Cytokine and Growth Factor Reviews 50 (2019) 1–12

Contents lists available at ScienceDirect

Cytokine and Growth Factor Reviews

journal homepage: www.elsevier.com/locate/cytogfr

The role of interleukin-18 in pancreatitis and pancreatic cancer

Zhiqiang Li[a,b], Xiao Yu[b], Jens Werner[a,c], Alexandr V. Bazhin[a,c,*,1], Jan G. D'Haese[a,1]

[a] Department of General, Visceral, and Transplant Surgery, Ludwig-Maximilians-University Munich, 81377 Munich, Germany
[b] Department of Hepatopancreatobiliary Surgery, The third Xiangya hospital, Central south university, Changsha 410013, Hunan, China
[c] German Cancer Consortium (DKTK), Partner Site Munich, 81377 Munich, Germany

ARTICLE INFO

Keywords:
IL-18
Acute pancreatitis
Chronic pancreatitis
Pancreatic cancer
Progression of AP to CP
CAR-T cells

ABSTRACT

Originally described as an interferon (IFN)-γ-inducing factor, interleukin (IL)-18 has been reported to be involved in Th1 and Th2 immune responses, as well as in activation of NK cells and macrophages. There is convincing evidence that IL-18 plays an important role in various pathologies (i.e. inflammatory diseases, cancer, chronic obstructive pulmonary disease, Crohn's disease and others). Recently, IL-18 has also been shown to execute specific effects in pancreatic diseases, including acute and chronic pancreatitis, as well as pancreatic cancer. The aim of this study was to give a profound review of recent data on the role of IL-18 and its potential as a therapeutic target in pancreatic diseases. The existing data on this topic are in part controversial and will be discussed in detail. Future studies should aim to confirm and clarify the role of IL-18 in pancreatic diseases and unravel their molecular mechanisms.

1. Introduction

Interleukin-18 (IL-18) was originally identified as interferon (IFN)-γ-inducing factor which was firstly purified from serum of mice after an intraperitoneal injection of an endotoxin [1]. Subsequently, it was cloned by Okamura et al. [2] in 1995 inducing further investigation of its biological properties. After that, it was defined as a new member of the IL-1 family of cytokines [3] and its name was changed into IL-18. As a unique cytokine, IL-18 has been found to be involved in activation and differentiation of various T cell populations. Together with IL-12, IL-18 activates CD4, CD8 T and NK cells through simultaneous activation of NF-kB by IL-18 and STAT-4 by IL-12, which results in IFN-γ production by the target cells [4]. However, in the absence of IL-12, IL-18 was found to be an inducer of differentiation of the naive T cells into Th2 cells producing IL-13 and IL-4 [5,6]. In addition, IL-18 also directly upregulates perforin- and FasL-dependent cytotoxicity of NK and $CD8^+$ T cells [7]. Accumulating evidence suggests that IL-18 is involved in the process of immunoregulation in various inflammatory and malignant diseases. Recently, the role of IL-18 in pancreatic disorders has also been clarified opening new avenues for potential therapeutic intervention recognizing IL-18 as a target.

Here, we aim to review recent reports about IL-18 to understand its role in pancreatitis and pancreatic ductal adenocarcinoma (PDAC). We furthermore aim to provide directions for further investigations of IL-18 and discuss potential therapeutic approaches.

2. IL-18 synthesis and maturation, its receptor and signaling pathway

The IL-18 gene is constitutively expressed in monocytes,

Abbreviation: 5-FU, 5-fluorouracil; AB1, TGF-β activated kinase 1 binding protein 1; ALI, Acute lung injury; AP, Acute pancreatitis; AP-1, Activator protein 1; ARDS, Acute respiratory distress syndrome; Breg, Regulatory B cells; CAR, Chimeric antigen receptor; CP, Chronic pancreatitis; CTLs, Cytotoxic T lymphocytes; DCs, Dendritic cells; FOX, Forkhead box; GPx, Glutathione peroxidase; ICE, IL-1β converting enzyme; IFN-γ, Interferon-γ; IKK, IκB kinase; IL, Interleukin; IL-18BP, IL-18 binding protein; IL-18R, IL-18 receptor; IRAK, IL-1 receptor associated kinase; JNK, c-Jun N-terminal kinase; MAPK, Mitogen-activated protein kinase; MKK, MPAK kinase; MSOF, Multiple systemic organ failure; MyD88, Myeloid differentiation factor 88; NLRP3, Nucleotide oligomerization domain-, leucine-rich, repeat-, and pyrin domain-containing protein 3; OS, Overall survival; PACs, Pancreatic acinar cells; PBMCs, Peripheral blood mononuclear cells; PC, Pancreatic cancer; PDAC, Pancreatic adenocarcinoma; PMN-E, PMNs elastase; PMNs, Polymorphonuclear neutrophils; PSCs, Pancreatic stellate cells; RAP, Recurrent AP; ROS, Reactive oxygen species; TAK1, Transforming growth factor β-activated kinase 1; Th cells, T help cells; TIR, Toll-like receptor/IL-1R; TRAF6, TNF receptor-associated factor 6; Treg, Regulatory T cells

* Corresponding author at: Department of General, Visceral, and Transplant Surgery, Ludwig-Maximilians-University Munich, Marchioninistr. 15, 81377 Munich, Germany.
E-mail address: alexandr.bazhin@med.uni-muenchen.de (A.V. Bazhin).
[1] These authors contributed equally.

https://doi.org/10.1016/j.cytogfr.2019.11.001
Received 2 September 2019; Received in revised form 30 October 2019; Accepted 4 November 2019
Available online 09 November 2019
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macrophages, dendritic cells (DC), endothelial cells, keratinocytes, and intestinal epithelial cells and is transcribed as an inactive precursor without any signal peptide [8,9]. Similar to IL-1β, the IL-18 precursor is preceded by an intracellular cleavage mainly by caspase 1. This enzyme also known as IL-1β converting enzyme (ICE) can be activated by various canonical inflammasomes including the best known one – NOD (nucleotide oligomerization domain)-, LRR (leucine-rich repeat)-, and PYD (pyrin domain)-containing protein 3 (NLRP3) inflammasomes, into its mature biological form [10–12]. Apart from caspase-1, some caspase 1-independent mechanisms of IL-18 cleavage have also been reported. In macrophages from Propiobacterium acnes-infected mice, Fas-ligand can process to activate IL-18 maturation via caspase-8 in a caspase-1-independent manner [13,14]. Moreover, the IL-18 precursor can also be processed by granzyme B from cytotoxic cells, chymase from mast cells or meprin-β from intestinal and kidney epithelial cells into the mature form [15–17]. Also, extracellularly the IL-18 precursor can be activated by neutrophil proteases 3 released from dying cells [18]. However, the NLRP3 inflammasome-caspase-1-dependent manner was the most common mechanism of IL-18 maturation.

