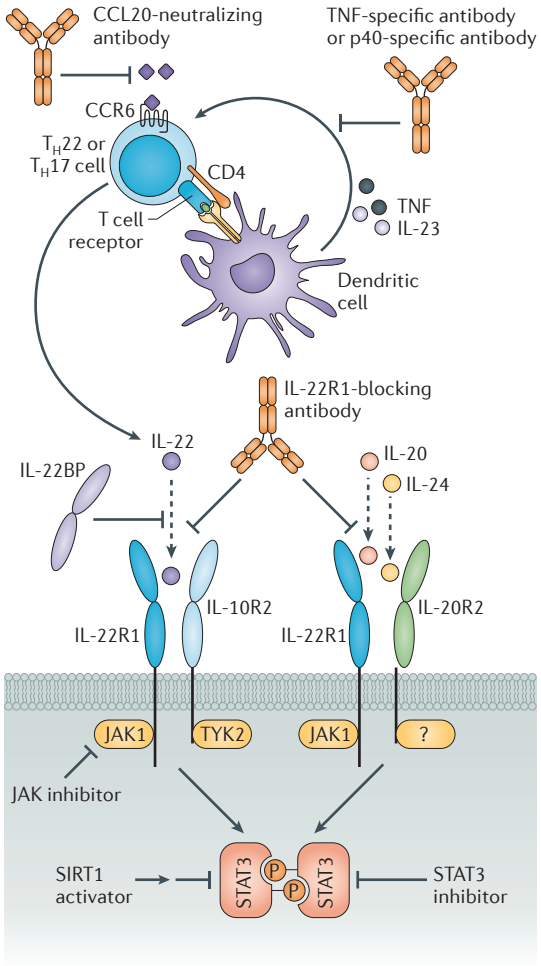

Figure 6 | **Options for therapeutic modulation of the IL-22–IL-22R1 system.** There are several potential therapeutic options for targeting the interleukin-22 (IL-22)–IL-22 receptor subunit 1 (IL-22R1) system. For instance, infiltration of IL-22-producing T helper (T_H) cells into the skin could be blocked by specific chemokine-neutralizing antibodies. Furthermore, cytokines that promote the activation and survival of these T_H cells, such as tumour necrosis factor (TNF) and IL-23, could be neutralized by respective antibodies, as successfully demonstrated in psoriasis therapy through the use of adalimumab (Humira; AbbVie) and ustekinumab (Stelara; Janssen). In addition, T_H cell-specific transcription factors that promote IL-22 production (such as the aryl hydrocarbon receptor) could be inhibited by antagonists. IL-22 itself could be neutralized by antibodies or through the use of IL-22 binding protein (IL-22BP). Moroever, IL-22R1 — the high-affinity receptor subunit of IL-22 — could be targeted by blocking antibodies, or signal transduction downstream of IL-22R could be inhibited using inhibitors of Janus kinases (JAKs) or signal transducer and activator of transcription (STAT) proteins. The latter (STAT inhibitors) include drugs that block STAT3 dimerization as well as activators of the class III deacetylase sirtuin 1 (SIRT1), which lead to decreased STAT3 acetylation. The use of IL-22R1-blocking antibodies appears to be the most suitable strategy for several reasons. This approach acts downstream in the IL-22–IL-22R1 system and is highly specific, limiting unwanted effects. In fact, IL-22R1 is expressed only by a limited number of cell populations in the body. It is absent on immune cells, so no major systemic immune activation or inhibition is expected. Most importantly, blocking IL-22R1 also prevents the IL-22-like effects of IL-20 and IL-24. These cytokines are frequently co-expressed with IL-22 by inflamed tissues and mediate IL-22-like effects through IL-22R1. CCL, CC-chemokine ligand; CCR, CC-chemokine receptor.

expression of genes that influence bone formation[161]. This suggests that IL-22 and IL-22R1 are promising targets for the treatment of enthesitis, with a safety profile that potentially exceeds that of current therapies.

