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Diverse effects of interleukin-22 on pancreatic diseases

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ABSTRACT

Interleukin-22 (IL-22) is involved in the development of lymphocytes and serves as a rapid and early source of the effector cytokines that are released in response to pathogen-induced changes in the microenvironment. Recent research has implicated IL-22 as a potential contributing factor to the spectrum of inflammation-related pancreatic diseases, particularly pancreatitis, fibrosis, carcinoma and diabetes. In this review, we summarize the current knowledge on the roles of IL-22 in the various pancreatic pathogenesis, providing insights into the underlying cellular and signaling mechanisms that will help guide future research into promising interventional targets with therapeutic potential.

Introduction

Interleukin (IL)-22 plays a crucial role in protection against injury, defense against pathogens, and regeneration; yet, like the other members of the IL-10 family of cytokines, it also has been shown to contribute to pathogenic processes [1]. In particular, IL-22 has been implicated in various common malignancies [1–6], (i.e. colon cancer, gastric cancer, liver cancer, breast cancer and cutaneous malignancies) and several autoimmune diseases [7–11] (i.e. rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, psoriasis and Crohn's disease). The roles played by IL-22 in inflammatory conditions are dynamic, wherein it can exert both protective and pathogenic functions, as has been shown for the inflammatory bowel diseases of ulcerative colitis and Crohn's disease [12,13].

Recently, the study of the pathogenic roles of IL-22 has expanded to include its impact on pancreatic diseases. To date, contributions of IL-22-producing cells have been reported in pancreatitis, pancreatic fibrosis, pancreatic cancer and diabetes [4,14–16]. Here, we summarize and discuss the most current knowledge on the effects and underlying mechanisms of IL-22 related to pancreatic damage with the aim of providing new diagnostic, prognostic or therapeutic insights for improved management of pancreatic diseases.

Biology of IL-22

Gene and protein structure of IL-22

IL-22, a member of the IL-10 family that comprises IL-10, IL-19, IL-20, IL-24, IL-26, IL-28α, IL-28β and IL-29, has been the focus of increasing attention due to the potential of its tissue protective effects [17]. The human IL-22 gene is located at chromosome 12q15, in the vicinity of the genes encoding IFN-γ and IL-26 [18]. The 537bp open reading frame of the IL-22 gene encodes a 179 amino acid protein that shares 79% homology between human and mouse [19]. The human IL-22 gene sequence includes a predicted 33 amino acid signal peptide that is removed prior to secretion of the 146 amino acids cytokine protein [20]. The tertiary structure of the IL-22 protein (as determined by expression in *Escherichia coli* and *Drosophila melanogaster* and by crystallization and X-ray diffraction [21]) consists of bundled α-helices (helices pre-A and helices A to F) and connecting loops, with two intramolecular disulfide bridges to provide stabilization. IL-22 harbors three potential N-linked glycosylation sites, two of which were observed as glycosylated in the crystallized IL-22 expressed in the *D. melanogaster* insect cells [22]. Although glycosylation was found to be associated with only

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minor changes in the IL-22 tertiary structure [22], the glycosylated form of the protein should be considered when generating neutralizing IL-22-specific monoclonal antibodies for therapeutic uses. The biologically active form of IL-22 seems to be a monomer [21,23,24]; however, non-covalent and non-intertwining dimers and—at high concentrations of IL-22—tetramers have also been observed [21,23].

Although the earliest studies found constitutive expression of IL-22 only in the thymus and brain [25], subsequent studies have found induced expression in such other tissues as gut, liver, lung, skin, spleen and pancreas [26]. Nevertheless, IL-22 is reported only secreted by T cells, including T helper (Th)1 cells, Th17 cells, Th22 cells, $CD8^+$ T cells, γδ T cells and natural killer T (NKT) cells [27–30].

Receptor complex of IL-22

IL-22 exerts its biological effects via binding to heterodimeric transmembrane receptor complexes. The receptor for IL-22 (IL-22R) has two heterodimeric subunits, IL-10R2 and IL-22R1, the latter of which is absent from immune cells but, is highly expressed in the skin, small intestine, colon, kidney, liver and pancreas [31,32]. In addition, Jones et al. reported a high affinity of IL-22 towards IL-22R1 [33]. IL-10R2 is almost completely incapable of binding IL-22 alone, but has a moderate affinity for the IL-22/IL-22R1 complex. Particularly, binding of IL-22 to IL-22R1 was also shown to occur at a 1:1 ratio initially, after which the IL-22/IL-22R1 complex binds to IL-10R2 to activate downstream signaling. The primary signaling targets of IL-22 are STAT1, STAT3 and STAT5, which are activated by the induction of phosphorylation of the tyrosine kinases Janus kinase 1 (Jak1; interacting with IL-22R1) and tyrosine kinase 2 (Tyk2; interacting with IL-10R2) [31]. IL-22 has also been shown to induce activation of the three major MAPK pathways of p38, ERK, and JNK [34,35]. These studies also suggest that the lymphocyte-derived IL-22 would only exert its effects on tissue cells.

