

Review

IL-17B: A new area of study in the IL-17 family

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ABSTRACT

The interleukin (IL)-17 superfamily, a relatively new family of cytokines, consists of six ligands (from IL-17A to IL-17F), which bind to five receptor subtypes (from IL-17RA to IL-17RE) and induce downstream signaling. IL-17A, a prototype member of this family, has been reported to be involved in the pathogenesis of allergies, autoimmune diseases, allograft transplantations, and malignancies. Unlike IL-17A, which is mainly produced by T helper 17 cells, IL-17B is widely expressed in various tissues. Recently, the biological function of IL-17B in diseases, particularly tumors, has attracted the attention of researchers. We previously reported that the expression of IL-17RB increased in gastric cancer tissues and demonstrated that IL-17B/IL-17RB signaling plays a critical role in gastric tumor progression. However, studies on IL-17B are scant. In this review, we detail the structural characteristics, expression patterns, and biological activities of IL-17B and its potential role in the pathogenesis of diseases.

1. Introduction

Cytokines are secretory regulatory peptides that mediate a broad range of biological activities by specifically binding to relative cell-surface receptors on target cells. Cytokines are key messenger molecules in cell-to-cell communication. They are also the major orchestrators of the immune system; for example, cytokines maintain homeostasis, participate in both innate and adaptive immune responses, and resolve the pathological status. The interleukin (IL)-17 family is a recently discovered group of cytokines, which share homology in amino acid sequences and have highly conserved cysteine residues (Kawaguchi et al., 2004). The IL-17 family and its receptors, which share minimal homology with other cytokines or known proteins, have been recognized as a distinct cytokine-receptor family and is crucial for normal host immune responses; this family is associated with many human pathogenesises, including those of inflammation and cancer (Iwakura et al., 2011; Kolls and Linden, 2004; Moseley et al., 2003).

IL-17A, the prototypic member of this family, was first identified in 1993 (Rouvier et al., 1993) and named CTLA8. It was subsequently renamed IL-17, and more recently, IL-17A. The gene location for IL-17A is 6p12, and human IL-17 is a 35-kDa, disulfide-linked, homodimeric protein with variable glycosylation (Moseley et al., 2003; Yao et al., 1995). Subsequent functional analyses have demonstrated its ability to induce the production of other cytokines such as IL-6, granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-

stimulating factor (GM-CSF), IL-1, transforming growth factor (TGF)- β , and tumor necrosis factor (TNF)- α . Furthermore, IL-17A induces the production of chemokines such as CXCL1, CXCL5, IL-8, CCL2, and CCL7, and matrix metalloproteinases (MMP1, MMP3, and MMP13) by fibroblasts, endothelial cells, and epithelial cells (Albanesi et al., 1999; Iwakura et al., 2011; Jovanovic et al., 1998). IL-17A is involved in the development of autoimmunity, inflammation, and tumors and plays major roles in host defenses against bacterial and fungal infections (Chae et al., 2010; Ishigame et al., 2009; Kolls and Linden, 2004; Schofield et al., 2016; Subbarayal et al., 2016).

In recent years, the availability of the human genome sequence and bioinformatics tools have facilitated gene discovery. The following five related members of the IL-17 gene family were recently identified within a short period between 2000 and 2002: IL-17B, IL-17C, IL-17D, IL-17E (also called IL-25), and IL-17F (Hymowitz et al., 2001; Lee et al., 2001; Li et al., 2000; Shi et al., 2000; Starnes et al., 2002). Among the IL-17 family members, the IL-17F isoforms 1 and 2 (ML-1) have the highest homology with IL-17A (55% and 40%, respectively), followed by IL-17B (29%), IL-17D (25%), IL-17C (23%), and IL-17E (17%), meaning that IL-17E is the most divergent member (Iwakura et al., 2011; Kolls and Linden, 2004). These molecules bear the maximum similarity at the C terminus and in five spatially conserved cysteine residues, four of which form a cystine-knot fold that differs from the canonical cystine knot found in bone morphogenetic proteins, TGF- β , nerve growth factor, and platelet-derived growth factor BB (Hymowitz

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et al., 2001; McDonald and Hendrickson, 1993). IL-17A and IL-17F are produced primarily in activated T cells, whereas IL-17B, IL-17C, IL-17D, and IL-17E are expressed in a wide range of tissues. The functions of these five cytokines partially overlap with those of IL-17A; however, they have not been thoroughly investigated.