IL-18 performs its biological function by ligation of IL-18 receptors (IL-18R) α and β. Mature IL-18 binds to IL-18Rα which is encoded by the gene IL-18R1 with a low affinity [19]. However, if IL-18Rβ encoded by the gene IL-18R accessory protein is simultaneously expressed, both α and β receptors form a high affinity dimer to induce IL-18 signaling after ligation [20]. As a consequence, the IL-18/IL-18Rα/IL-18Rβ complex recruits myeloid differentiation factor 88 (MyD88) due to interaction between the Toll-like receptor/IL-1R (TIR) domain of MyD88 and cytoplasmic IL-18R [21,22]. Subsequently, the death domain of MyD88 interacts with IL-1 receptor associated kinase (IRAK)-4 to recruit and phosphorylate IRAK [23]. Phosphorylated IRAK dissociates from the complex to translocate into the cytoplasm where it ubiquitinates TNF receptor-associated factor 6 (TRAF6). This chain of events allows TGF-β Activated Kinase 1 Binding Protein 1 (TAB1) to phosphorylate transforming growth factor β-activated kinase 1 (TAK1) [24]. Phosphorylated TAK1 can in turn activate both IκB kinase (IKK) and mitogen-activated protein kinase (MAPK) kinase (MKK) [25]. The activation of IKK results in the IkB degradation followed by activation of nuclear factor kappa-light-chain-enhancer of activated B (NF-κB) signaling pathway with its translocation to the nucleus inducing expressions of certain cytokines [25]. In addition, MKK can further activate Jun N-terminal kinase (JNK)/p38 MAPK pathway promoting some cytokines' transcription through activation of the activator protein 1 (AP-1) [25] (Fig. 1). In addition, IL-18 has also been shown to induce phosphorylation of STAT3 in the NK cell line 92 and hippocampal HT-22 cells [26,27].

Thus, the maturated form of IL-18 is involved in activation of NF-κB and JNK/p38 MAPK pathways through ligation of its receptors. Regarding the biochemical functions of IL-18 described above, it becomes clear that this cytokine is involved in the development and progression of inflammation. Therefore, we need to discuss this point in more details.

3. IL-18 and inflammation

As a pro-inflammatory cytokine, IL-18 has been shown to be associated with T help (Th) 1 and Th2 immune response. After stimulation with an antigen and IL-12, naïve Th cells develop into Th1 lymphocytes producing a small amount of IFN-γ and expressing IL-18R. Additional IL-18 stimulation synergistically combined with IL-12 induces further an abundant production of IFN-γ from Th1 cells [20,28]. In addition, NK and $CD4^+$ NKT cells constitutively express IL-18R, which can also induce production of IFN-γ after stimulation with IL-18 and IL-12 [4,29,30].

IL-18 cannot have direct effects on Th2 cells due to the absence of IL-18R expression on their surface [4]. Nevertheless, IL-18 can newly polarize Th1 cells influencing them to secret IL-9 and IL-13, and additional IL-2 stimulation can further augment this effect of Th1 cells [31]. Moreover, in the absence of IL-12, co-stimulation of IL-18 with IL-2 activates NK and $CD4^+$ NKT cells to produce IL-3, IL-9 and IL-13 [5,6]. Basophils and mast cells can also express IL-18α after the continual treatment with IL-3 so that IL-18 can stimulate basophils to produce Th2 cytokines (IL-4 and IL-13) and therefore promote mast cells to produce IL-13 [32]. Interestingly, IL-18 alone has been shown to stimulate naïve $CD4^+$ T cells to produce IL-4 and further promote production of IgE from B cells, which indicates that IL-18 could potentially initiate Th2 differentiation [6]. Therefore, IL-18 exerts a property to be involved in Th2 response.

Furthermore, IL-18 has also been shown to enhance cytotoxic activities of NK as well as $CD8^+$ T cells [7].

4. IL-18 and acute pancreatitis

4.1. IL-18 as a predictor of the severity of acute pancreatitis

Acute pancreatitis (AP) is an inflammatory disease of the pancreas. It develops from pancreatic acinar cells (PACs) due to an injury leading to the intracellular activation of trypsinogen. AP has been classified into mild, moderate and severe pancreatitis depending on the extent of local injury of the pancreas as well as systemic injury of other related organs in the new Atlanta classification system [33,34]. Over 80% of AP is mild which is self-limiting and usually rehabilitates without complications. 20% of all AP causes are moderate to severe and are associated with major morbidity or mortality [35,36]. Moderate AP is characterized by transient organ failure which lasts less than 48 h and severe AP by persistent organ failure [34]. Inflammatory reaction induced by the destruction of pancreatic parenchyma is the main characteristic in the early phase of AP. In some cases, the systemic inflammatory response syndrome can be occurred to trigger organ failure leading potentially to high morbidity and mortality [37]. Some pro-inflammatory mediators released due to inflammatory reaction are found to be associated with severity of AP. Serum IL-6 was firstly observed to have a correlation with AP severity [38]. Also, serum IL-8, IL-1, TGF-β, and TNF-α concentrations were reported to be significantly elevated in patients suffered from severe AP compared to the mild ones [39–42].

Recently, serum IL-18 concentration has also been found to correlate with the severity of AP. A significant increase in the serum IL-18 concentration has been demonstrated within 24 h after the onset of symptoms in AP patients compared to healthy donors. Importantly, the concentration of this cytokine was much higher in the severe AP patients than in mild ones [43]. However, IL-18 was returned to normal level if no complications occurred keeping a slight high level for the whole 10-day observation [43,44]. For patients who developed pancreatic necrosis or systemic complications inducing pulmonary, renal, cardiocirculatory and hepatic failure as well as multiple organ dysfunction syndrome, the level of circulating IL-18 started to further increase around the third to fifth day when local or systemic complications occurred [43]. Then its concentration stayed stable within the observation period of the first 10 days [44] and even increased 4 weeks after admission of hospital [45]. Therefore, serum IL-18 concertration can be used to reflect the severity of AP. However, for the fact that serum IL-18 concentration increases around period of complications occurrence, it is not clear whether the increase of IL-18 in serum induces the occurrence of complications or vice versa. If IL-18 is one of factors which increase the frequency of complications occurrence, it means IL-18 plays a destructive role in AP and inhibition of IL-18 will be a promising strategy for treatment of AP.

In addition, the IL-18 concentration in the serum of AP patients can not only be used to reflect the severity of AP, but also to predict its severity since presenting a positive correlation with polymorphonuclear neutrophils elastase (PMN-E) - a sensitive early marker predicting the severity of AP [44–46].

Tissue injury induces the excessive activation of polymorphonuclear neutrophils (PMNs) which are essential components of the innate immune system [47–50]. PMNs activation in the early phases of inflammation increases leukocyte aggregation and tissue infiltration