IL-22 and pancreatic diseases

It is well known that IL-22 is involved in a variety of diseases including the pathogenic processes leading to pancreatic injury by various stresses, such as pancreatic inflammation, pancreatic fibrosis, pancreatic cancer and diabetes. In the following sections, we will discuss the effects and the underlying mechanisms of IL-22/IL-22R signing in various pancreatic diseases.

IL-22 and pancreatic inflammation

Pancreatic inflammation or pancreatitis is a disease of the pancreas caused by trypsin-mediated self-digestion. Under normal circumstances, there is no detectable trypsin activity within pancreatic tissue. The pancreatic juice constantly goes into the duodenum through the pancreatic duct via the sphincter of Oddi. The duodenal mucosa secretes enterokinase that activates trypsinogen to give active trypsin. If the outflow tract is obstructed and the active enzyme is confined, pancreatitis occurs. In general, there are two types of pancreatitis: acute pancreatitis (AP) and chronic pancreatitis (CP).

Considering that IL-22 is a well-documented survival factor for hepatocytes and liver cancer cells [36], and pancreatic acinar cells express high levels of the IL-22 receptor subunit IL-22R1[37], it has been hypothesized that IL-22 may also protect against acinar cell death and pancreatitis. Recently, Feng et al. demonstrated that IL-22 can effectively protect mice from cerulein-induced pancreatitis [5]. Despite the beneficial effects of IL-22 on pancreatitis, there has also been report that IL-22 functions differently among the different types of AP. AP is a disorder characterized by parenchymal injury of the pancreas that is mediated by immune cell-related inflammation, and includes two subtypes: severe AP and mild AP. Recent studies have shown that in a mild AP model, endogenous IL-22 is a predominantly anti-inflammatory mediator that inhibits inflammatory cell infiltration via the induction of Reg3 proteins in acinar cells, but does not protect against acinar injury in the early stage of AP [14]. However, when applied in the severe animal models of AP, IL-22 demonstrated markedly protective effects against the inflammation-mediated acinar injury [14].

The protective mechanisms of IL-22 might include the induction of B cell lymphoma/leukemia-2 (Bcl-2) and B cell lymphoma/leukemia-X_L (Bcl-X_L) gene expression in the pancreas and subsequent reduction of autophagosome formation, a critical step in the initialization of pancreatitis [38–41]. Autophagy comprises two key sequential steps: first, the formations of autophagosomes that sequester the organelles destined for degradation; and second, the fusion of autophagosomes with lysosomes to form autolysosomes, wherein materials are degraded by such hydrolases as the cathepsin family of proteases. The three major pathways that regulate autophagy are the inhibitory mammalian target of rapamycin (mTOR) pathway, the stimulatory beclin-1 (also called ATG6) pathway, and the stimulatory LC3-II/Atg5-Atg12-Atg16 pathway [40]. Recent studies have suggested that Bcl-2 and Bcl-X_L play an important role in inhibiting the stimulatory beclin-1 pathway by binding to beclin-1 and subsequently inhibiting autophagy [42]. IL-22 activation of STAT3 leads to up-regulation of the genes downstream of STAT3, which include Bcl-2 and Bcl-X_L. Increased Bcl-2 and Bcl-X_L subsequently bind to beclin-1, inhibiting autophagosome formation and ameliorating acinar cell damage in pancreatitis (Fig. 1).

These observations agree with the recent finding that patients with alcoholic pancreatitis, a leading cause for both acute and chronic pancreatitis, exhibit local depletion of lysosomal-associated membrane protein-2 (Lamp-2, a kind of lysosomal protein) and subsequent inhibition of the fusion of lysosomes and autophagosomes [43]. Though IL-22 level was observed up-regulated in the early stage of alcoholic pancreatitis, regardless of disease severity [44], it remains to be elucidated whether IL-22 directly regulates Lamp-2 gene expression and subsequently ameliorates alcoholic pancreatitis (Fig. 1).

In contrast to the early stage of AP, the production of IL-22 was found to be reduced at the late stage of AP when the numbers of IL-22 producing $CD4^+$ T cells were significantly decreased in the pancreas [14]. However, ILCs, another type of IL-22 producing cells, were highly increased in the inflamed pancreas at this stage, and thus partially restored the IL-22 production [2]. Nevertheless, it is known that there are also pro-inflammatory modulators including IL-1, IL-6, IL-8, platelet activating factor and chemokines in AP [45,46]. Therefore, when the pro-inflammatory response is not sufficiently countered by an anti-inflammatory mechanism such as IL-22, IL-10 and IL-1ra in AP [45,46], a cascade of inflammatory reactions can lead to a systemic response and result in AP or even multiple organ dysfunction syndrome (MODS) [46,47].

IL-22 and pancreatic fibrosis

IL-22 has been demonstrated to be protective in fibrosis, involving the pathogenic states of pulmonary fibrosis [48], renal fibrosis [49], intestinal fibrosis [11], cardiac fibrosis [50] and liver fibrosis [51]. Therefore, it could be speculated that IL-22 might also exert certain protective effects on the tissue damage in pancreatic fibrosis.

CP induces persistent and permanent damage to pancreatic tissues, disrupting various molecular mechanisms and impairing

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