The IL-17R family involves five receptor subunits, IL-17RA to IL-17RE (Aggarwal and Gurney, 2002). All members ranging in size from 499 to 866 amino acids are single transmembrane proteins that contain fibronectin type-III (FnIII) domains within the extracellular portions and a unique structural motif within the cytoplasmic tails termed the SEFIR [SEF (similar expression to fibroblast growth factor genes) and IL-17R] domain (Ely et al., 2009; Gaffen, 2009). The IL-17R family mediates signaling events that differ from those mediated by other cytokines, particularly in those that are usually involved in adaptive immunity (Maitra et al., 2007; Zhang et al., 2014). The cytokines of the IL-17 family mediate signaling through a novel ACT1-dependent pathway, culminating in the activation of proinflammatory factors, such as nuclear factor (NF)- κ B, which are typically associated with innate immune signaling (Chang et al., 2006; Gaffen, 2009).

Current knowledge on the biological functions of IL-17B, IL-17C, and IL-17D in the IL-17 family is limited. In this review, we describe the recent progress of functional studies elucidating the role of IL-17B in diseases and discuss areas for future research.

2. Structural characteristics of IL-17B

IL-17B was initially cloned using a homology-based expressed sequence tags (EST) database, followed by amplification from a fetal tissue cDNA library (Li et al., 2000; Shi et al., 2000). The human IL-17B, an 800-bp mRNA transcript gene, was mapped to the human chromosome 5q32–34. The amino acid sequence of IL-17B contains a hydrophobic motif at the N terminus, which has been identified to function as an 18–20-amino acid secretion signal sequence. The C-terminal half of the protein exhibits several conserved amino acids, including a tryptophan residue and five cysteines (Li et al., 2000; Shi et al., 2000). IL-17B is secreted as a noncovalent dimer glycoprotein consisting of 180 amino acids and has a predicted molecular mass of approximately 41 kDa (Iwakura et al., 2011; Kolls and Linden, 2004). A putative murine ortholog of IL-17B was identified in a mouse EST database and found to be 88% similar to human IL-17B (Shi et al., 2000).

3. Expression patterns of IL-17B

For the first time, Li et al. (2000) examined the expression of IL-17B through RNA blot analysis by using probes derived from the coding sequences of IL-17B. They observed the IL-17B mRNA expression in tissues from the pancreas, small intestine, and stomach of adult humans. However, the expression in the testis tissue was weaker than that in the aforementioned tissues. Unlike IL-17A, which is mainly produced by T helper 17 (Th17) cells, the expression of IL-17B mRNA is not found in activated T cells (Li et al., 2000). Furthermore, Shi et al. (2000) also observed IL-17B mRNA expression in the spinal cord and relatively low expression in the prostate tissue, colon mucosal lining, and ovary as well as in the K-562 chronic myelogenous leukemia cell line. A weak transcript was observed in the tissue of the trachea, uterus, adrenal gland, substantia nigra, and fetal kidney through northern blot analysis (Shi et al., 2000). Recent investigations have revealed that the epithelium weakly expresses IL-17B, whereas some connective tissue cells express IL-17B strongly in a healthy colon. Colorectal cancer cells also express IL-17B (Al-Samadi et al., 2016). Moreover, the synovial membrane in patients with RA was demonstrated to predominantly express IL-17B, and the neutrophils were found to contain significant amounts of IL-17B protein (Kouri et al., 2014). IL-17B expression has also been detected in neuronal cells, mouse embryonic limb buds, chondrocytes, germinal center (GC) B cells, and naive and memory B cells (Ferretti et al., 2016; Kokubu et al., 2008; Moore et al., 2002; Yamaguchi et al.,

2007; You et al., 2005).

