Role and functional mechanisms of IL-17/IL-17R signaling in pancreatic cancer (Review)

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Abstract. Interleukin-17 (IL-17), an inflammatory cytokine primarily secreted by T helper 17 cells, serves a crucial role in numerous inflammatory diseases and malignancies via its receptor, IL-17R. In addition to stimulating inflammatory responses, IL-17 exhibits dual functions in tumors, exerting both pro- and antitumor effects. Pancreatic ductal adenocarcinoma (PDAC) is the most common pancreatic malignancy and accounts for >90% of pancreatic cancer cases. PDAC is characterized by a prominent stromal microenvironment with significant heterogeneity, which contributes to treatment resistance. IL-17/IL-17R signaling has a notable effect on tumorigenesis, the tumor microenvironment and treatment efficacy in various cancer types, including PDAC. However, the specific mechanisms of IL-17/IL-17R signaling in pancreatic cancer remain uncertain. This review presents a brief overview of the current knowledge and recent advances in the role and functional mechanisms of IL-17/IL-17R signaling in pancreatic cancer. Furthermore, the potential of IL-17-targeted therapeutic strategies for PDAC treatment is also discussed.

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1. Introduction

Pancreatic cancer, predominantly consisting of pancreatic ductal adenocarcinoma (PDAC) cases, ranks among the most lethal neoplasms with a 5-year survival rate of only 12% (1). Despite accounting for only 3% of all tumors, PDAC is the fourth leading cause of cancer-related death (2). PDAC exhibits extreme resistance to traditional chemotherapy and radiotherapy. Furthermore, while immunotherapy has achieved considerable milestones in treating various tumors, standalone immunotherapy has not exhibited an equal efficacy against pancreatic cancer (3). Therefore, exploring innovative targets and mechanisms to enhance the therapeutic effects of chemotherapy and immunotherapy is critical for improving the clinical prognosis of patients with PDAC.

The inflammatory cytokine interleukin-17 (IL-17), primarily released by T helper 17 (Th17) cells, is also produced by other cell populations such as neutrophils, γδT cells, $CD8^+$ cytotoxic T cells and natural killer T cells (NKTs) (4). IL-17 and its receptor, IL-17R, play pivotal roles not only in allergic and autoimmune diseases, inflammation (5) and in response to COVID-19 (6), but also in the microenvironment of various tumors, including PDAC (7-9). The activation of IL-17/IL-17R and downstream signaling pathways, including the nuclear factor κB (NF-κB) and mitogen-activated protein kinase (MAPK) pathways, regulates tumor progression and resistance to chemotherapy in several tumor types (10-12). Due to

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Abbreviations: Act1, NF-κB activator 1; ADM, acinar-to-ductal metaplasia; CAF, cancer-associated fibroblast; iCAF, inflammatory CAF; CTLA-4/8, cytotoxic T-lymphocyte-associated protein 4/8; EMT, epithelial-mesenchymal transition; ERK, extracellular signal-regulated kinase; GVAX, GM-CSF-modified tumor cell vaccine; ICI, immune checkpoint inhibitor; IL-17, interleukin-17; IL-17R, interleukin-17 receptor; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor κB; NKT, natural killer T cell; PanIN, pancreatic intraepithelial neoplasia; PDAC, pancreatic ductal adenocarcinoma; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; ROS, reactive oxygen species; SEFIR, SEF/IL-17 receptor; Tc17, Type 17 $CD8^+$ cytotoxic T cell; Th17, T helper 17 cell; TLS, tertiary lymphoid structure; TME, tumor microenvironment; TRAF, TNF-receptor associated factor; Treg, regulatory T cell

Key words: IL-17, pancreatic cancer, cytokines, TME, immunotherapy

the functions and properties of IL-17 in diverse malignancies, comprehensive investigations into the role and mechanisms of IL-17/IL-17R signaling in the pathogenesis of PDAC could reveal a potentially beneficial strategy for improving therapeutic outcomes.

This review presents a comprehensive exploration of the biology of IL-17/IL-17R signaling and its associated pathogenic mechanisms in pancreatic cancer. It provides an in-depth review of the substantial effects of IL-17/IL-17R in PDAC from the perspective of the tumor microenvironment (TME) and treatment responsiveness at the cellular and molecular levels. The present review aims to offer novel insight into the therapeutic management of pancreatic cancer.

2. IL-17/IL-17R family: Structure, function and signaling pathways

IL-17 family. The cytokine family IL-17 comprises six distinct members: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (also known as IL-25) and IL-17F. Among this family, IL-17A [or IL-17, alternatively known as cytotoxic T-lymphocyte-associated protein (CTLA)-8], is the prototypical and most extensively studied member (5,13,14). Besides Th17 cells, IL-17 is produced by other cell types including Type 17 $CD8^+$ cytotoxic T cells (Tc17), NKTs, innate lymphoid cells and neutrophils (15,16). Functioning as an immune effector cytokine, IL-17 is derived from both adaptive and innate immune cells, facilitating an integral nexus between adaptive and innate immunity.

Serving as the hallmark of Th17 cells, IL-17A plays a pivotal role in the development of autoimmune diseases, inflammation and tumorigenesis (5). Increased levels of IL-17A have been implicated as a key driver in a series of autoimmune diseases (17) including psoriasis (18), rheumatoid arthritis (19) and multiple sclerosis (20), which are primarily characterized by chronic inflammation. In previous years, an increasing number of studies have focused on the role of IL-17A in tumors. For instance, in lung cancer cell lines, IL-17A stimulation triggers the phosphorylation and activation of extracellular signal-regulated kinase (ERK)1/2, which subsequently phosphorylates a myriad of cytoplasmic proteins, thereby regulating various crucial cellular processes such as proliferation, differentiation, invasion and apoptosis (21). A recent study indicated that the transcriptional activation of IL-17A by Oct4 regulates the p38 signaling pathway and encourages the polarization of M2 macrophages, thereby promoting the metastasis of cervical cancer (22). IL-17B is widely expressed across diverse tissues, including the stomach, intestine and pancreas, and is intimately correlated with tumorigenesis and the progression of tumors, as observed in gastric and pancreatic cancer (23). This underscores an emerging field of research into the IL-17 family. Additionally, IL-17B expression is positively correlated with an unfavorable prognosis in breast (24), lung (25) and pancreatic (26) cancer. IL-17C is predominantly localized within the mucosal epithelium of the oral cavity, skin and respiratory tract (27), and responds to various cytokines and pathogenic stimuli at the mucosal surfaces, thereby orchestrating inflammation, autoimmune diseases and bacterial infections (28,29). Furthermore, in lung cancer, IL-17C contributes to the growth and proliferation of tumor cells by recruiting neutrophils into the TME (30). Conversely, few studies have investigated IL-17D; although its receptor remains obscure, evidence suggests that it may play an immunoregulatory role in tumors and infectious diseases (31). IL-17E, also known as IL-25, is extensively distributed in a number of tissues (32), exerts potent proinflammatory effects, and stimulates Th2 responses. Additionally, it induces IL-4 and IL-13 production in various tissues, and fosters eosinophil expansion by inducing IL-5 release (33). IL-17F, the last member of the IL-17 family, shares >50% amino acid sequence homology with IL-17A. Typically produced by the same cells, IL-17F and IL-17A unite to create homo or heterodimers and execute similar functions (5). IL-17F serves as a less potent inducer of inflammation than IL-17A, displaying notably reduced signaling intensity and downstream gene activation (34).