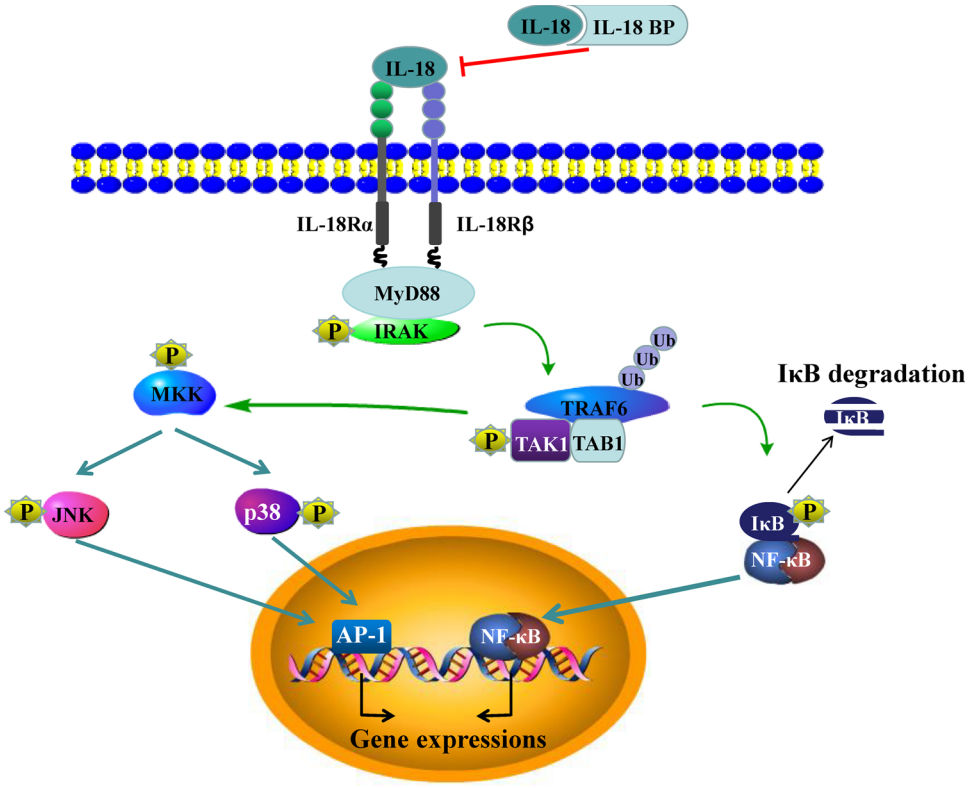

Fig. 1. IL-18 signaling pathway.
After binding to IL-18R, IL-18 phosphorylates IRAK by recruiting MyD88 and then ubiquitylates TRAF-6 which activates TAK1 by recruiting TAB1. This chain of events results in nuclear translocation of NF-κB and also in activation of the JNK/p38-MAPK signaling pathway to induce expression of different cytokines, such as IL-8, IL-6 and TGF-β. IL-18BP has been shown to bind to IL-18 inhibiting the bio-activity of IL-18.

leading to the release of toxic reactive oxygen species (ROS) which cause cellular oxidative stress, tissue injury, and endothelial cell damage resulting in organ dysfunction [51–53]. Function of the selenium-dependent glutathione peroxidase (GPx) is an important defense mechanism for limitation of the toxic activity of ROS to maintain membrane integrity and protect injury from oxidative stress [54,55]. Oxidative stress was found to occur in the early phase of AP and is correlated with AP severity [54–58]. Therefore, neutrophil activation and oxidative stress assessment is important to predict AP severity in the patients.

PMN-E is a serine protease secreted from the azurophilic granules of PMNs. It degrades basal membrane proteins, elastin, collagen, fibronectin and so on playing an important role in the modulation of local inflammation [52,59]. Plasma PMN-E levels can normally be used to reflect PMN activation and its concentration can be used as a sensitive early predictive marker of AP severity [60–62]. Plasma PMN-E level has been found to be increased in AP patients compared to healthy people and, the severe form of AP is characterized by a higher concentration of PMN-E compared with the mild form of AP [63]. Moreover, the median peak value of PMN-E concentration in the serum was reached on the first day of admission preceded the one of CRP which is the most common marker to predict the severity of AP, so the concentration of PMN-E represents a reliable earlier indicator over CRP [61].

Serum IL-18 level has been reported to be positively correlated with plasma PMN-E concentration and negatively correlated with serum selenium and GPx levels on the first day of admission [44,64]. Selenium which has been found to decrease in AP patients [65], negatively correlates with plasma PMN-E concentration [64] based on the down-regulation of IL-18 expression [66]. Besides, IL-18 exerts important effects to activate neutrophils by inducing productions of cytokines and chemokines from neutrophils [67] increasing elastase release via p38 MAPK activation [68]. Importantly, IL-18 knockout significantly reduced neutrophil infiltration in the damaged pancreas and neutrophil maturation in spleen of SAP mice [69]. Therefore, IL-18 can be used as early predictive marker for the severity of AP with advantage over PMN-E.

However, there are no consistent conclusions about the correlation of serum IL-18 levels and survival of AP patients yet. Endo et al. [70] reported that serum IL-18 was significantly higher in the non-survivors than the survivors between 17 patients recruited. However, Ueda et al. [45] didn't get a significant correlation between survival and serum IL-18 levels in AP patients. Therefore, more investigations with large patients' populations are needed to clarify this issue. For AP patients, there are two peaks of mortality the first one of which is induced by organ failure at early stage and the second one results from infection at stage after organ failure [71]. Importantly, the concentration of IL-18 in serum has been showed to mainly be associated with organ dysfunction [43]. Therefore, it will be more possible that serum IL-18 concentration has a correlation with the first peak of mortality. For this reason, further investigations should be focused on this to better expound the role of IL-18 in AP.

These facts discussed above showed the relationship between serum IL-18 level and complications due to AP and its severity. Hence, serum IL-18 level can be used to assess even predict the severity of AP.

4.2. *Destructive or protective effect of IL-18 on AP?*

As discussed above, serum IL-18 concentration usually increases around occurrence of AP-associated complications suggesting that IL-18 is potentially involved in exacerbation of AP [43]. Indeed, IL-18 deletion has been shown to significantly decrease the severity of SAP mice [69]. Mechanistically, IL-18 has two-faced functions in term of the Th-cell differentiation. In the presence of IL-12, IL-18 promotes the Th1 response, but in the absence of IL-12, it induces Th2 response [4]. Co-stimulation with both - IL-18 and IL-12 takes effect mainly through production of IFN-γ. There are two kinds of forms for IL-12, one of which namely IL-12p70, induces the Th1 response, and the other one-IL-12p40 inhibits the Th1 immune response [72,73]. Interestingly, Pezzilli et al. [74] demonstrated that IL-12p70 concentration in the serum was increased only on the first day of admission and then remained at a significantly lower level in AP patients on the third and fourth day of admission. At the same time, IL-12p40 concentration was significantly increased during the total observation period of 5 days [74]. Similarly, Rodriguez et al. [75] found a higher serum IFN-γ concentration only within the first 24 h of admission in patients with severe or moderated AP than in those with mild AP. Furthermore, there is no any significant

difference in IFN-γ concentrations between patients with and without complications when observing a period of 14 days after admission [43]. More importantly, no correlation of IL-18 with IFN-γ concentration was detected in the AP patients' groups [43,75]. Sendler et al. [69] observed also the reduction of IL-12p70 and IFN-γ in SAP mice. Therefore, IL-18 does not exert the property to facilitate Th1 response. Interestingly, Th1/Th2 balance has been confirmed to be shifted to the Th2 direction in both AP patients and SAP mice [69,76]. In addition, IL-18 deficiency reduced Th2 response in SAP mice. Hence, IL-18 contributes to the severity of AP by enhancing Th2 response.