4. Biological activities of IL-17B

In contrast to the high level of IL-6 secretion stimulated by IL-17A, IL-17B failed to induce IL-6 secretion in fibroblasts; however, it significantly enhanced the TNF- α -induced production of G-CSF and IL-6 in the fibroblasts (Kouri et al., 2014; Li et al., 2000). IL-17B induced an increased production of TNF- α and IL-1 β in the monocytic cell line, namely THP-1, whereas no induction of IL-1 α , IL-6, IFN- γ , or G-CSF was observed in the THP-1 cells (Li et al., 2000). Furthermore, IL-17B could not induce the production of cytokines (IL-6, IL-8, TNF- α , IFN- γ , IL-3, and G-CSF) in HeLa, CHO, or 293T cells in vitro (Shi et al., 2000). IL-17A, IL-17B, and IL-17C all induced mRNA expression of the inflammatory cytokines IL-1 α , IL-6, and IL-23 in the 3T3 cell line and peritoneal exudate cells (Yamaguchi et al., 2007). Intraperitoneal injection of rhIL-17B caused indirect recruitment of neutrophils to the peritoneal cavity in the gastrointestinal tract by binding to cell-surface receptors on the stromal cells or other connective tissue elements, thereby possibly triggering the expression and secretion of chemoattractive factors from these cell types (Shi et al., 2000). Recently, Ferretti et al. reported, for the first time, that IL-17B induced the migration of CXCR4+ or CXCR5+ GC B cells to CXCL12 and CXCL13 by down-regulating the expression of RGS16, the negative controller of signaling through these chemokine receptors (Ferretti et al., 2016).

5. Potential roles of IL-17B in diseases

5.1. IL-17B in embryonic development

Murine IL-17B mRNA, which is approximately 87.8% similar to the human sequence, was detected with the strongest signal in the brain, heart, and testis tissues of mice, and the signal was relatively weaker in the lung, liver, and skeletal muscle tissues (Shi et al., 2000). Through Northern blot analysis, Moore et al. discovered that the expression of IL-17B during mouse development exhibited dynamic changes; first, a weak signal was observed at day 11; it peaked at day 15 and then decreased at day 17 (Moore et al., 2002). Similarly, You et al. identified IL-17B expression from the articular cartilage of 2- to 3-month-old calf joints, whereas IL-17B expression was not detected in adult cow cartilage (Moseley et al., 2003). Thus, they speculated that IL-17B might be predominantly expressed in the early stages of cartilage and might be correlated to bone development. Subsequently, they found that the mouse IL-17B mRNA was barely detectable at 10.5 days post coitum (dpc) limb buds and that it increased slightly to 4-fold until 11.5 dpc. During these stages, the mesenchymal cells in the limb buds proliferated rapidly. Upon mesenchymal condensation, IL-17B mRNA expression continued to increase significantly by up to 64-fold until 12.5 dpc. The expression increased drastically to 256-fold at 13.5 dpc, and when the condensed mesenchymal cells differentiated into chondrocytes, the expression reached its peak level (588-fold) at 14.5 dpc. The primary ossification centers first appeared in the long bones of mouse embryonic limbs at 14.5 dpc. Thereafter, the expression attenuated to an extremely low level till birth at 19.5 dpc. The dynamic expression pattern of IL-17B indicates its role in the differentiation of mesenchymal cells or preosteoblasts into osteoblasts (You et al., 2005). IL-17B expression was also detected in other nonskeletal embryonic tissues. These results suggest that IL-17B might have certain functions in the general process of organogenesis. The mechanisms underlying the precise control of IL-17B expression through growth factors and the orchestration of organogenesis by IL-17B remain largely unknown. Clarifying the biological activity of IL-17B in the embryonic development may facilitate the exploration of new methods for the early diagnosis and treatment of congenital diseases (Fig. 1).

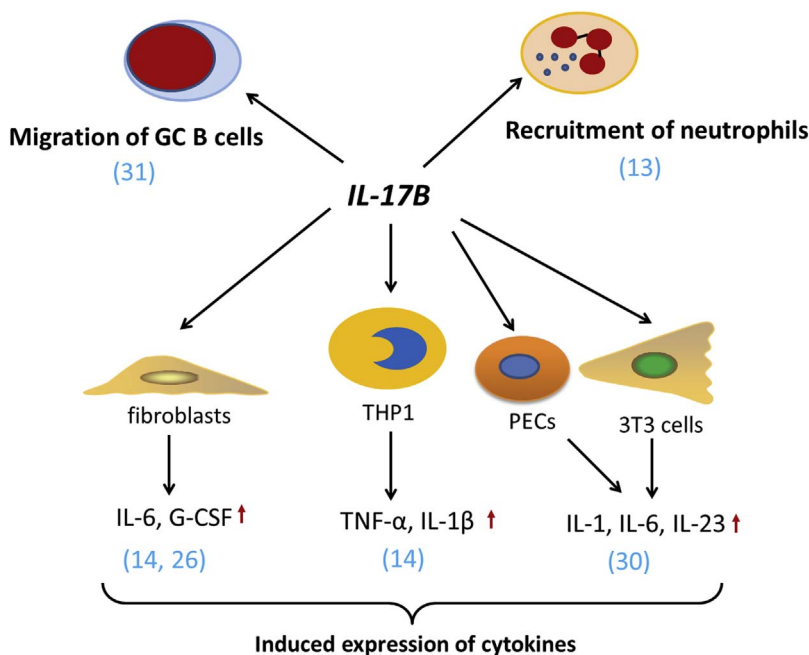


Fig. 1. The biological activity of IL-17B.