IL-17R. The cytokine, IL-17, interacts with IL-17R to transmit upstream signals. The IL-17R family consists of five members, ranging from IL-17RA to IL-17RE. The IL-17R transmembrane protein comprises a fibronectin type III domain situated extracellularly and a conserved Sef/IL-17R (SEFIR) domain at the cytoplasmic terminus (5,34). During this process, the NF-κB activator 1, Act1, is recruited downstream of the IL-17R complex upon recognizing the SEFIR domain, thereby relaying IL-17-induced inflammatory response signals (35,36).

Mechanistically, the interaction between IL-17 and IL-17R is not straightforward; it involves the formation of homodimers or heterodimers between IL-17Rs. For instance, IL-17RA functions as a common receptor of the IL-17 family, forming heterodimers with IL-17RC to transmit upstream IL-17A and IL-17F signals in most cases, which is a characteristic feature of IL-17/IL-17R signaling (34,35). Similarly, IL-17RA can form heterodimers with IL-17RB and IL-17RE, which recognize homodimeric IL-17B/IL-17E and IL-17C proteins, respectively (37).

IL-17RB, often referred to as IL-25R, serves as a receptor for IL-17B and IL-17E and exhibits widespread expression across various organs and tissues, including the liver, kidney and mucosal epithelium (25). IL-17B signaling via IL-17RB can promote tumor growth, migration and invasion. Furthermore, activating IL-17B/IL-17RB directly stimulates the proliferation and migration of malignant cells and induces resistance to conventional chemotherapy (38). The downstream signaling pathway of IL-17RB is unclear. However, a recent study revealed the proximal signal transduction pathway of IL-17RB when stimulated by IL-17B in pancreatic cancer. This involves IL-17RB recruiting mixed-lineage kinase 4 to phosphorylate the Y447 residue of IL-17RB. Subsequently, phosphorylated IL-17RB recruits a ubiquitin ligase, tripartite motif containing 56, which adds K63-linked ubiquitin chains onto the K470 residue of IL-17RB. Mutation of either the Y447 or K470 of IL-17RB subsequently propagates downstream oncogenic signaling through assembling Act1 and other factors (39). IL-17RC, also known as IL-17RL, serves a crucial functional role in modulating IL-17-mediated responses, particularly through interactions with IL-17A and IL-17F (40). A recent study suggested that IL-17RC could be a key factor in IL-17-induced responses in tumor cells by regulating the activation of classical IL-17A target genes and proteins such as C-X-C motif chemokine ligand 1 (CXCL1), colony stimulating factor (CSF)1 and programmed death-ligand 1 (PD-L1)

at a molecular level. Thus, IL-17RC may serve as a possible indicator of the impact of IL-17/IL-17R signaling on tumor advancement (41).

New evidence shows that IL-17RD forms a heterodimer with IL-17RA, exclusively binding to the IL-17A homodimer instead of the IL-17A/F or IL-17F/F heterodimers (42). This updates the previous understanding that IL-17RD functions as an orphan receptor. The downregulation and loss of IL-17RD have been documented in a range of malignancies, with mounting evidence indicating its involvement in tumorigenesis (43). Mechanistically, the expression of IL-17RD may regulate the aggressiveness of tumor cells by modulating the biological responses to EGF, FGF and Wnt signaling pathways (43). IL-17RE has been less investigated compared with the other IL-17 receptors. However, previous studies revealed interactions between IL-17RE and IL-17C in inflammatory and immune responses (44,45). Additionally, an increased IL-17RE expression level corresponds to a poor prognosis in patients with hepatocellular carcinoma (46).

IL-17/IL-17R signaling. As a pivotal proinflammatory cytokine, the physiological functions of IL-17 are predominantly mediated via the initiation of downstream signaling cascades upon its interaction with IL-17R. In the process of IL-17/IL-17R signal transduction, the intracellular domain of IL-17R includes a conserved SEFIR domain that orchestrates an interaction with the corresponding SEFIR motif on Act1, thereby activating a wide range of downstream signaling pathways (47). Act1 harbors a TNF receptor-associated factor (TRAF) binding site, facilitating interaction with TRAF family proteins (35,36). The binding of TRAF6 to Act1 effectively activates the downstream NF-κB and MAPK pathways, thereby activating a cascade of transcriptional regulatory alterations (48). Additionally, NF-κB participates in a series of physiological and pathological processes, including inflammation, oxidative stress, cell metabolism, proliferation and apoptosis, and exerts pervasive regulatory effects (49-51). Furthermore, the binding of TRAF2 and TRAF5 to Act1 enhances posttranscriptional mRNA stability through the modulation of diverse RNA-binding proteins, such as human antigen R (HuR) and AT-rich interactive domain-containing protein 5a (Arid5a) (5).

The binding of IL-17R to Act1 via the SEFIR domain is the initial step in IL-17/IL-17R signal transduction (5,52). By serving as an E3 ubiquitin ligase, Act1 recruits and ubiquitinates TRAF6, subsequently recruiting and activating transforming growth factor β-activated kinase 1 and inhibitor of NF-κB kinase (IKK). The activated IKK complex promotes the phosphorylation and degradation of the IκB subunit on the NF-κB/IκB complex, resulting in the exposure of the nuclear localization signal on NF-κB. This process enables the rapid translocation of NF-κB to the nucleus and the induction of inflammatory gene transcription (52). Furthermore, activated TRAF6 triggers the phosphorylation and activation of the MAPK pathway (5,52). Notably, CCAAT/enhancer-binding protein β (C/EBPβ) is another significant transcription regulatory factor activated directly by IL-17R through the C/EBPβ activation domain. C/EBPβ activation can also occur as a secondary response to the activation of the aforementioned MAPK pathway (5,52).

Compared with the transcriptional regulation mediated by transcription factors, IL-17 triggers posttranscriptional regulation by stabilizing specific mRNAs and proteins, which can be more potent but less well-defined. The complex formed by TRAF2 and TRAF5 binding with Act1 acts as an RNA-binding protein, interacting with target mRNAs, such as CSF2 and CXCL2, and facilitating their fates (53). Consequently, the complex directly influences mRNA metabolism, stability and translation. Additionally, Act1 promotes the binding of HuR to mRNA, enabling mRNA to translocate to polysomes for translation (52). Similarly, the expression of Arid5a, an RNA-binding protein, is upregulated by IL-17, which competes with Regnase-1 to stabilize IL-17-induced transcripts by binding to TRAF2 (54). In addition, IL-17 promotes the interaction between Act1, IKK and TANK-binding kinase 1, resulting in the translocation of these proteins to the nucleus and the phosphorylation of splicing factor 2 (SF2), which in turn inhibits mRNA degradation mediated by SF2 (53). Notably, the IL-17-induced posttranscriptional regulation of mRNA is a component of its self-enhancement mechanisms, amplifying the activity of IL-17 (55).