Surprisingly, Ueno et al. [77] reported that IL-18 knockout mice suffered from AP showed a significant increase in the serum concentration of amylase and lipase compared to AP wild-type (WT) mice. Furthermore, the degree of vacuolization was significantly increased in the pancreas of IL-18 knockout mice compared to wild-type animals with AP. Pretreatment of the knockout mice with recombinant mouse IL-18 decreased the level of serum enzymes mentioned above and the degree of vacuolization. From this view, IL-18 seems to have a protective function in AP. Unfortunately, this study did not show any histopathological change either in WT or in IL-18 deficiency AP mice with IL-18 pretreament or not. Importantly, Ueno et al. [77] just presented the results mentioned above at 6 h after the beginning of AP induction which can not entirely reflect the severity of AP. Differently, Sendler et al. [69] observed that IL-18 deficiency reduced the severity of AP by collecting blood and pancreas to detect at 72 h after the beginning of AP induction which better assessed effect of IL-18 on the severity of AP overall. Therefore, taking everything into consideration, IL-18 mainly plays a role in exacerbation of AP. In the future, it is worth to explore the correlation of IL-18 treatment or deletion with complications occurrence or survival of AP mice for further confirming its protective effect.

In conclusion, we confirmedly speculate that IL-18 is a promising target for the treatment of AP.

4.3. IL-18 and AP-associated lung injury

Multiple systemic organ failure (MSOF) is the major cause of death for patients with severe AP at early phase [78,79]. In extra-pancreatic organ failure, acute lung injury (ALI) is the most prominent. About 20% of severe AP patients potentially develop acute respiratory distress syndrome (ARDS). One third of these patients die during the early stage of severe AP and half of those result from ARDS [78,79]. It is known that the serum concentration of IL-18 but not of IL-1β, IL-6, IL-8, and TNF-α is elevated at admission in AP patients who later developed respiratory failure [80]. When the respiratory failure occurs, the serum IL-18 level was still considerably higher in AP patients with respiratory failure compared to those without the failure. It should be stressed that the level of this cytokine was even higher in AP patients with ARDS than those with ALI [80]. Besides, serum IL-18 concentration is able to predict pulmonary dysfunction with sensitivity of 58% and up to 100% specificity [80]. Therefore, IL-18 is a predictive marker of pulmonary dysfunction of AP patients.

Regarding the question, whether elevated level of serum IL-18 is the cause or the consequence of pulmonary dysfunction, Sendler et al. [69] observed that IL-18 deletion significantly alleviated AP-associated pulmonary injury. In addition, Pastor et al. [81] explored the correlation of IL-18 expression in the lung and pulmonary injury in a rat AP model. They found that pulmonary injury appeared within 2 h after pancreatitis induction but IL-18 levels in the lung significantly increased at 18 h after pancreatitis induction. Moreover, IL-18 was mainly localized in the inflammatory cells infiltrated in the lung [81]. Therefore, the upregulation of IL-18 expression in the lung mainly originates from invading inflammatory cells after lung injury. In addition, Hoshino et al. [82] established a genetic mouse model in which animals constitutively overexpressed mature IL-18 in the lung only. They found out that local over-expression of IL-18 in the lung induced pulmonary lung inflammation with the appearance of $CD8^+$ T cells, macrophages, neutrophils, and eosinophils [82]. Further, although IL-18 administration alone did not affect the survival of WT mice, IL-18 in synergy with IL-2 which has been shown to increase in the serum of SAP mice [83] induced lethal lung injury in WT mice but not IL-18Rα-deficient mice [84]. Therefore, It is tempting to speculate that local and systemic elevation of IL-18 level is directly involved in AP-associated lung injury.

5. IL-18 and chronic pancreatitis

Chronic pancreatitis (CP) represents an inflammatory disease characterized by inflammation-induced progressive pancreatic destruction which results in pancreatic fibrosis replacing the pancreatic acini and leading to both irreparable exocrine and endocrine insufficiency [85,86]. Factors contributing to the development of CP are varied and multifactorial, including alcohol and cigarette consumes, genetic factors [87] as well as a history of AP, especially recurrent AP (RAP) [88]. AP has been identified as a risk factor of CP progression. A meta-analysis showed that 10% of patients with one episode of AP and 36% patients with RAP can eventually progress into CP [88]. Among all etiologies, pro-inflammatory and pro-fibrotic factors play a very important role in promoting the disease progression. As discussed above, IL-18 has a major effect on AP progression and is associated with several fibrotic diseases, including liver fibrosis [89], cardiac fibrosis [90] and lung fibrosis [91]. Therefore, it is tempting to speculate that IL-18 could be also involved in the pathogenesis of CP.

5.1. Serum IL-18 levels and severity of chronic pancreatitis

Schneider and colleagues [92] reported that IL-18 concentration in the fasting serum was significantly increased in 76% of patients with CP compared to healthy donors. Using a mouse CP model, Kavitha et al. [93] confirmed elevated serum IL-18 in the CP-suffering animals. To further investigate the source of elevated IL-18 in serum, Schneider et al. [92] measured the expression of IL-18 at the mRNA and protein level in peripheral blood mononuclear cells (PBMCs) isolated from CP patients and healthy donors. However, they found no significant difference in IL-18 expression either with or without stimulation of PBMCs. These data suggest that blood immune cells cannot be the main cause of the elevated serum IL-18. This led to the idea that cytokines and other soluble factors involved in the progression of pancreatic fibrosis are produced by resident pancreatic cells as well as by recruited immune cells [94], Schneider et al. [92] indeed found that IL-18 expression was increased in pancreatic tissue with CP. This expression was mainly localized in PACs and infiltrating mononuclear cells, such as macrophages. In consistence, Manohar et al. [95] detected an upregulation of IL-18 expression in pancreatic tissue in mice from a CP model. Based on these results, it becomes evident that IL-18 is closely associated with CP.

In detail, Zhang et al. [96] found that blockade of the purinergic 2×7 receptor, which is a key regulatory protein of NLRP3 inflammasome activation, significantly down-regulated the IL-18 expression in the inflamed pancreatic tissue and thereby decreased fibrosis in a mouse model of CP. Kanak et al. [97] also reported that withaferin A, a small molecule inhibitor of NF-kB, could decrease the IL-18 expression and prevent disease progression of CP in a mouse model. These studies suggest a close association of IL-18 with CP progression, and further research on human CP is advised.

5.2. IL-18 and pancreatic acinar cell injury in CP

The main characteristic of CP, namely the PAC injury, is known as the initial trigger of CP due to the secretion of different cytokines. The necrosis-fibrosis hypothesis [98] describes an important mechanism of CP progression: Necrotic injury of PACs can form an inflammatory environment when AP occurs by secreting various cytokines and recruiting inflammatory cells.