IL-17B promoted the TNF- α -induced production of G-CSF and IL-6 in the fibroblasts. IL-17B induced increased production of TNF- α and IL-1 β in THP-1. IL-17B induced the inflammatory cytokines expression of IL-1 α , IL-6, and IL-23 in the 3T3 cell line and peritoneal exudate cells. Intraperitoneal injection of rhIL-17B caused indirect recruitment of neutrophils to the peritoneal cavity. IL-17B induced the migration of CXCR4+ or CXCR5+ GC B cells to CXCL12 and CXCL13.

5.2. IL-17B in tissue regeneration

Kokubu et al. reported that the expression of IL-17B was strong in primitive and prehypertrophic chondrocytes 1 and 2 weeks after fracture. Moreover, IL-17B receptors (IL-17RB) were found to be localized in the primitive and prehypertrophic chondrocytes, osteoblasts in the trabecular bone, and mesenchymal stromal cells in the fibrous tissue. IL-17B signaling was implicated in the progression of bone fracture healing (Kokubu et al., 2008). Similarly, Ichinohe et al. (2017) found, through GeneChip[®] analysis, that the expression of IL-17RB significantly increased in small hepatocyte-like progenitor cells (SHPCs) from livers that received transplanted Thy1+ cells. Furthermore, the number and size of SHPCs clusters increased in the liver at 14 days after transplantation. Moreover, extracellular vesicles (EVs) separated from the conditioned medium of Thy1+ cell culture induced IL17B and IL25 expression in sinusoidal endothelial cells (SECs) and Kupffer cells, and IL17B stimulated the growth of small hepatocytes (SHs) in culture. These results indicate that Thy1-EVs coordinate IL17RB signaling to promote liver regeneration by targeting SECs, Kupffer cells, and SHPCs (Ichinohe et al., 2017). In 1998, Reddi proposed that tissue regeneration is, in part, a recapitulation of embryonic development and morphogenesis (Reddi, 1998). Additional studies regarding organize-specific gene knockouts and conditional mutants of the IL-17B signaling system in mice can clarify the role of IL-17B in embryonic organogenesis and tissue regeneration (Fig. 2).

5.3. IL-17B in chromosome-related diseases

IL-17B has been mapped to human chromosome 5q32–34 (Li et al., 2000), and this region has been previously shown to be related to a rare autosomal recessive form of Charcot–Marie–Tooth demyelinating disease (LeGuern et al., 1996). Moore et al. demonstrated high IL-17B expression in the central and peripheral nervous system, and IL-17B is primarily localized to neuronal cell bodies and axons. However, they found no differences in the coding sequences of IL-17B from two affected individuals and one unaffected individual from the same consanguineous Algerian pedigree. They speculated that the significant alteration in IL-17B expression level may play a role in myelination (Moore et al., 2002). Ryan et al. assayed genetic variations at the IL-17B loci in a sample of 409 cases of coeliac disease (CD) and 355 controls; however, they did not find evidence that these loci were associated with

CD in their sample population (Ryan et al., 2005). Although neither of these studies identified links between IL-17B gene loci and the chromosome 5q-linked form of CMT demyelinating disease or genetic predisposition-related CD, the potential roles of human chromosome 5q32–34 must be further investigated.