Overall, the IL-17/IL-17R signaling cascade is centered on Act1. On the one hand, it activates downstream signaling primarily through the NF-κB and MAPK pathways, thereby regulating the expression of corresponding target genes transcriptionally. On the other hand, it exerts a robust proinflammatory effect through posttranscriptional regulation, principally by enhancing the stability of target mRNAs and protein translation. The classification and structure of IL-17 cytokine family members and the corresponding downstream IL-17R, as well as the intracellular IL-17/IL-17R signal transduction pathways are summarized in Fig. 1.

IL-17/IL-17R signaling in tumors. IL-17/IL-17R signaling serves a crucial role in the tumorigenesis and progression of diverse neoplasms by stimulating distinct pathways and downstream effectors. For instance, IL-17 upregulates zinc finger E-box binding homeobox 1, a pivotal regulator of epithelial-mesenchymal transition (EMT) through NF-κB, thus fostering tumor cell invasion and metastasis by precipitating EMT (11). Additionally, it has been demonstrated that IL-17 expression is positively correlated with the activation of STAT3 (56). Facilitated by the intermediary IL-6, IL-17 can accelerate the activation of the STAT3 pathway within tumor cells. This leads to resistance to apoptosis and an increase in angiogenic factors, consequently promoting tumor cell growth and angiogenesis, thereby advancing tumor progression (57,58).

IL-17/IL-17R signaling not only has protumor effects but can also achieve antitumor effects by regulating adaptive immune responses. These include the recruitment of T lymphocytes, the enhancement of NKT activity and the stimulation of cytotoxic T lymphocyte (CTL) production (59-61). For instance, mice lacking IL-17 displayed reduced levels of IFN-γ^+ T cells infiltrating colon cancer cells (62). This resulted in an increased tumor volume and number of metastases. Similarly, there is an inverse relationship between the expression of IL-17 and tumor invasion in esophageal squamous cell carcinoma. By contrast, a positive correlation was observed between IL-17 expression and the abundance of CTLs, NKTs and dendritic cells (DCs) (59). The different roles and corresponding

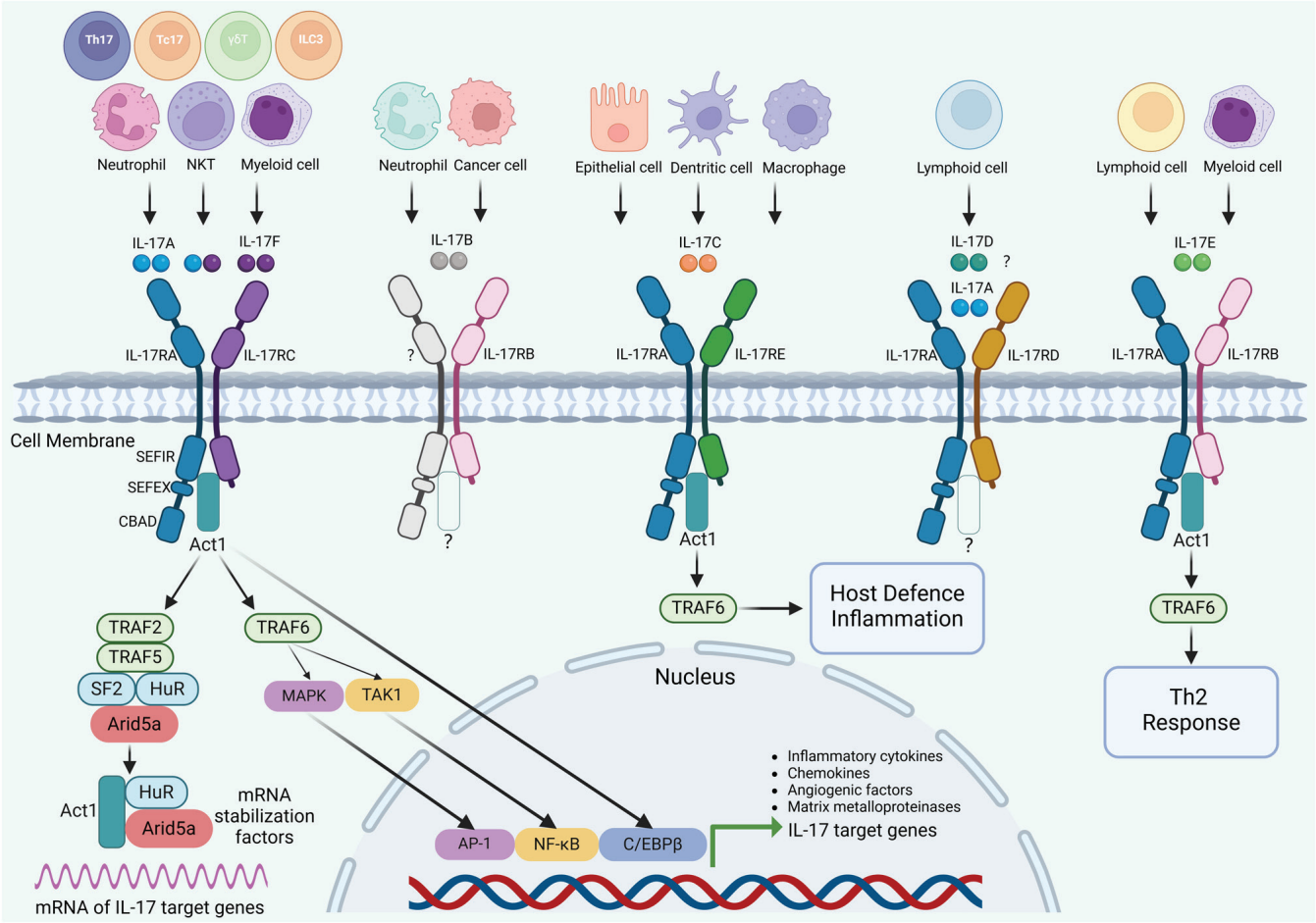

Figure 1. IL-17 family members and intracellular signal transduction pathways. The IL-17 family comprises six cytokine members (IL-17A to IL-17F) and five receptor members (IL-17RA to IL-17RE). In addition to Th17 cells, IL-17-producing cells include NKT cells, Tc17 cells, ILCs and neutrophils. A homodimer or heterodimer formed by IL-17A and IL-17F binds to the IL-17RA/RC complex, functioning as a hallmark of IL-17/IL-17R signaling. The downstream signaling pathways of IL-17B/IL-17RB have not been thoroughly investigated. After recognizing the IL-17RA/RE complex, the IL-17C homodimer triggers downstream signaling pathways involved in host defense and inflammation. Although the receptor for the IL-17D homodimer remains unidentified, the IL-17RA/RD complex exclusively binds to the IL-17A homodimer. The IL-17E homodimer binds to the IL-17RA/RB complex, activating downstream Th2 responses. The intracellular signaling pathways and critical signaling molecules downstream of the activation of the IL-17RA/RC complex are summarized. Act1, NF-κB activator 1; AP-1, activator protein-1; Arid5a, AT-rich interactive domain-containing protein 5a; C/EBP, CCAAT enhancer-binding protein; CBAD, C/EBPβ activation domain; HuR, human antigen R; IL, interleukin; IL-R, IL-receptor; ILC, innate lymphoid cell; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor κB; NKT, natural killer T cell; SEFIR, SEF/IL-17 receptor; SEFEX, SEFIR-extension sequences; Tc17, Type 17 $CD8^+$ cytotoxic cell; Th17, T helper-17 cell; TRAF, TNF-receptor associated factor; TAK1, transforming growth factor-β-activated kinase-1.

mechanisms of IL-17/IL-17R signaling in various tumors are summarized in Table I.