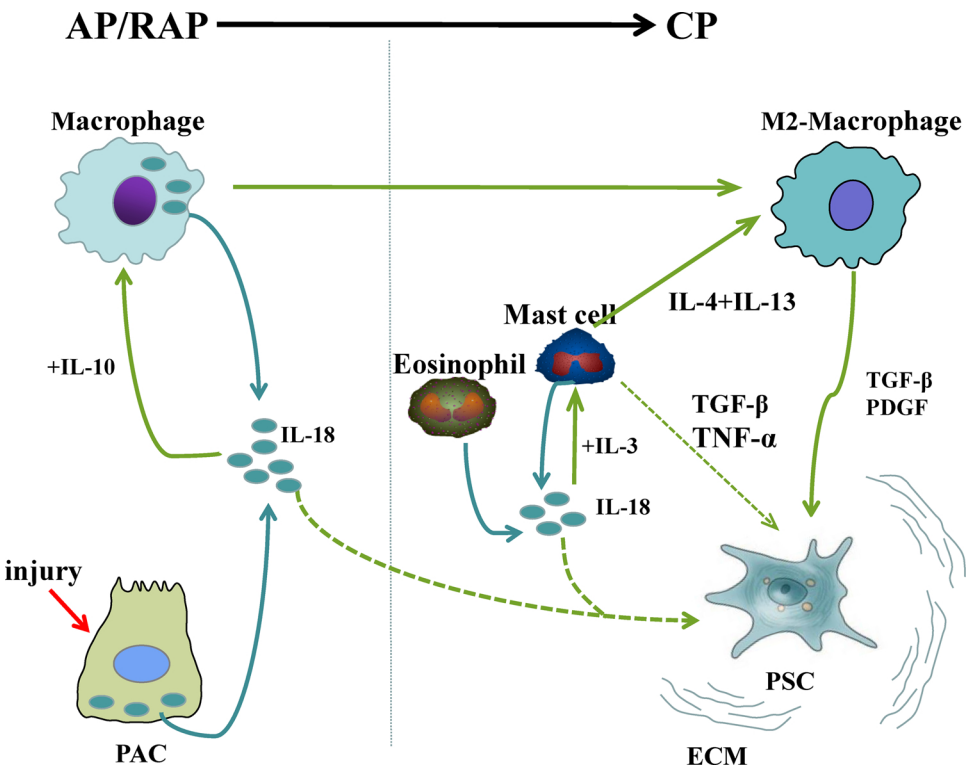

Fig. 2. IL-18 is potentially involved in the progression of AP/RAP to CP.
When AP/RAP occurs, injured PACs and macrophages can produce IL-18 locally in the pancreas. On the one hand, under co-stimulation with IL-10, local IL-18 can induce the polarization of M2 macrophages which are the dominant type of macrophages infiltrated in CP pancreatic tissue. These cells further produce TGF-β and PDGF-β to activate PSCs inducing pancreatic fibrosis. On the other hand, extracellular IL-18 might directly activate PSCs, but this event has not yet been confirmed and is desirable for further investigations. In addition, infiltrating eosinophils and mast cells could also be the potential source of IL-18 in the microenvironment of pancreatic tissue with CP. Moreover, in collaboration with IL-3, IL-18 can promote activation of mast cells producing IL-4 as well as IL-13 to further augment the amount of M2 macrophages. Besides, activated mast cells have also been shown to induce activation of PSCs via the production TGF-β and TNF-α.

Persisting inflammation due to AP gradually results in irreversible fibrosis by activating pancreatic stellate cells (PSCs). Sankaran et al. [88] demonstrated that patients suffering from RAP have a high risk to develop pancreatic fibrosis. Also, in a standard mouse model of CP which is induced by repetitive intraperitoneal injections of caerulein, mice progress from RAP to chronic pancreatitis. These clinical and experimental data support the necrosis-fibrosis hypothesis.

Based on the literature on the association of IL-18 with acute pancreatitis, IL-18 secreted from PACs may play a role in progression of AP/RAP to CP. Schneider et al. [92] reported that IL-18 may be produced by PACs in human pancreatic tissue with CP. However, Gu et al. [99] did not find an exact co-localization of IL-18 with α-amylase which is a maker of PACs by immunofluorescence staining in human pancreas with CP, but in RAP which also showed fibrosis [99,100]. They further localized IL-18 in a CP mouse model induced by long-term ethanol feed and found that about 18% of PACs express IL-18 in cytoplasm under such treatment. Interestingly, treatment with lipopolysaccharide (LPS) for another 24 h after long-term ethanol feed can further induce acute inflammation on the background of CP and therefore significantly increase percentage of PACs expressing IL-18 up to over 60% [95]. So, the attack of acute inflammation under the state of CP is able to induce PAC injury to therefore secrete IL-18. Importantly, Inhibition of the NLRP3 inflammasome which reduces secretion of IL-18 has been shown to attenuate CP induced by repeated caerulein injections [96,97]. Besides, IL-18 has been shown to be associated with various organs' fibrosis [99–102] and induce extracellular matrix components' production promoting migration and proliferation of cardiac fibroblast [101]. Therefore, it is likely that IL-18 secreted from PACs under acute inflammatory conditions can activate PSCs to induce fibrosis making IL-18 as one of the most important cytokines involved in necrosis-fibrosis transformation during CP progression. Therefore, IL-18 is a promising potential target to attenuate the progression of AP/RAP to CP. Further investigations should be focus on the role of IL-18 in the context of PSCs activation to better expound the mechanism by which IL-18 is involved in the progression of AP/RAP to CP.

5.3. IL-18 and macrophages in CP

Macrophages can be generally divided into two lineages based on their function and expressions of surface markers. One macrophage lineage represents classically activated macrophages (M1 macrophages). These are induced mainly by IFN-γ and/or LPS to produce ROS playing a critical role in the host defense and anti-tumor immunity [102]. The other one is alternatively activated macrophages (M2 macrophages), characterized by involvement in control of parasitic infection, tissue remodeling, immune regulation, tumor promotion, and efficient phagocytic activity upon exposure to IL-4/IL-13/IL-10/TGF-β [102]. Recent studies showed that macrophages were associated with several fibrotic diseases [103] and could be involved in the pathogenesis of CP due to the activation of PSCs through the production of TGF-β and PDGF-β [104–106]. Besides, macrophages exert a property to produce the tissue inhibitor metalloproteinase 2 and matrix metalloproteinase 9 which regulate extracellular matrix turnover being associated with fibrosis [102].

According to recent data, IL-18 accumulated in the microenvironment of pancreatic tissue with CP correlates with the macrophage polarization. On the one hand, the NLRP3 inflammasome has been shown to be activated in macrophages making infiltrated macrophages as another source of IL-18 under the state of acute pancreatic inflammation [101]. On the other hand, IL-18 has been shown to play a synergistic role with IL-10 to amplify M2 macrophage polarization in vitro [107]. Therefore, IL-18 can be involved in CP progression via M2 macrophage polarization which has been showed to indirectly activate PSCs by production of TGF-β and PDGF-β. Thus, the macrophage polarization associated with IL-18 is another mechanism supporting the fact that IL-18 participates in the progression of CP induced by AP/RAP (Fig. 2).

5.4. IL-18 and mast cells in CP

Mast cells are well-known effector cells involved in immediate-type allergic reactions [108]. The amount of mast cells is significantly increased in pancreatic tissue with CP compared to normal pancreatic tissue. They are localized around residual acinar tissue suggesting an association with the process of pancreatic destruction [109]. IL-18 was

reported to induce intestinal mucosal mast cell accumulation synergistically with IL-12 [110]. Stimulation with a mixture of IL-18 and IL-3 can influence mast cells to produce IL-4 and IL-13 [32] which are associated with M2 macrophages polarization in CP [102]. In addition, activated mast cells have been observed to induce expression of type-I collagen in mouse skin fibroblast through secretion of TNF-α and TGF-β [111]. Moreover, Lorentz et al. [112] showed that human mast cells are capable to directly secret IL-18. Therefore, mast cells infiltrated in pancreatic tissue with CP is one potential source of elevated IL-18 which is involved in secretion of cytokines from mast cells to activate PSCs and therefore induce fibrosis (Fig. 2).