5.4. IL-17B in inflammation and autoimmune diseases

Experimental studies have shown that IL-17B receptor (IL-17BR) is dramatically upregulated in induced inflammation of rat intestine receiving consecutive indomethacin injections (Shi et al., 2000). In addition, IL-17B induced the activation of NF- κ B and the production of proinflammatory IL-8 (Lee et al., 2001). These studies indicate that IL-17B is likely involved in inflammatory disease. Studies have demonstrated that the mRNA expressions of IL-17B and the gene for the receptor IL-17BR in the arthritic paws of collagen-induced arthritis (CIA) mice were elevated compared with controls, and IL-17B was expressed exclusively in the inflammatory cartilage of CIA mice. Adoptive transfer of IL17B-gene-transduced CD4+ T cells exacerbated CIA and increased TNF production, whereas the disease was ameliorated in mice treated with IL-17B neutralizing antibodies. These results indicate that IL-17B plays a crucial role in the pathogenesis of inflammatory arthritis (Iwakura et al., 2011; Yamaguchi et al., 2007). In 2017, Cao et al. found that IL-17B concentrations were significantly elevated in patients with community-acquired pneumonia relative to their corresponding healthy controls and that IL-17B could induce gene and protein expression of IL-8 in human bronchial epithelial cells; this expression was regulated by the activation of Akt, p38 mitogen-activated protein kinase, extracellular signal-regulated kinase (ERK), and NF- κ B signaling pathways (Zhou et al., 2017). In addition, IL-17B levels were more significantly elevated in patients with systemic lupus erythematosus than in the control group, and the highest levels of IL-17B were found in the active phase of the disease compared with patients in the inactive phase and those in the control group, implying its involvement in the pathogenesis of the disease (Robak et al., 2013). Kouri et al. (2014) found that IL-17B was the predominantly expressed cytokine in rheumatoid synovial tissue and that IL-17B may contribute to chronic diseases and tissue destruction in arthritis by promoting neutrophil proliferation and survival (Kouri et al., 2014). These studies reveal that IL-17B is a proinflammatory cytokine involved in the pathogenesis progression of inflammatory and autoimmune diseases. Hence, further research is

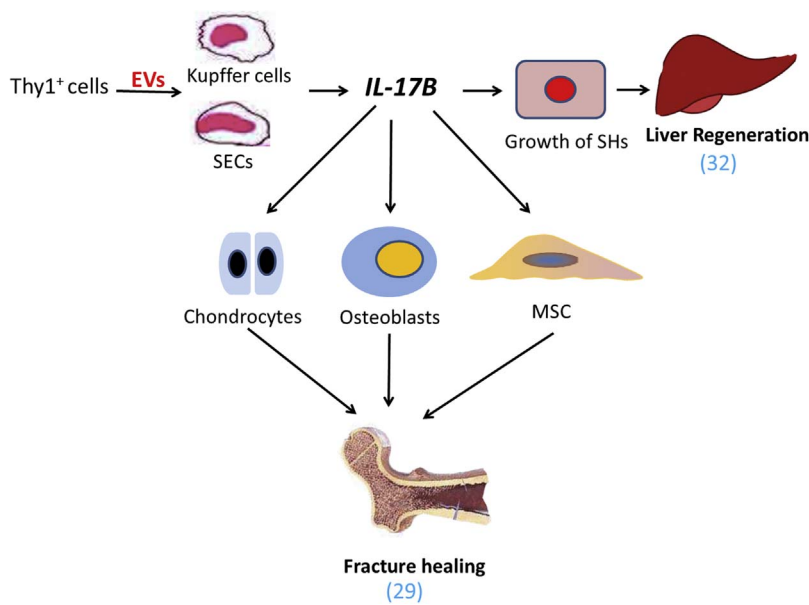


Fig. 2. The role of IL-17B in tissue regeneration.

IL-17B receptors (IL-17RB) localized in the primitive and prehypertrophic chondrocytes, osteoblasts in the trabecular bone, and mesenchymal stromal cells in the fibrous tissue. IL-17B signaling was implicated in the progression of bone fracture healing. Thy1-EVs coordinate IL-17B/IL17RB signaling to promote liver regeneration by targeting SECs, Kupffer cells, and SHPCs.