3. IL-17/IL-17R signaling in the pathogenesis of PDAC

PDAC, which is derived from pancreatic epithelial cells, is the most common exocrine tumor of the pancreas and accounts for >90% of all pancreatic cancer cases (63). In the presence of oncogenic Kras mutations and acute or chronic inflammatory stimuli, mature pancreatic acinar cells display marked plasticity and undergo differentiation into duct-like cells with ductal features. This transformation, known as acinar-to-ductal metaplasia (ADM), subsequently progresses to pancreatic intraepithelial neoplasia (PanIN) and ultimately gives rise to PDAC (63). A notable increase in the levels of Th17 and IL-17 in the peripheral blood of patients with PDAC is positively correlated with the tumor stage. Moreover, the abundance of Th17 and IL-17A within the TME of patients with PDAC significantly exceeds their level in peripheral blood and adjacent normal tissue of the same patients (64). IL-17/IL17R signaling involves a multitude of pathogenetic processes in PDAC, including ADM, PanIN and advanced tumor progression (65-67).

During the precancerous stages of PDAC (ADM and PanIN), IL-17A can accelerate the process of pancreatic ADM while also assisting in the maintenance of stem cell features in tumor cells and the recruitment of immune-suppressive granulocytes (65). IL-17 released from Th17 and γδT17 cells interacts with the IL-17RA located in PanIN epithelial cells, resulting in the expansion of the tumor stroma and the development of PanIN, which can be effectively suppressed pharmacologically by inhibiting the signal transduction of IL-17 (65). In pancreatic epithelial cells with the $Kras^{G12D}$ mutation, IL-17A can directly stimulate the pancreatitis mediator, regenerating islet-derived 3-β, leading to the activation of STAT3, thereby furthering the development of ADM and PanIN (68). Moreover, IL-17/IL-17R

Table I. Functions and mechanisms of IL-17/IL-17R signaling in tumors.

Effect	Tumor	Mediator	Mechanism	(Refs.)
Pro-tumor	Lung cancer	IL-17	Induces EMT via the IL-17/NF-κB/ZEB1 pathway and promotes invasion and metastasis	(11)
		IL-17A	Elicits the phosphorylation activation of ERK1/2 and modulates cell proliferation and invasion	(21)
	Liver cancer	IL-17	Facilitates angiogenesis and tumor progression via the IL-6/STAT3 pathway	(57)
		IL-17	Induces the transformation of LPCs into CSCs through the downregulation of miR-122 activity	(102)
	Pancreatic cancer	IL-17A	Accelerates the development of ADM and PanIN	(65, 103)
		IL-17B/ IL-17RB	Facilitates the recruitment of neutrophils, lymphocytes and endothelial cells	(26, 89)
		Tc17	Mediates Tc17-iCAFs interaction, alters the transcriptional profile of tumor cells and promotes proliferation and metabolism	(58)
	Colorectal cancer	IL-17	Potentiates tumor progression and resistance to chemotherapy via the IL-17/CXCL17/GPR35 axis	(104)
		IL-17A	Induces mitochondrial dysfunction and cell pyroptosis via the ROS/NLRP3/capsase4/GSDMD pathway	(10)
	Cervical cancer	IL-17A	Encourages polarization of M2 macrophages and promotes metastasis through the OCT4/IL-17A/p38 pathway	(22)
	Breast cancer	IL-17RB	Promotes tumorigenesis through the inhibition of cell apoptosis mediated by NF-κB	(24)
	Gastric cancer	IL-17B/ IL-17RB	Drives tumor cell proliferation and migration via AKT-β-catenin activation	(105)
	Prostate cancer	IL-17	Attracts M2 macrophages and promotes tumor growth	(106)
	Oral squamous cell carcinoma	IL-17A	Co-mediates the protumor phenotype of neutrophils and EMT with TGF-β1	(107)
Antitumor	Esophageal squamous cell carcinoma	IL-17	Enhances the cytotoxic activity of NKTs and the migration of T cells and DCs	(59)
	Melanoma	Th17	Stimulates $CD8^+$ cytotoxic T lymphocyte responses	(60)
	Thymoma	Th17	Facilitates diverse inflammatory leukocyte recruitment ($CD4^+$, CD8+ T cells and DCs)	(61)

ADM, acinar duct metaplasia; AKT, AKT serine/threonine kinase; CSC, cancer stem cell; CXCL17, C-X-C motif chemokine ligand 17; DC, dendritic cell; EMT, epithelial-mesenchymal transition; ERK, extracellular signal-regulated kinase; GPR35, G protein-coupled receptor 35; GSDMD, Gasdermin D; iCAF, inflammatory cancer-associated fibroblast; IL, interleukin; IL-R, interleukin receptor; LPC, liver progenitor cell; NF-κB, nuclear factor κB; NKT, natural killer T cell; NLRP3, NLR family pyrin domain containing 3; OCT4, octamer-binding protein 4; p38, mitogen-activated protein kinase 14; PanIN, pancreatic intraepithelial neoplasia; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3; Tc17, Type 17 CD8+ cytotoxic cell; TGF-β1, transforming growth factor β1; Th17, T helper-17 cell; ZEB1, zinc finger E-Box binding homeobox 1.

signaling acts synergistically with the Notch pathway and aids the differentiation of Th17 cells, to also promote PanIN and PDAC development (68). Furthermore, IL-17 can modulate the stem cell features of PanIN, leading to an enhanced embryonic stem cell signature represented by doublecortin like kinase 1, POU class 2 homeobox 3 and aldehyde dehydrogenase 1 family member A1 and an increased expression level of IL-17RC through the canonical NF-κB and MAPK pathways. This ultimately promotes the initiation and progression of PanIN (69). Similarly, the impact of IL-17 on promoting the tumorigenic potential of cancer stem-like cells has also been observed in ovarian cancer (70).

As PDAC progresses, IL-17/IL-17R signaling also plays a pivotal role. For instance, IL-17A collaborates with IL-4 to activate NF-κB within PDAC tumor cells, thereby inducing the expression of dual oxidase 2 (DUOX2), triggering the accumulation of extracellular hydrogen peroxide and reactive oxygen species (ROS)-induced oxidative stress-related DNA damage and consequently fostering tumor progression (71). Additionally, activating IL-17B/RB on tumor cells can subsequently phosphorylate and activate ERK1/2, enhancing the production of a series of chemokines, such as C-C motif chemokine ligand (CCL)20, CXCL1, IL-8 and trefoil factor 1,

ultimately facilitating the recruitment of neutrophils, lymphocytes and endothelial cells, which assists the invasion and metastasis of PDAC (26). Moreover, activating the IL-17B/RB pathway in activated pancreatic stellate cells can also enhance the metabolism and proliferation of PDAC tumor cells (72). Furthermore, in a KPC-OG murine model designed to study antigen-specific immune responses in the context of PDAC, enhanced inflammation, fibrosis and neovascularization were observed in KPC-OG lesions after IL-17 stimulation through the phosphorylation and activation of ERK, STAT3, and EGFR (73).