5.5. IL-18 and eosinophils in CP

Eosinophils are elevated in CP tissue which has been reported elsewhere. Juniper et al. [113] firstly reported a significant increase of eosinophils in the peripheral blood of a patient with chronic relapsing pancreatitis with pleural effusion. Subsequently, a study of 122 patients with CP reported marked eosinophilia in 21 cases (17.2%) [114]. Another study performed by Wang showed that CP patients developed eosinophilia with higher incidence of pancreatic ascites and pancreatic enlargement which suggests the occurrence of eosinophilia might be responsible for the progression of pancreatic inflammation and fibrosis [115]. Furthermore, Manohar et al. [95] discovered that eosinophils accumulated in CP tissue of human and mice. Depletion of IL-5 which is a factor of eosinophils growth, differentiation, and survival, significantly down-regulated IL-18 expression in CP pancreatic tissue and reduced pancreatic damage. Therefore, infiltrated eosinophils are another source of IL-18 in pancreatic tissue with CP. In addition, overexpression of IL-18 has also been shown to promote accumulation of eosinophils in eosinophilic esophagitis [116,117] and airway hyperresponsiveness [118]. Hence, IL-18 is also involved in the development of CP through interaction with eosinophils.

6. IL-18 and pancreatic cancer

6.1. Pathophysiology of pancreatic cancer

Pancreatic cancer (PC) includes exocrine and endocrine malignant. Exocrine malignant tumors represent more than 95% of all pancreatic cancer and comprise themselves different histological features, i.e. i) PDAC representing by far the largest group ii) cystadenocarcinoma and iii) other (sarcomas, metastatic etc) malignant tumors [119]. PC is one of the deadliest cancers in the world. It ranks fourth amongst cancer-associated deaths in both men and women [120] and is predicted to be the second leading cause of cancer-associated deaths by 2030 [121]. Patients with PC have an especially poor prognosis, with 5-year survival rates of only ~1% and median survival of 4–6 months [122]. Upon tumor resection, 5-year survival rates increase to approximately 15%, and a 25% survival is attained in the context of adjuvant chemotherapy [123]. There are many important risk factors, including overweight, long-term diabetes mellitus, smoking, alcohol abuse, CP, family history, age and other risk factors [124,125]. Pancreatic intraepithelial neoplasm, intraductal papillary neoplasm and mucinous cystic neoplasms are precursor diseases of PC [119]. Genetically, KRAS mutation is regarded as the main early event and p53 loss is the late event [119].

6.2. Current therapy of PDAC

The reasons for such a poor prognosis of PDAC are multiple, including rapid tumor dissemination and latent nonspecific symptoms that are associated with a delayed diagnosis [126]. Meanwhile, current therapy has been proven ineffective for the treatment of patients with PDAC. Surgery remains the main therapy for PDAC patients and is the only chance to cure. Recently, the operation has evolved to a relatively safe approach in some experienced centers, but only a minority of PDAC patients have the chance to be candidates for surgery since local invasion or distant spread and delayed diagnosis [127,128]. In addition, more than 90% of patients die of this disease after radical surgery without additional therapy [127]. Therefore, adjuvant treatment strategies have been evaluated in recent decades. From mono-chemotherapy, such as 5-fluorouracil (5-FU), gemcitabine, to combination chemotherapy including S-1 (a combination of tegafur, gimeracil and oteracil potassium), gemcitabine plus capecitabine, nab-paclitaxel plus gemcitabine and FOLFIRINOX [119], undeniably, these strategies did improve 5-year survival rate of PDAC patients after surgery from 15% to 25% [123]. However, adjuvant chemotherapy is just applicable for a monitory of PDAC patients who have chance for surgery [119]. A majority of patients with unresectable or borderline resectable tumor cannot benefit from these strategies [119]. Based on this reason, neoadjuvant chemotherapy mainly for borderline resectable and locally advance unresectable PDAC emerges [129]. This strategy increases resection rates of borderline resectable and unresectable cancer [130]. However, response to this approach was shown not to be reflected by radiographic indicators [131], highlighting the necessary for multidisciplinary discussions. Importantly, high-quality randomized controlled trials about its effect are lacking. Therefore, further investigations are warranted. In addition, some target agents have been evaluated in metastatic PDAC, but most of them cannot improve survival of patients [119]. Excitingly, some stroma target agents, such as secreted protein acidic and rich in cysteine, PEGPH20 and calcipotriol, have been shown to decrease fibrosis and therefore improve drug delivery to enhance chemotherapeutic efficacy [119]. However, the stroma partially protects against tumour progression when it impairs drug delivery into tumor [119]. Therefore, more investigations are warrant to find the better approach which can optimally target the stroma so as not to compromise its protective role. From the above, although there are many strategies for treatment of PDAC, their efficacy by far is not so good that the survival of PDAC patients still remains low. More effective approaches are imperative to develop.

PDAC possesses a highly immunosuppressive milieu [132]. Therefore, immunotherapy might be considered as an attractive approach to combat PDAC [133]. However, immunological trials including interferon-α, or blockage of immune check point molecules did not show any significant improvement in PDAC patients' survival [134,135]. Therefore, new immunotherapeutic strategy should be designed and proved in a clinical setting.

6.3. Immunotherapy of solid tumors with IL-18

Systemic administration of IL-18 has been shown to significantly suppress progression of several kinds of carcinoma in clinical trials by promoting immunity [136–139], suggesting IL-18 as a potent immunotherapeutic substance against cancer. Some phase I clinical trials of recombinant human IL-18 have been conducted in patients with advanced renal cell cancer, melanoma, or lymphoma who were refractory to standard therapy or for whom no effective therapy was available. These studies demonstrated that IL-18 can be safely administered to patients with advanced cancers and partly reveal its antitumor activity by activating monocytes, NK and T cells [136–138]. A phase II clinical trial involved patients with previously untreated metastatic melanoma and showed its limited anti-tumor activity as a single agent with partial response of one patient and capacity of stabling disease for four patients [139].

Recently, IL-18 was also shown to have certain effects on PDAC.

6.4. Correlation of IL-18 with overall survival of patients with PDAC

IL-18 has been shown to be associated with the prognosis of PDAC

even though its exact role has not yet been completely expounded. It is consistent in different studies that IL-18 is significantly increased in the serum of patients with PDAC compared to healthy donors [140–143]. Moreover, IL-18 in the serum of patients with PDAC was higher than in patients with pancreatitis or other common gastrointestinal malignancies including hepatic cancer, cholangiocarcinoma, duodenal carcinoma, gastric carcinoma, and colorectal carcinoma [143]. However, a correlation analysis of the IL-18 concentration in serum with overall survival (OS) of PDAC patients showed inconsistent results by different research groups. Bellone et al. [140] found that the PDAC patients with lower IL-18 level in their serum had longer OS. On the other hand, Guo et al. [143] demonstrated a shorter OS for PDAC patients with lower IL-18 level in their serum. Finally, Usul et al. [142] showed no significant correlation between them. The different conclusions from the mentioned investigations may be resulted from the difference of recruited patients. Majority (76%) of Patients recruited by Usul et al. [142] received chemotherapy, but the case was the opposite in investigation of Bellone with 63% of patients who underwent surgery [140]. Importantly, for patients recruited by Bellone, method of therapy showed influence on OS making it as a confounding factor. In addition, the age range of patients enrolled by Usul et al. [142] was so wide that younger patients showed longer OS than older, therefore, age could be a confounding factor to affect the conclusion about correlation of serum IL-18 concentration with OS. Unfortunately, Guo et al. [143] did not showed the baseline information of patients they recruited. So, it is necessary for exploring their correlation to recruit patients with less confounding factors in baseline information, such as enrolling a large amount of PDAC patients with same therapy and small age range for further investigation.