Cancer

The IL-22–IL-22R1 system is an important novel target in cancer research. The neoplastic proliferation of IL-22R-bearing cells derived from the intestinal tract, liver, pancreas and respiratory tract is very common, and the presence of IL-22 and/or T_H22 cells has been demonstrated within colonic, gastric and hepatocellular as well as small- and large-cell lung carcinomas[162–165]. Furthermore, STAT3 — the major downstream signalling molecule of IL-22 — is well established as an oncogene that is associated with the development and progression of many epithelial tumours. IL-22 itself does not appear to promote oncogenesis, as an IL-22-transgenic mouse strain that is characterized by constant overproduction of IL-22 in the liver did not have a clearly increased incidence of spontaneous tumours, including liver tumours[87]. Similarly, in another transgenic mouse model, IL-22 overexpression in adipose tissue did not favour spontaneous tumour development in mice that were fed a normal diet[166].

Rather, IL-22 accelerates the development of ongoing or induced cancers. Indeed, in a model of carcinogen-induced hepatocellular carcinoma, increased tumour formation was observed in IL-22-overexpressing mice, and decreased tumour formation was observed in IL-22-deficient mice[87,164]. Furthermore, mice that over-expressed IL-22 in adipose tissue and that were fed a high-fat diet for several months developed liposarcoma in sub-epididymal adipose tissue[166].

Recent studies in mice have also suggested that IL-22 could increase tumorigenesis in the colon under certain conditions[68,167]. In a mouse model that combined colitis with carcinogen treatment, as well as in a genetic model of colorectal cancer (that is, *Apc*$^{Min/+}$ mice that were crossed with IL-22BP-deficient mice), enhancement of IL-22 activity resulted in greater tumour burden. This effect was probably due to the IL-22-induced increase in the proliferation and apoptotic resistance of epithelial cells during tumorigenesis. However, ablating the IL-22 pathway reduced tumorigenesis solely in the genetic model[68] while the absence of IL-22 even increased tumorigenesis in the colitis-associated model, probably because of prolonged barrier disruption and consequent stronger inflammation. This latter assumption matches the fact that the chronic inflammation observed in

Box 2 | **Therapeutic use of TNF blockers and an IL-23-neutralizing antibody**

Tumour necrosis factor (TNF) blockers bind to and thereby prevent the action of TNF, which is a cytokine that acts on almost all immune and tissue cells and that mostly induces and amplifies inflammatory responses. So far, the drugs in this class that have been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are infliximab (Remicade; Janssen), etanercept (Enbrel; Amgen/Pfizer), adalimumab (Humira; AbbVie), certolizumab pegol (Cimzia; UCB Pharma) and golimumab (Simponi; Janssen). These drugs have revolutionized the therapy of specific chronic inflammatory diseases. For example, adalimumab has been approved for the treatment of plaque psoriasis, Crohn's disease, ulcerative colitis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis and juvenile idiopathic arthritis, and had worldwide sales of US$9.265 billion in 2012. So far, the FDA and EMA have approved one antibody that neutralizes interleukin-23 (IL-23), ustekinumab (Stelara; Janssen), for the treatment of plaque psoriasis. This antibody binds to the p40 subunit of IL-23 and IL-12. In this way it prevents the development of and — in part — the activity of T helper 1 (T_H1), T_H17 and T_H22 cells, which have an important pathogenetic role in chronic immune-mediated diseases but are also essential for the development of protective immunity in young individuals.

patients with ulcerative colitis contributes to the development of colorectal cancer. In another study, in which colon cancer was induced in B cell- and T cell-deficient mice (that is, *Rag*$^{-/-}$ mice) by infection with *Helicobacter hepaticus* and carcinogen injection, blocking IL-22 — which was locally produced by ILCs — reduced the number of colorectal tumours[167].

Collectively, these studies suggest that IL-22 supports the transition from pre-existing inflammation to colon cancer, as well as the maintenance of established colon cancers. However, the role of IL-22 in tumorigenesis may be complicated as IL-22 might primarily inhibit inflammation and therefore also counteract tumorigenesis. Indeed, IL-22 diminishes epithelial damage, accelerates epithelial repair and reduces the number of bacteria during inflammation and infection, which reduces the duration and extent of inflammatory signals. In summary, inhibition of the IL-22–IL-22R1 system may represent a late-phase treatment option in colorectal cancer.