In general, these findings underscore the significant role of IL-17/IL-17R signaling and its associated pathways in the tumorigenesis and progression of PDAC, suggesting that IL-17/IL-17R is a promising target for therapeutic interventions against PDAC. In particular, studies on the effect of IL-17 on PDAC tumor cells have focused primarily on the initial phases of the tumor, wherein IL-17 modulates the stem cell features of tumor cells, and on the inflammation-cancer transformation of epithelial cells. Therefore, it is imperative to delve further into the involvement of IL-17/IL-17R signaling in the advanced stages of PDAC, as this will provide more compelling evidence for the targeting of IL-17 in PDAC. IL-17/IL-17R signaling in the pathogenesis of PDAC is summarized in Fig. 2.

4. IL-17/IL-17R signaling in the PDAC TME

The TME of PDAC, characterized by markedly high stromal density and spatial heterogeneity, encompasses a plethora of cell components, such as fibroblasts, endothelial cells and immune cells, that are surrounded by an extracellular matrix and different types of signaling molecules (74). Compared with those of the normal pancreas, the distinct milieu of the PDAC TME exhibits a series of changes in immune cells and immunomodulatory molecules. A study has shown a reduction in regulatory T (Treg) cells and increased IL-17A expression levels in the TME of patients with PDAC in the stable or remission phases. Conversely, patients with unresectable advanced PDAC exhibit elevated Treg infiltration and reduced expression levels of IL-17A in the TME (8). Growing evidence indicates that tumor cells within the PDAC microenvironment promote cell proliferation and immune escape by engaging neighboring immune cells and the tumor stroma (74,75). Activation of IL-17/IL-17R signaling and downstream pathways occurs to varying degrees in different cells within the TME and contributes to shaping an immunosuppressive microenvironment together, thus promoting the progression of PDAC (9,76).

Th17 differentiation from naïve $CD4^+$ T cells can be induced by DCs located in the TME of PDAC. This is achieved through the secretion of cytokines, including IL-23, IL-6 and TGF-β (76). Consequently, Th17 differentiation stimulates the synthesis of IL-17 and the progression of PDAC. Notably, IL-17-stimulated tumor cells can recruit neutrophils through the release of several cytokines and chemokines (CCXL5, CXCL3, CSF3, CCL20 and CCXL1), triggering neutrophil extracellular traps (NETs) and cytotoxic $CD8^+$ T-cell exclusion and maintaining the immunosuppressive microenvironment (12). Nonetheless, research has indicated that neutrophils can suppress IL-17^+ γδT cells through ROS signaling, thereby exerting antitumor effects (77). A recent study indicated that eliminating IL-17RA in PDAC tumor epithelial cells could lead to the enhanced infiltration of $CD8^+$ T cells into the TME. Mechanistically, IL-17/IL-17R signaling regulates immune responses via the expression of the co-stimulatory molecule, B7-H4, in tumor cells, hence promoting an immunosuppressive microenvironment (78).

A prominent feature of the PDAC TME is its high stromal density, where cancer-associated fibroblasts (CAFs) contribute greatly (76). A previous study has demonstrated that IL-17 can activate fibroblasts through metabolic reprogramming and proliferation enhancement via the induction of hypoxia inducible factor 1 subunit α (HIF1α) expression (7). Accordingly, depletion of IL-17A in the TME of PDAC can reshape the features of CAFs and the tumor stroma, resulting in increased IL-17F levels in the serum and elevated IL-17R expression levels in CAFs, ultimately fostering an antitumor microenvironment. Specifically, the presence of IL-17A leads to collagen accumulation and a progressive increase in stiffness in the TME, thus hindering immune cell infiltration and promoting EMT (9). Conversely, IL-17A depletion in PDAC causes enhanced infiltration of α smooth muscle actin $(\alpha SMA)^+$ fibroblasts, macrophages (especially $CD80^+$ macrophages), $CD3^+$ T cells and $CD8^+$ T cells and downregulated infiltration of Treg cells (9). The influence of IL-17/IL-17R signaling on CAFs is also evident in the interaction between Tc17 cells and inflammatory CAFs (iCAFs). IL-17A secreted by Tc17 cells may synergistically promote the differentiation of protumor iCAFs upon TNF stimulation, and activated iCAFs can in turn promote the differentiation of Tc17 cells through an IL-6 positive feedback loop. iCAFs activated by Tc17 cells can transform PDAC tumor cells toward a 'basal-like' transcriptional subtype signature, with enhanced proliferation and metabolism (58).

Macrophages also play an essential role in modulating the immunosuppressive microenvironment of PDAC. Depletion of IL-17A in the TME can reshape macrophage characteristics through metabolic reprogramming, with reduced tumor-associated macrophage (TAM) and Treg infiltration and increased $CD8^+$ T-cell infiltration (79). Notably, receptor-interacting serine/threonine-protein kinase 1 suppression in TAMs can trigger a distinctive 'mixed' Th1/Th17 cell phenotype in PDAC, which is associated with the superior efficacy of immunotherapy (80).

The influence of the gut microbiome on the TME has been extensively documented (81). Recent research has indicated that gut dysbiosis triggered by enteric IL-17RA deficiency results in the expansion and infiltration of Th17 and $CD20^+$ B cells in PDAC. Specifically, there exists a compensatory IL-17 loop between extra-tumoral sites, such as the gut, and the PDAC TME. In this context, the deficiency of IL-17RA in enteric epithelial cells leads to gut microbial changes, which in turn drive systemic IL-17 production and promote the growth of pancreatic tumors through IL-17RA signaling pathways within tumor cells. In tumor cells, IL-17/IL-17RA signaling stimulates tumor growth through the activation of the oxidative stress-related gene, DUOX2 (82). Another study demonstrated that the inhibitory effect of gut microbiome depletion by antibiotics on pancreatic tumor growth was mitigated in mice following treatment with an IL-17 neutralizing antibody (83). This underscores the significant role of IL-17 signaling in the interaction between the gut microbiome and pancreatic cancer