In addition, all of these investigations did not take the expression of IL-18 binding protein (IL-18BP) into account. IL-18BP has been identified as an endogenous antagonist of IL-18 and can inhibit IL-18 activity by binding to IL-18 to prevent IL-18 interaction with its receptors. If IL-18BP co-exists with mature IL-18 in the serum, part of the mature IL-18 will be bound to IL-18BP and cannot be bio-active [144,145]. Therefore, a single detection of total IL-18 in the serum may not veritably reflect its exact effect on PDAC.

To further describe the correlation of free IL-18 with OS, researchers from the Bellone's group measured the concentration of IL-18BP and free IL-18 in the serum of PDAC patients [146]. This work found significantly elevated serum IL-18 as well as IL-18BP levels in PDAC patients compared to healthy controls [146]. Furthermore, a higher free IL-18 serum concentration was detected in patients with locally advanced or metastatic PDAC [146]. At last, the authors showed that both IL-18BP and free IL-18 in the serum of PDAC patients were positively correlated with the tumor TNM stage, and only free IL-18 level had a significant inverse correlation with OS of PDAC patients [141]. Thus, free IL-18 is a negative prognostic marker for survival of PDAC patients.

6.5. The potential effect of IL-18 on pancreatic cancer

Secretion of IL-18 from PDAC cells has been claimed as one possible source of IL-18 in patients' serum. Bellone et al. [140] detected IL-18 in the supernatants of different PDAC cell lines. They further determined the localization of IL-18 in PDAC tissues of patients by immunohistochemistry which exhibited intense cytoplasmic expression in the tumor cells. Guo et al. [143] using an antibody specific to mature IL-18, detected the cytoplasmic localization of IL-18 in PDAC tissues by immunohistochemistry. Generally, as mentioned before, IL-18 can be secreted extracellularly after activation mainly by caspase-1 [144]. In line of this, Gansauge et al. [147] detected a significantly elevated cytoplasmic caspase-1 expression in PDAC tissues compared to normal pancreatic tissues, which was further confirmed by the Carbone group [141]. Furthermore, these authors also showed that treatment of PDAC patients with 5-FU increased IL-18 level in the serum of PDAC patients. These data suggested that chemotherapy potentially increases the secretion of IL-18 from cancer cells in PDAC patients.

Furthermore, IL-18 derived from PDAC cells has been identified to induce regulatory B cells (Breg) to promote immune tolerance. Zhao et al. [148] showed a positive correlation between Breg population in the peripheral blood and the serum IL-18 level. Mechanistically, IL-18 binds to its receptor on the surface of Bregs to therefore stimulate the PD-1/PD-L1 pathway. Finally, the authors showed that a combination of IL-18BP with PD-1/PD-L1 inhibitors suppressed tumor growth and metastasis of PDAC in an orthotopic implantation mice model. However, another investigation from the same group demonstrated that treatment with recombinant human IL-18 increased the populations of cytotoxic T cells and NK cells in PBMCs isolated from healthy donors [143].

However, IL-18 could execute its effects on tumor cells not only through the activation or inhibition of the immune system, but also directly. Gou et al. [143] demonstrated that recombinant IL-18 treatment of immunosuppressed PDAC-bearing mice decreased the OS of the animals. At the same time, no effect on OS was shown in wild-type (with intact immune system) PDAC-bearing mice. Based on this evidence, a diverse effect of IL-18 on tumor cells could be suggested: (i) a direct effect promoting growth and expansion of PDAC cells by activation of NF-κB signaling pathway, and (ii) an indirect effect (through activation of anti-tumor immune response) inhibiting PDAC growth. Although IL-18 also exerts a dual effects on the immune system - its promotion and suppression [143,148]. The overall effect is activation of immunity since recombinant IL-18 has been showed to have an obvious anti-tumor effect when its direct effect on PDAC cells was inhibited by NF-κB inhibitor. The dual effects of IL-18 on PDAC could be recognized as a promising fact improving its immunotherapeutic value (Fig. 3). However, data of clinical trials are needed to make a definitive conclusion about IL-18 for immunotherapy of PDAC.

6.6. IL-18 enhances immunotherapy with DCs vaccines and CAR-T

DCs play a very important role in primary immune response by activating T cells as effective antigen presenting cells. DCs vaccine pulsed with tumor lysate which induces abundant antigens associated with tumor has been shown to elicit specific T-cell response against the tumor [149,150]. However, some solid tumors including osteosarcoma and fibrosarcoma are partially or completely resisted to such vaccines. Tang et al. [151] tried to explore its effect on PDAC and found that up-regulation of the IL-18 gene significantly increased the efficacy of DCs vaccines pulsed by tumor lysate through augmenting IFN-γ release. This may enhance cytotoxicity of T and NK cells to increase tumor cells death (Fig. 3).

CAR-T cells are one sort of patient's T cells modified ex vivo with a chimeric antigen receptor (CAR). CAR can activate T cells and enhance tumor-targeting specificity by redirecting T cells toward the cancer cells through an antibody-derived binding domain [152]. Once the CAR engages its cognate target, CAR-T cells will be activated and release pro-inflammatory cytokines to eliminate the target cancer cells [153]. CAR-T cells have become one of the most promising breakthrough strategies of cancer immunotherapy. It has been shown to obviously control progression of certain cancers in the long term [152]. However, when used to treat large solid cancers, it has been less promising so far. Very few patients were responding, and only transient or minor tumor remission was observed. Stable disease was achieved in 24–70% of treated patients [154–156]. Abken et al. [157] hypothesized that the observed poor clinic effects for solid tumors resulted from an unfavorable microenvironment with an immune-suppressive stroma in cancer tissues which induced T cells dysfunction and exhaustion.

Chmielewski et al. [158] engineered CAR-T cells with inducible IL-18 release and found that this cytokine can induce a T-Bet^{high} FoxO1^{low} signature in CAR-T cells. FoxO1 is a member of the forkhead box (Fox)