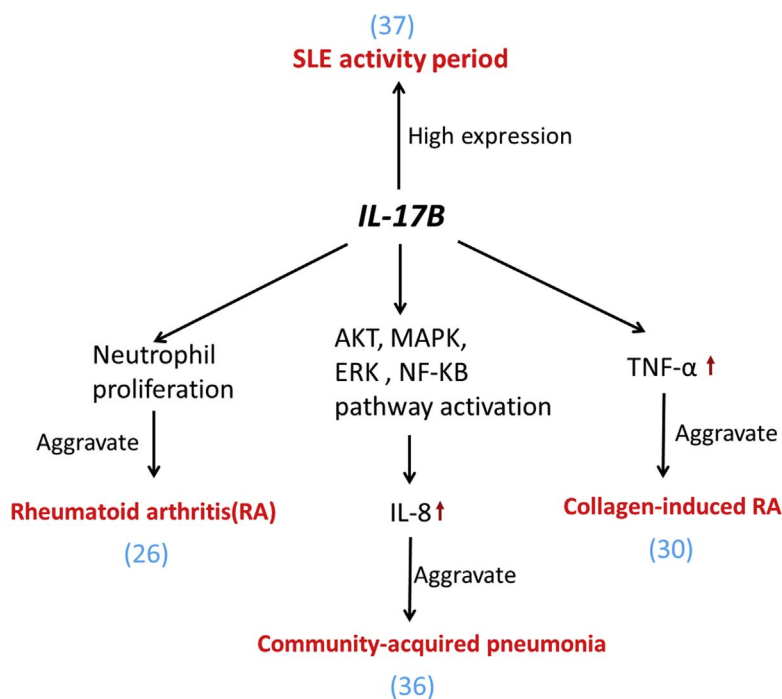


Fig. 3. The action of IL-17B in inflammation and autoimmune diseases.

The inflammatory cartilage in CIA mice expressed IL-17B. Adoptive transfer of IL17B-gene-transduced CD4⁺ T cells exacerbated CIA and increased TNF production. IL-17B concentrations were significantly elevated in patients with community-acquired pneumonia and IL-17B could induce gene and protein expression of IL-8 in human bronchial epithelial cells. IL-17B levels were more significantly elevated in the active phase of the patients with SLE. IL-17B contributed to chronic diseases and tissue destruction in rheumatoid arthritis by promoting neutrophil proliferation and survival.

needed to obtain a complete understanding of the biological function of IL-17B in inflammation and immunity for making it as an effective therapeutic target (Fig. 3).

5.5. IL-17B in tumors

In the nineteenth century, links between cancer and inflammation were first put forward on the basis of the observation that tumors often arise at sites of chronic inflammation (Balkwill and Mantovani, 2001). Tian et al. (2000) argued that the increased and uncoordinated expression of IL-17RB may lead to myeloid leukemia, implicating the oncogenic role of this receptor for the first time (Tian et al., 2000). Fourteen years later, Lee et al. (2015) reported that the expression of IL-17RB in breast cancer cells was high and that IL-17B, the ligand of IL-17RB, was expressed in both normal and tumor cells. They demonstrated that the amplified IL-17RB/IL-17B signaling promoted breast

tumorigenicity and impeded acinus formation in immortalized normal mammary epithelial cells and induced etoposide resistance by activating NF-κB to upregulate antiapoptotic factor Bcl-2 (Huang et al., 2014). Thereafter, they found the overexpression of IL-17RB is strongly correlated with postoperative metastasis and inversely correlated with progression-free survival in patients with pancreatic cancer. Furthermore, ex vivo results further validated that IL-17B/IL-17RB-activated CCL20, CXCL1, IL-8, TFF1 chemokine expression via the ERK1/2 pathway promote cancer cell invasion, macrophage and endothelial cell recruitment at primary sites, and cancer cell survival in distant organs (Wu et al., 2015). Blocking the IL-17B/IL-17RB signal effectively attenuated breast tumorigenicity. Moreover, it not only reduced pancreatic tumor metastasis but also significantly prolonged survivals in a mouse xenograft model (Huang et al., 2014; Lee et al., 2015; Wu et al., 2015) (Fig. 4).