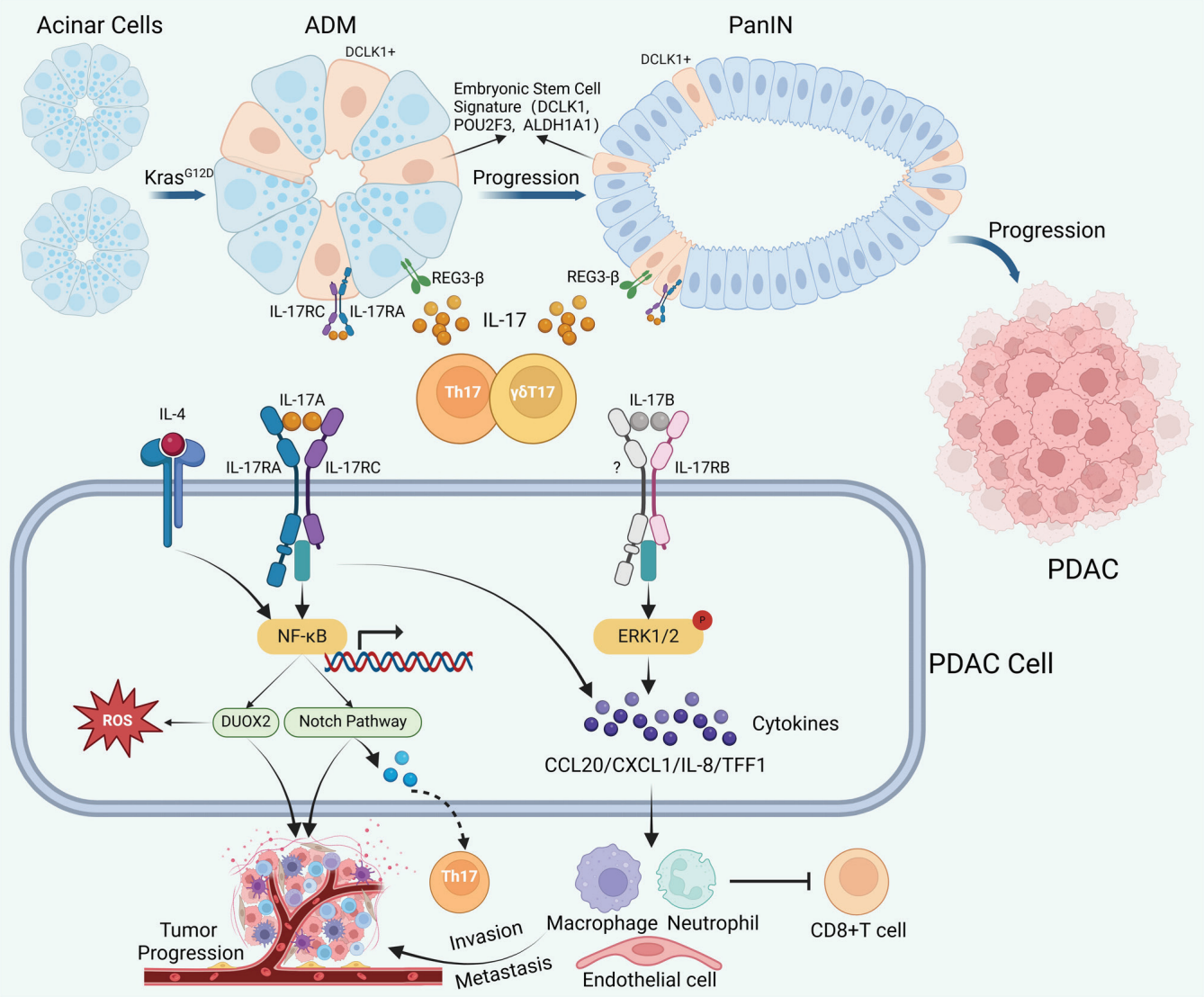

Figure 2. IL-17/IL-17R signaling in the pathogenesis of PDAC. In the presence of the oncogenic Kras^{G12D} mutation, mature pancreatic acinar cells can differentiate into duct-like cells. These duct-like cells subsequently progress through stages of PanIN leading to PDAC. During this process, IL-17A released from Th17 and γδT cells stimulates REG3-β in pancreatic epithelial cells to promote the progression of ADM and PanIN. IL-17A helps to maintain the stem cell features of PanIN cells, leading to an enhanced embryonic stem cell signature and expression of IL-17RC. IL-17A collaborates with IL-4 to activate NF-κB in PDAC, thus inducing the expression of DUOX2 and consequently promoting tumor progression by triggering the ROS signature. The activation of NF-κB leads to overexpression of the Notch pathway in PanIN and PDACs. This promotes the progression of PanIN and PDAC and facilitates the differentiation of Th17 cells. Activating IL-17B/RB in PDAC tumor cells can subsequently phosphorylate and activate ERK1/2, enhancing the production of a series of chemokines and facilitating the recruitment of neutrophils, lymphocytes, and endothelial cells, which ultimately contributes to the invasion and metastasis of PDAC. ADM, acinar duct metaplasia; DUOX2, dual oxidase 2; ERK, extracellular signal-regulated kinase ; IL, interleukin; IL-R, IL-receptor; NF-κB, nuclear factor κB; PanIN, pancreatic intraepithelial neoplasia; PDAC, pancreatic ductal adenocarcinoma; ROS, reactive oxygen species; Th17, T helper-17 cell; REG3-β, regenerating islet-derived 3β; DCLK1, doublecortin like kinase 1; POU2F3, POU class 2 homeobox 3; ALDH1A1, aldehyde dehydrogenase 1 family member A1; CCL20, C-C motif chemokine ligand 20; CXCL1, C-X-C motif chemokine ligand 1; TFF1, trefoil factor 1.

progression. A potential mechanism of IL-17 signaling in the progression of pancreatic cancer mediated by alterations in gut microbiota involves the elevation of the *Bacteroides* phylum, as observed in mice with enteric epithelial IL-17RA deficiency [Il17ra(-/-) and Il17ra(fl/fl); Villin-Cre mice] (82). Similarly, it has been reported that a reduction in the levels of *Bacteroides* phylum in the gut microbiome can impede Th17 cell differentiation and IL-17 production, resulting in the suppression of pancreatic tumor growth (84).

These findings provide significant evidence for the role of IL-17 in shaping the immunosuppressive environment of PDAC. Although the specific underlying mechanisms remain intricate and require further exploration, previous studies on neutrophils (12,65) and CAFs (58) have established a strong basis for understanding the potential immunosuppressive effects of IL-17/IL-17R signaling in the TME. Future research should place more emphasis on specific cell subtypes in the microenvironment to uncover the precise mechanisms by which IL-17/IL-17R signaling influences the modulation of the PDAC TME. This detailed exploration will enhance the understanding of the PDAC TME and pave the way for novel immunotherapeutic strategies for PDAC. IL-17/IL-17R signaling involved in the PDAC TME is summarized in Fig. 3.