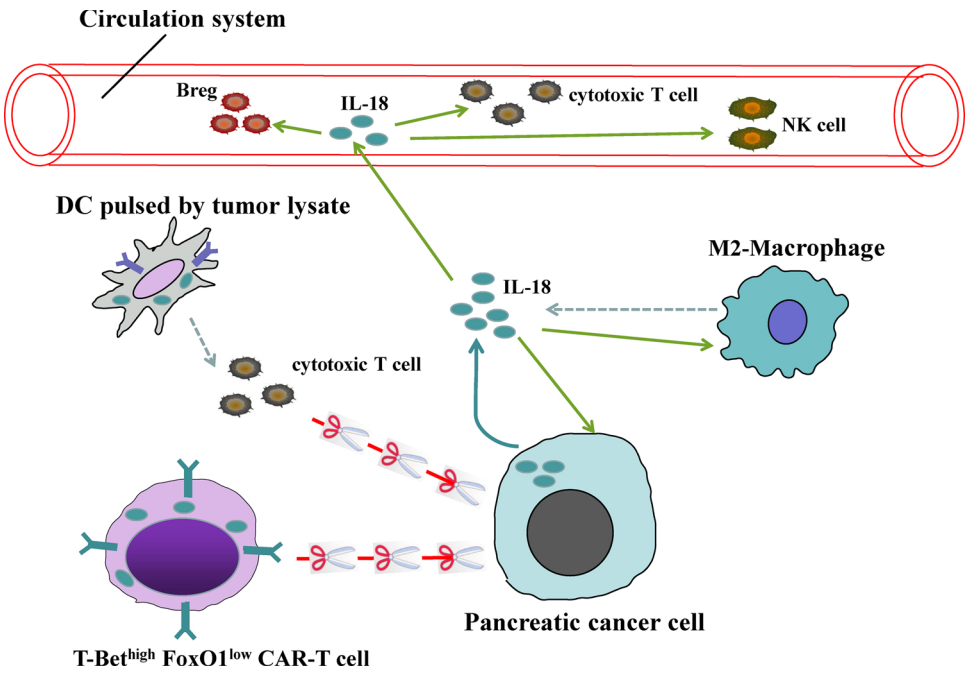

Fig. 3. The diverse effect of IL-18 on PDAC cells.
PDAC cells are the defined source of IL-18 accumulating in the local pancreatic tissue with PDAC. Based on existing evidence, IL-18 could have a diverse effect on PDAC cells: (i) a direct effect promoting proliferation, migration and invasion of PDAC cells via activation of NF-κB pathway, and (ii) an indirect anti-tumor effect through increasing the populations of cytotoxic T and NK cells in the circulation system. In addition, circulating IL-18 has also been shown to induce immunosuppression by activating Breg. Moreover, upregulation of IL-18 in DCs vaccines pulsed by PDAC lysates enhances their therapeutic efficacy on PDAC potentially associated with augmented cytotoxicity of T and NK cells. Similarly, overexpression of IL-18 in CAR-T cells improves their anti-tumor activity through downregulation of FOX1 inhibiting expression of PD-1 and therefore reducing exhaustion of CAR-T cells. In addition, IL-18 might be involved in the polarization of M2 macrophages which are the dominant immunosuppressing cells in the microenvironment.

family of transcription factors and is regulated by T-bet transcription factor activity in chronic infection [159]. FoxO1 has been shown to stimulate the differentiation of terminally exhausted cytotoxic T lymphocytes (CTLs) and therefore induce T cell dysfunction by sustaining the expression of the immune checkpoint receptor PD-1 [160]. The downregulation of FoxO1 in the CAR-T cells with IL-18 release reduced the expression of PD-1. Finally, a continual response of CTLs can continuously enhance anti-tumor activity of CAR-T cells. Chmielewski et al. [158] demonstrated that the orthotopically transplanted PDAC model in mice induced immune suppression and was resisted to CAR-T cells without IL-18 release at advanced stage. However, when these mice were treated with CAR-T cells with inducible IL-18 secretion, their immune suppression was converted into a stronger inflammatory immune response reflecting the infiltration of activated DCs, activated NK cells, and tumor-associated M1 macrophages. At the same time, the frequency of CAR^+ $FoxP3^+$ regulatory T cells (Treg) was decreased. Ultimately, CAR-T cells which can secret IL-18 improved the OS of mice with advanced PDAC [158]. The enhanced anti-tumor activity of CAR-T cells with IL-18 could be linked to the fact that IL-18 can augment the anti-tumor effects of CAR-T cells by promoting their proliferation depending on the T cell receptor and IL-18R [161]. Moreover, it can further strengthen anti-tumor effects of PD-1 inhibition via an accumulation of pre-mature NK cells and memory $CD8^+$ T cells and via suppressing Treg activation [162].

In aggregation, elevated IL-18 levels detected in the serum and tumor tissue of patients with PDAC are associated with PDAC progression. Therefore, a combination of IL-18 and NF-κB inhibitors, or a combination of IL-18BP and PD-1 inhibitor, or CAR-T cells/DCs vaccines with IL-18 release could be considered for the development of new therapeutic strategies for PDAC.

7. Conclusion

Being involved in Th1 and Th2 immune responses, as well as in activation of NK cells and macrophages, IL-18 plays certain roles in different pathologies. Throughout this review, we discussed effects of IL-18 in pancreatic diseases. In AP, the serum IL-18 level positively correlates with the severity of AP and can be an early potential predictive marker, importantly, IL-18 elevation exacerbates AP through activation Th2 response and is involved in AP-associated lung injury. In patients with CP, the level of IL-18 is increased both in the serum and in pancreatic tissue. IL-18 is presumably involved in progression of AP/RAP into CP due to interactions with PACs, immune cells and PSCs. PDAC cells can secret IL-18 which in turn potentially promotes cancer cell proliferation but on the other hand enhances immune response. Furthermore, overexpression of IL-18 in DCs vaccines and in CAR-T cells can enhance their cytotoxicity against PDAC. However, existing data are in part controversial. Therefore, more studies devoted to IL-18 in pancreatic diseases are desirable.

Funding support

This study was supported by National Natural Science Foundation of China (81570585).

Conflicts of interest

The authors declare that they have no conflicts of interest.

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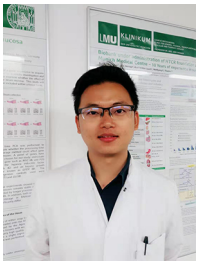

Zhiqiang Li started to study human science of pancreatic diseases as a MD student in the Department of General, Visceral and transplant surgery, Ludwig-Maximilians-University (LMU) Munich after he finished his MD project in China since two years ago. In China, he focused his research on the mechanism by which Exenatide induces pancreatic fibrosis through inhibition of autophagy. He is currently a MD student of LMU and is finishing his project that the role of IL-18 in chronic pancreatitis with emphasis on the activation of pancreatic stellate cells.

Xiao Yu studied human medicine in Shanghai (China), Heidelberg (Germany) and Chicago (USA). He is currently a full surgery professor, Director and Chair of Department of Hepatopancreatobiliary Surgery, Central South University and focusing his research on pancreatitis and pancreatic cancer.

Jens Werner M.D., MBA studied medicine in Heidelberg (Germany), Birmingham (UK) and Baltimore (USA). He is currently full professor, Director and Chair of the Department of General, Visceral, and Transplant Surgery at the Ludwig-Maximilians-University Munich. He is focusing his research on experimental and clinical surgery, particularly on pancreatitis, pancreatic tumors and especially on pancreatic cancer.

Alexandr V. Bazhin studied biology and obtained his PhD in biochemistry at Moscow State University. In 2014 he moved to German Cancer Research Center where he started his postdoctoral training in immunology in the Department of Dirk Schadendorf. Alex is currently a Head of Surgical Research and adjunct professor at the Department of General, Visceral, and Transplant Surgery, Ludwig-Maximilians-University Munich. Presently, cancer immunology is his main research topic.

Jan G. D'Haese studied medicine in Heidelberg (Germany), Lund (Sweden) and Melbourne (Australia). He is currently a senior physician and assistant professor at the Department of General, Visceral, and Transplant Surgery, Ludwig-Maximilians-University Munich. His research is dedicated mainly to pancreatitis and pancreatic cancer.