Our results confirmed that the expression of IL-17RB in gastric

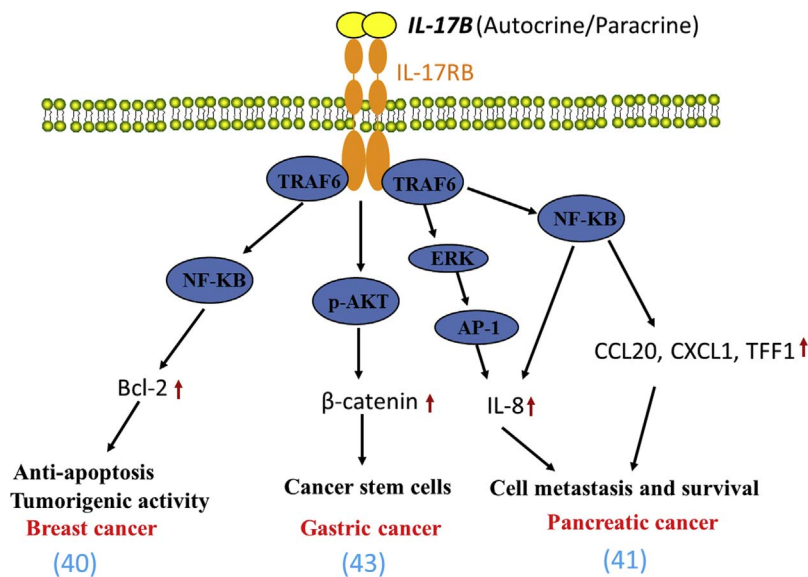


Fig. 4. IL-17B/IL-17RB signaling pathway and its roles in tumor cells. The amplified IL-17RB/IL-17B signaling promoted breast tumorigenicity and induced etoposide resistance by activating NF-κB to upregulate anti-apoptotic factor Bcl-2. IL-17B/IL-17RB signaling activated CCL20, CXCL1, IL-8, TFF1 chemokine expression via the ERK1/2 pathway promoted pancreatic cancer cell invasion, macrophage and endothelial cell recruitment at primary sites, and cancer cell survival in distant organs. IL-17B/IL-17RB signal promotes the growth and migration of tumor cells and enhances cell stemness by activating the AKT/β-catenin pathway in gastric cancer.

cancer tissues was significantly higher than the paired noncancerous tissues and that the overexpression of IL-17RB was associated with the poor prognosis of patients with gastric cancer (Bie et al., 2016). We detected IL-17B mRNA expression in the stomach of adult humans, but we did not detect IL-17B expression in a panel of human gastric cancer cell lines (SGC-7901, MKN-45, BGC-823, MGC-803, and HGC-27). We demonstrated that exogenous rIL-17B dose-dependently and significantly enhanced the colony forming and migratory ability in GFP-shRNA-transfected MGC-803 control cells; however, exogenous rIL-17B lost its effect when the expression of IL-17RB was deleted in MGC-803 cells. We first found positive correlations between IL-17RB and stemness-related factors. Exogenous rIL-17B stimulated not only significantly increased the expression of the stemness-related factor (Oct4, Nanog, Lgr5, and Sall4) mRNA in a dose-dependent manner but also increased the ability of adipogenic differentiation of gastric cancer cells. We indicated that the IL-17B/IL-17RB signal promotes the growth and migration of tumor cells and enhances cell stemness by activating the AKT/β-catenin pathway in gastric cancer (Bie et al., 2016). Considering the relationship between IL-17B and stemness, we further explored the effect of IL-17B on mesenchymal stem cells (MSCs) in the microenvironment of a tumor (Bie et al., 2017). We found the supernatants collected from MSCs treated with rIL-17B promoted the proliferation and migration of MGC-803 gastric cancer cells, which might be attributed to IL-17B prompting the expression of soluble factors IL-6, IL-8, TGF-β, and CCL-5 in MSCs. The aforementioned soluble factors have been demonstrated to facilitate tumor progression. Moreover, we suggested that rIL-17B not only promoted the proliferation and migration of MSCs but also enhanced the expression of the stemness-related genes Sox2, Oct4, and Nanog as well as the ability of adipogenic differentiation in a dose-dependent manner in MSCs by activating NF-κB, STAT3, and β-catenin (Bie et al., 2017). Recent studies have revealed that IL-17, mainly produced by T helper (Th17) cells and macrophages, contributed to ovarian cancer malignancy by promoting the self-renewal of CD133 + cancer stem-like cells (Xiang et al., 2015) and that IL-17 promoted the transformation of quiescent gastric cancer stem cells (CSCs) into invasive gastric CSCs (Jiang et al., 2017). We previously found that exogenous rIL-17B prompted the expression of IL-17RB in a dose-dependent manner in MGC-803 cells (Bie et al., 2016). We hypothesized that IL-17B upregulated the stemness of gastric cancer cells by influencing the self-renew ability of gastric CSCs; however, this requires further study.

Furthermore, the expression of IL-17B in colorectal cancer (CRC) was proven to be elevated, with neutrophils being the main source of IL-17B in the stroma (Al-Samadi et al., 2016). However, a later study

indicated that IL-17B may function in an antiangiogenic manner and suggested that rhIL-17B inhibited HECV endothelial cell-matrix adhesion and cellular migration in vitro. Furthermore, at higher concentrations, rhIL-17B substantially reduced tubule formation in treated cells compared with untreated HECV cells in a Matrigel tubule formation assay (Sanders et al., 2010). We believe that the antiangiogenic activity of IL-17B may be induced at higher concentrations. Targeting IL-17B and IL-17RB might be a useful approach for treating cancers in which this pathway is activated (Fig. 5).