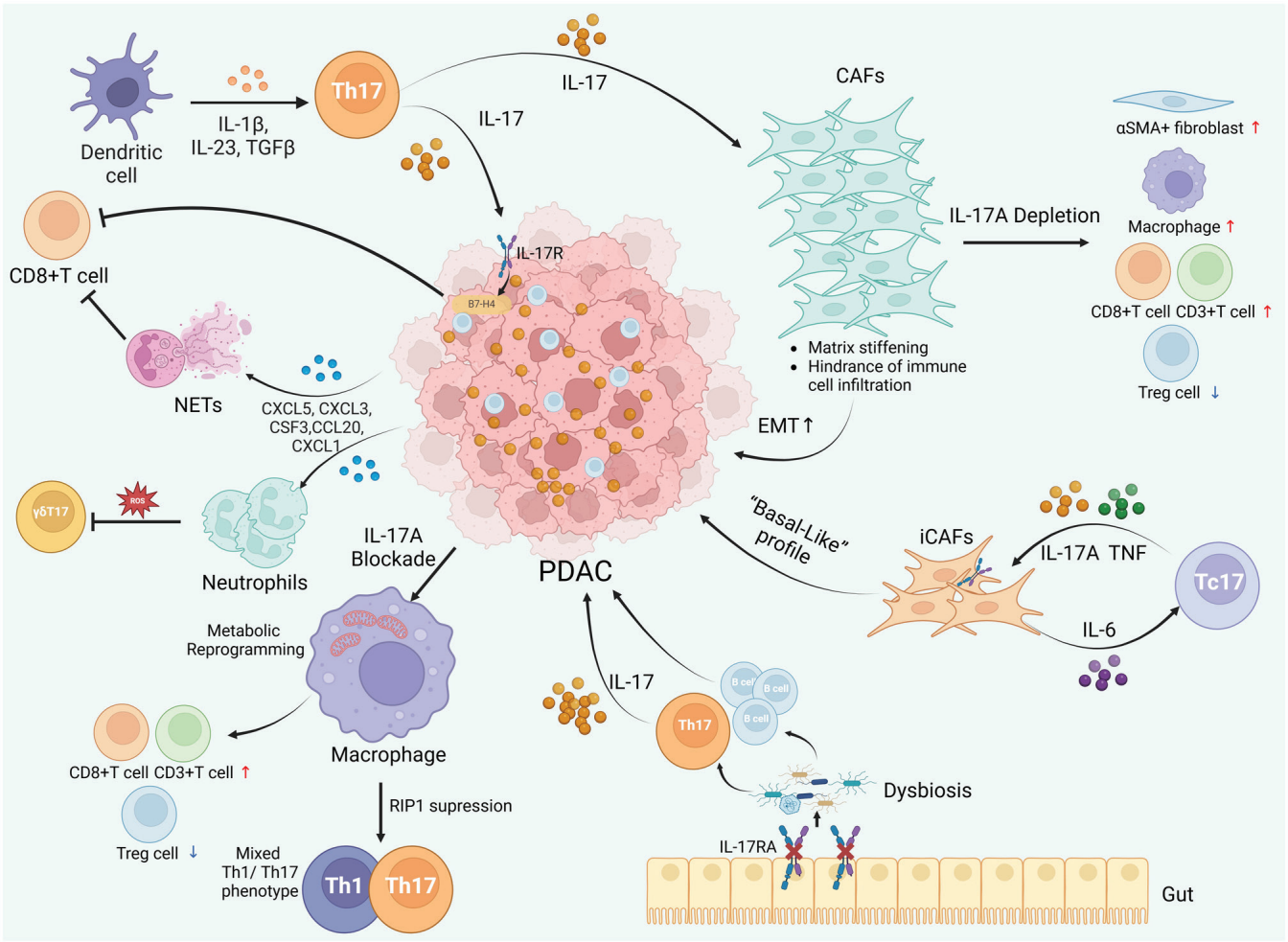

Figure 3. IL-17/IL-17R signaling in the PDAC tumor microenvironment. A schematic diagram depicting the role of IL-17 in maintaining the immunosuppressive microenvironment of PDAC. IL-23, IL-6 and TGF-β released by dendritic cells stimulate the differentiation of Th17 cells. IL-17-stimulated tumor cells recruit neutrophils through the release of several cytokines and chemokines, triggering NETs and cytotoxic $CD8^+$ T-cell exclusion. Neutrophils in the TME can suppress IL-17^+ γδ T cells via ROS signaling. IL-17/IL-17R regulates the expression of the co-stimulatory molecule B7-H4 in PDAC tumor epithelial cells, thereby downregulating the infiltration of $CD8^+$ T cells. IL-17A in the TME can reshape the PDAC stromal microenvironment and CAF characteristics, with a progressive increase in stiffness in the presence of IL-17A. Conversely, IL-17A depletion causes the enhanced infiltration of αSMA^+ fibroblasts, macrophages, $CD3^+$ T cells and $CD8^+$ T cells and downregulated infiltration of Treg cells. Tc17 cells interact with iCAFs through a positive feedback loop featuring IL-17A, TNF and IL-6. Depletion of IL-17A in the TME can also reshape macrophage characteristics through metabolic reprogramming and the recruitment of effector T cells. RIP1 suppression in PDAC tumor-associated macrophages can trigger a distinctive 'mixed' Th1/Th17 cell phenotype. Additionally, gut dysbiosis triggered by enteric IL-17RA deficiency induces tumor-promoting Th17 and B cells, with systemic increases in IL-17 levels and the subsequent growth of PDAC. CAFs, cancer-associated fibroblasts; iCAFs, inflammatory CAFs; IL, interleukin; IL-R, IL-receptor; EMT, epithelial-mesenchymal transition; NETs, neutrophil extracellular traps; TME, tumor microenvironment; CCL20, C-C motif chemokine ligand 20; CXCL, C-X-C motif chemokine ligand; PDAC, pancreatic ductal adenocarcinoma; ROS, reactive oxygen species; Th17, T helper-17 cell; αSMA, α smooth muscle actin; RIP1, receptor-interacting serine/threonine-protein kinase 1; Treg, regulatory T cell.

5. IL-17/IL-17R signaling in PDAC cancer therapy

Chemotherapy. Chemotherapy remains the cornerstone of non-surgical treatment for patients with PDAC, and gemcitabine is one of the first-line chemotherapeutic agents (85). Nevertheless, the clinical efficacy of gemcitabine is often limited by the rapid emergence of resistance that arises within a brief timeframe for a number of patients (86). Studies have validated the contribution of cytokines in the TME, such as interleukins and TNF, to the emergence of chemotherapy resistance (87). Notably, IL-17 has been identified as a promoter of resistance to chemotherapy across various tumor types (88). Within PDAC, elevated IL-17RB levels are closely associated with the enhanced expression of mucin (MUC)1 and MUC4. The upregulated production of these MUCs by IL-17RB contributes to the enhancement of tumor stem cell-like features and resistance to gemcitabine (38). Moreover, another study revealed that IL-17RB may serve as a predictive marker for the prognosis of patients with surgically resectable PDAC and the efficacy of gemcitabine therapy (89). Therefore, targeting IL-17RB and MUC1/4 may represent a viable strategy for overcoming resistance to gemcitabine (38). Another noteworthy discovery is that the combination of the IL-17A antibody with gemcitabine can induce a distinctive 'M1-like' phenotype in macrophages, with an increased phagocytosis rate and enhanced antitumor response (79). Notably, IL-17F may be linked to improved outcomes for patients with PDAC treated with gemcitabine (90). Consequently, improving the efficacy of chemotherapy in PDAC may involve the administration of gemcitabine in conjunction with IL-17A blockade

Table II. IL-17/IL-17R signaling in PDAC treatment response.