Future directions

Accumulative results strongly suggest that the inhibition of IL-22 and/or IL-22R1 activity may be beneficial in several diseases, whereas strengthened IL-22R1-mediated signalling might alleviate several other conditions (TABLE 2). In disorders in which the IL-22–IL-22R1 system is hyperactive, such as psoriasis and certain tumours, options for intervention include inhibition of IL-22 generation, tissue infiltration or IL-22 production by IL-22-producing cells, as well as the neutralization of secreted IL-22, blockade of IL-22R1 or inhibition of IL-22R1 signalling (FIG. 6). Each of these approaches has its legitimacy and may be appropriate in a specific situation. However, if permitted by pharmacokinetics and/or pharmaceutical formulations, blocking of IL-22R1 seems to be the most appropriate strategy. This approach is advantageous owing to its specificity and, in contrast to the neutralization of IL-22, it also simultaneously inhibits the IL-22R1-mediated (and IL-22-like) effects of IL-20 and IL-24.

In psoriasis in particular, the therapeutic use of TNF blockers or antibodies that neutralize IL-23 subunits (BOX 2) has proven to have great therapeutic success[168–170]. As TNF and IL-23 are key inducers of IL-22 production, and TNF enhances some of the effects of IL-22, this success should be at least partially based on the indirect attenuation of IL-22R1 activity. However, owing to the broad role of TNF, IL-12, IL-23 and IL-17 — the latter being a novel promising target in psoriasis[171,172] — in the body, the long-term application of these therapies might increase the risk of infections and tumours. Moreover, the long-term application of these therapies is often associated with reduced activity of the respective biological agent. Therefore, in our opinion there is a continuous appreciable medical need for drugs that inhibit the IL-22–IL-22R1 system for the treatment of psoriasis.

As the 5-year survival rates of patients with colon cancer vary between 5% and 95% depending on the tumour stage, there is an enormous medical need for novel therapies for this condition as well. Again, the advantage of therapeutically inhibiting the IL-22–IL-22R1 system lies in the direct targeting of tumour cells, as this provides a higher specificity and a lower expected risk of adverse effects than existing treatments. In particular, as targeting IL-22R1 does not negatively influence the immune system, which is common for cytostatic drugs, this approach might be very helpful for patients with cancer, either as a basic therapy or in combination with cancer immunotherapy. Nevertheless, adverse effects associated with therapies targeting the IL-22–IL-22R1 system cannot be excluded. Owing to the protective and antimicrobial effects mediated by IL-22–IL-22R1, caution is needed in patients who are at risk of developing epithelial infections or who suffer from liver and pancreas damage — for example, as a result of alcohol abuse.

Conversely, strengthening the activity of the IL-22–IL-22R1 system appears to be indicated in conditions that are associated with damage to IL-22R1-expressing tissues, such as ulcerative colitis, asthma and — in particular — pancreatitis, acute liver damage, GvHD and transplantation of the lung, pancreas and kidney. Increasing IL-22–IL-22R1 activity could achieved by supporting the generation and/or stability of IL-22-producing cells, increasing IL-22 production by these cells or by direct IL-22 application. The definitive approach taken should depend on the localization and extent of the disease and the required duration of therapy. For example, short-term IL-22 protein application after transplantation may be feasible by intravenous injection, whereas for long-term prevention of GvHD the use of small IL-22-inducing molecules (for example, agonists of the aryl hydrocarbon receptor such as the tryptophan derivative 6-formylindolo(3, 2-b)carbazole) may be more suitable.

In our opinion, there is an enormous medical need for some of the above mentioned diseases. In fact, the mortality rate of pancreatitis is about 10% and the 5-year survival rates after lung transplantation are only 50%. Owing to the restricted target range of IL-22, especially its lack of influence on immune cells, strengthening of IL-22R1

signalling might be a relatively safe approach, particularly for the treatment of GvHD, organ damage and transplantation. Nevertheless, unwanted adverse effects may occur in individuals who are genetically predisposed to develop certain disorders following long-term intervention. For example, IL-22 may trigger skin acanthosis or even psoriasis. IL-22 may also promote the development of existing cancers. However, short-term or intermittent activation of the IL-22–IL-22R1 system — in conjunction with proper monitoring tools — to enhance epithelial host defence and to restore epithelial homeostasis may be justifiable in diseases with a considerable unmet medical need. Nevertheless, IL-22 should not be considered a harmless tool for the regeneration or rejuvenation of the skin and other organs.

In the light of the high frequency of the disorders described above, their associated considerable burdens on individuals and on society as a whole, and — in many cases — the lack of alternative treatment options, we hope that pharmaceutical and biotech companies will take up the idea of therapeutically modulating the IL-22– IL-22R1 system in these settings.

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Competing interests statement

The authors declare competing interests: see Web version for details.

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