6. Conclusion

In this review, we summarized the structural characteristics, expression patterns, and biological activities of newly identified IL-17B and its potential role in diseases. Although IL-17B mRNA was identified in 2000, studies on IL-17B are scant. Recent reports have mainly focused on IL-17B/IL-17RB signaling involved in tumor progression. Lee et al. first suggested the correlation between increased IL-17RB/IL-17B signaling and poor prognosis of patients with breast cancer. Furthermore, the overexpression of IL-17RB was suggested to play an essential role in pancreatic cancer metastasis and malignancy and share an inverse correlation with progression-free survival in patients with pancreatic cancer. We also found that the expression of IL-17RB in gastric cancer tissues was significantly higher than that in the paired noncancerous tissues. Moreover, we indicated, for the first time, that the IL-17B/IL-17RB signal upregulates cell stemness through the activation of the AKT/β-catenin pathway in gastric cancer and IL-17B enhances the progression of gastric cancer by activating MSCs. CSCs are considered major causes of tumor recurrence, metastasis, and resistance, and targeting IL-17B or IL-17RB will be an effective therapeutic target in the future.

Conflicts of interest

The authors declare that there are no conflicts of interest in relation to this manuscript.

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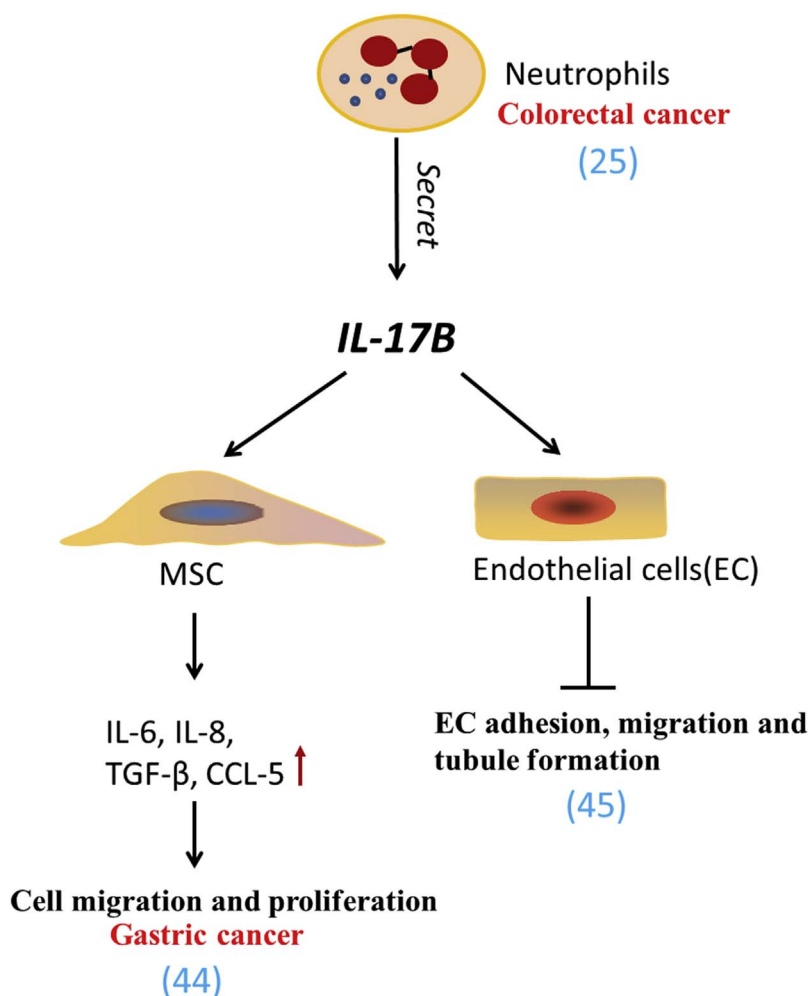


Fig. 5. Interaction between IL-17B and tumor-microenvironmental cells. IL-17B prompted the expression of soluble factors IL-6, IL-8, TGF- β , and CCL-5 in MSCs and these aforementioned soluble factors facilitated the proliferation and migration of gastric cancer cells. The expression of IL-17B mainly by neutrophils in colorectal cancer (CRC) was elevated. rhIL-17B inhibited HECV endothelial cell-matrix adhesion and cellular migration in vitro and, at higher concentrations, rhIL-17B substantially reduced tubule formation in a Matrigel tubule formation assay.

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