Therapeutic strategy	Mediator	Biological effect and mechanism	(Refs.)
Gemcitabine	IL-17RB	Benefits gemcitabine resistance by upregulating MUC1 and MUC4 expression	(38)
Gemcitabine	IL-17A	Remodels the phenotype of macrophages, improving gemcitabine resistance with the IL-17A antibody	(79)
Gemcitabine	IL-17F	Associated with favorable outcomes in patients with PDAC undergoing gemcitabine treatment	(90)
Anti-PD-1/CTLA-4	IL-17A/ IL-17RA	Enhances the responsiveness of ICIs via $CD8^+$ T cell activation after IL-17 blocking	(12)
Anti-PD-1/CTLA-4	Th17	$CD25^+$ Th17 impedes the function of Tc cells by overexpressing CTLA-4; increases Th17 levels in mice following anti-PD-L1 immunotherapy	(95, 96)
GVAX	Th17	Stimulates the production and development of tertiary lymph nodes in PDAC and serves as a prognostic indicator for patients with PDAC post-GVAX immunotherapy	(99)
Anti-intestinal microbiome	IL-17	Reduces the level of IL-17-producing cells with oral broad-spectrum antibiotics, thus inhibiting PDAC growth	(83)

CTLA-4, cytotoxic T-lymphocyte-associated protein 4; GVAX, GM-CSF-modified tumor cell vaccine; ICI, immune checkpoint inhibitor; MUC, mucin; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1.

therapies, including either neutralizing antibodies or small molecule inhibitors.

Indeed, these discoveries are currently insufficient to overcome the major challenge of overcoming chemotherapy resistance in patients with PDAC. Further investigations are required to explore the potential mechanisms and contributors to IL-17-mediated chemoresistance and the development of novel PDAC chemotherapeutic strategies.

Immune checkpoint inhibitors (ICIs). The combination of immunotherapy approaches, chiefly based on ICIs, has yielded noteworthy therapeutic advantages for patients with PDAC in recent years (91). According to recent research, members of the IL-17 family are indicators of the potential therapeutic effect of ICIs and are related to the infiltration of immune cells in tumors (92). The impact of IL-17 and Th17 cells on the therapeutic efficacy of ICIs has been reported in different types of tumor (7,93,94). For instance, in cutaneous squamous cell carcinoma, the IL-17-Act1-HIFα pathway facilitates the proliferation and collagen deposition of CAFs, promoting resistance to αPD-L1 (7). In colorectal cancer, a similar increase in resistance to αPD-L1 is attributed to the activation of the p65/nuclear respiratory factor 1/miRNA-15b-5p axis induced by IL-17A (94). PD-L1/programmed death-1 (PD-1) expression levels are reduced after IL-17 depletion, which modulates the function and frequency of myeloid-derived suppressor cells and enhances antitumor responses in breast cancer (93). In essence, anti-IL-17 sensitization to ICI immunotherapy is effective across different types of cancer.

In PDAC, the function of $CD8^+$ T cells can be inhibited by $CD25^+$ Th17 cells through CTLA-4-dependent mechanisms, thereby decreasing the concentration of IL-17. This finding indicates the potential role of Th17 and IL-17 in PDAC immunotherapy (95). Coincidentally, the combined use of IL-17 blockade with αPD-1 or αCTLA-4 effectively reduces pancreatic tumor volume by activating $CD8^+$ T cells and mitigating the resistance caused by the single use of the aforementioned drugs (12). This observation underscores the promising clinical application of such combination strategies in PDAC. The relevance of Th17 cells to therapeutic efficacy was demonstrated in a preclinical study that investigated combination immunotherapy for PDAC. This study revealed that Th17 levels increased in a pancreatic cancer mouse model following anti-PD-L1 immunotherapy. Notably, Th17 cells increased both at the onset of PDAC and post-immunotherapy, indicating the context dependency of this signaling pathway, as Th17 cells play distinct roles across different stages of PDAC (96). Mechanistically, research has indicated that although IL-17 regulates the expression of PD-L1 in myeloid cells, it is not directly responsible for the expression of PD-L1 in tumor cells (97). This discovery suggests that IL-17 mediates the sensitivity of PDAC to anti-PD-L1 immunotherapy through complex interactions with components of the TME. Further comprehensive studies are required to elucidate these interactions.

In a recent study, the application of virus-like vesicles for the delivery of three immunomodulators (IL-12, PD-L1 short hairpin RNA and dnIL17-RA), in combination with IL-17 blockade and αPD-L1, decreased tumor growth and prolonged the overall survival of mice (98). The future implementation of innovative immunotherapies targeting IL-17 in combination with immune checkpoint molecules holds significant potential and prospects for PDAC treatment.

Innovative immunotherapy strategies. Tumor vaccines have represented a burgeoning field in tumor immunotherapy in recent years. A previous study has indicated that IL-17 may inhibit the therapeutic efficacy of tumor vaccines by restricting the development of efficient antitumor $CD8^+$ T-cell responses (98). A previous study on the application of the GM-CSF-modified

tumor cell vaccine (GVAX) in patients with PDAC revealed that following GVAX vaccine immunotherapy, Th17 signaling was enhanced, while Treg signaling was weakened in tertiary lymphoid structures (TLSs), which was correlated with prognosis (99). Moreover, a study has confirmed that Th17 signaling can stimulate the production and development of TLSs in PDAC (100). Thus, the IL-17/IL-17R signaling-based Th17 signature could serve as a prognostic indicator for patients with PDAC after GVAX vaccine immunotherapy.

The gut microbiome has garnered increasing attention in the field of immunotherapy in recent years. Researchers have shown that the gut microbiome and its products can promote the progression of gastrointestinal tumors through interactions with the host immune system (101). A study has shown that the oral administration of broad-spectrum antibiotics can reduce the number of IL-17-producing cells and increase the number of IFN-γ^+ T cells, thereby inhibiting the growth of PDAC (83). Hence, regulating the gut microbiome could become a new strategy for PDAC immunotherapy. The IL-17/IL-17R signaling involved in different PDAC treatments is summarized in Table II.

6. Conclusion and perspectives

In summary, the present review provides a detailed discussion on the functional mechanisms involving the IL-17 family and its receptors in the tumorigenesis and progression of pancreatic cancer. These findings highlight the crucial roles played by IL-17/IL-17R signaling and the associated pathways in this exceptionally malignant tumor, when considering both the TME and treatment responsiveness. Treating pancreatic cancer presents a considerable challenge when focusing on a single target, such as ICIs or IL-17, owing to the unique characteristics of the TME. An enhanced understanding of the interplay among immune cells, tumor cells and diverse regulatory factors of the immune system is imperative for developing more efficacious therapeutic approaches. At present, monoclonal antibodies targeting IL-17, such as brodalumab and secukinumab, have received approval for treating autoimmune diseases (5). We consider that IL-17 blockade could serve as a propellant to overcome chemotherapy resistance in various malignancies, including PDAC, and will serve as a crucial component of future immunotherapeutic innovations.

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Availability of data and materials

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Authors' contributions

WL and XW contributed equally to this manuscript. WL was responsible for the initial conceptualization of the review, developed the research questions and coordinated the overall writing process. XW also conducted the literature search, selected relevant studies and drafted the initial section on 'IL-17/IL-17R signaling in the pathogenesis of PDAC'. XW assisted with the writing of the background section and the implications of the findings in the context of 'IL-17/IL-17R signaling in PDAC cancer therapy'. Additionally, XW assisted in the revision of the manuscript and responded to reviewer comments. WW was responsible for the overall coordination and supervision of the project, ensured the integrity and coherence of the manuscript, facilitated communication with the co-authors and managed the submission process. WW also contributed to the writing of the introduction and conclusion sections, providing a comprehensive overview of the objectives and implications of the review. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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