The role of IL17 in cancer progression

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Abstract. The interleukin-17 (IL-17) family comprises a class of cytokines that are essential regulators within the immune system. Recent evidence indicates that IL-17A and IL-17F exert complex and often opposing influences on tumor initiation and progression. These cytokines activate signaling cascades—including NF-κB, MAPK, and STAT3—via the IL-17RA/RC receptor complex, thereby modulating the production of inflammatory mediators, chemokines, and matrix-degrading enzymes. In contrast, IL-17F has been reported to provide protective effects in certain malignancies, such as colorectal cancer, suggesting that it has the function of tissue specificity. Additional family members, including IL-17B, IL-17C, and IL-17E (also known as IL-25), also play important but contradictory roles in tumor progression. Numerous studies have suggested that IL-17 signaling facilitates cancer progression not only by forming a chronic inflammatory microenvironment but also by enhancing invasion and metastasis through mechanisms such as maintaining cancer stem cell characteristics, recruiting immunosuppressive cells, and synergizing with growth factor signals. However, under specific circumstances, IL-17 may mediate anti-tumor actions by inducing cell pyroptosis or enhancing anti-tumor immune responses. This duality makes IL-17 both a potential driving force for cancer occurrence and development and an immunotherapy target with promising application prospects. This article systematically reviews the roles and mechanisms of the IL-17 family across different cancer types, aiming to provide a theoretical basis and research directions for future IL-17-related anti-cancer immunotherapy.

Keywords: IL-17 cytokine, Cancer, Tumor microenvironment (TME).

1. Introduction

The IL-17 family is composed of six related cytokines (IL-17A to IL-17F), each contributing to immune regulation. Among them, IL-17A was the first identified and is regarded as both a key driver of autoimmune pathology and a prototypical pro-inflammatory cytokine. Other members—including IL-17B, IL-17C, IL-17D, IL-17E (also referred to as IL-25), and IL-17F—participate in processes essential for maintaining mucosal barriers, promoting tissue repair, and shaping the tumor microenvironment [1]. Th17 cells serve as the primary source of IL-17 family cytokines, although additional immune subsets such as $CD8^+$ T cells, γδ T cells, and NK cells also contribute to their secretion [2].

The biological activity of IL-17 family cytokines is mediated through heterodimeric receptor complexes. Each receptor contains a conserved SEFIR domain that enables interaction with adaptor proteins such as Act1, thereby initiating downstream signaling [3]. For example, IL-17A binds to the IL-17RA/RC complex, activating a wide range of pro-inflammatory pathways including NF-κB, MAPK, C/EBP, JAK/STAT, and PI3K/Akt. In contrast, IL-17C and IL-17E engage alternative receptor pairs—RA/RE and RA/RB, respectively—to regulate barrier defense and mucosal inflammation [4]. Collectively, these pathways promote the expression of chemokines, inflammatory mediators, antimicrobial peptides, and matrix metalloproteinases, all of which contribute to remodeling the tissue microenvironment and recruiting specific immune cell populations.

Although IL-17 has been targeted therapeutically in autoimmune disorders, its role in cancer is far more complex. Initially recognized for its involvement in host defense and infection control, IL-17 is now understood to exert context-dependent effects in tumors. On one hand, it facilitates tumor progression by promoting cell proliferation, angiogenesis, and immune evasion, often through neutrophil recruitment and activation of MDSCs. On the other hand, in certain cancer settings, IL-17 can instead trigger anti-tumor responses by enhancing immune activation and suppressing tumor

growth [5]. Notably, IL-17A, IL-17B, and IL-17F are frequently upregulated in solid tumors, including colorectal, lung, and breast cancers, where they drive epithelial–mesenchymal transition (EMT), stimulate immunosuppressive cell recruitment, and support tumor proliferation [1].

Recent evidence highlights that IL-17 family members, particularly IL-17A and IL-17F, display dual and sometimes opposing activities, functioning either synergistically to promote tumor growth or, under different circumstances, to enhance anti-tumor immunity. Deciphering the mechanisms underlying these divergent effects is essential, as it can deepen our understanding of the interplay between inflammation and cancer and inform the design of novel therapeutic strategies. Monoclonal antibodies directed against IL-17A or its receptors (e.g., secukinumab, brodalumab) are already in clinical use for inflammatory diseases and are being investigated in oncology. Importantly, their combination with immune checkpoint inhibitors may provide more precise and effective approaches for cancer immunotherapy [2].

This article aims to review the diverse mechanisms through which the IL-17 family contributes to cancer initiation and progression. It also summarizes recent research advances on IL-17 across different cancer types and evaluates its potential and limitations as a therapeutic target, thereby offering a theoretical foundation and future directions for anti-tumor immunotherapy.

2. IL-17 receptors and downstream signalling pathways

The biological functions of the IL-17 cytokine family are mediated through its receptor subtypes, IL-17RA through IL-17RE. Although these receptors all share a conserved SEFIR domain, they exhibit considerable diversity in their pairing preferences, expression profiles, and downstream signaling outcomes. The best-characterized receptor complex is IL-17RA/RC, which serves as the primary binding site for IL-17A, IL-17F, and their heterodimers (Figure 1). Interestingly, while IL-17A exerts strong pro-inflammatory and tumor-promoting effects, IL-17F displays weaker activity and may even have protective roles in certain cancers such as colorectal cancer, highlighting functional divergence between these two ligands. Other receptor-ligand interactions include IL-17RB, which primarily binds IL-17B and IL-25 (IL-17E); IL-17RE, which mediates IL-17C signaling; and IL-17RD, which may participate in IL-17A signal transduction in specific tissues, though its mechanisms remain unclear [3].

Signal initiation begins when the adaptor protein Act1 is recruited via SEFIR domain interactions. Act1 functions not only as a scaffold but also as an E3 ubiquitin ligase and an RNA-binding protein. Through its TRAF-binding sites, Act1 recruits factors such as TRAF6 and TRAF2/5, activating two major signaling axes: NF-κB and MAPK. These pathways drive the expression of inflammatory mediators and are further amplified by transcription factors like C/EBPβ and IκBζ to enhance target gene transcription [6]. Although both IL-17A and IL-17F signal through Act1, emerging evidence suggests that IL-17F induces a weaker inflammatory response and may even contribute to tumor suppression in certain contexts [3]. Additionally, the unique CBAD domain in IL-17RA facilitates negative feedback by recruiting inhibitory molecules including TRAF3 and A20, thus finely controlling the intensity and duration of IL-17-driven inflammatory signaling.

Additionally, the IL-17 signalling pathway also exhibits a complex regulatory mechanism at the post-transcriptional level. Act1 can directly bind to the SEFIR binding elements (SBE) in the 3' untranslated region of target mRNAs (such as CXCL1, TNF, etc.), thereby stabilizing the mRNA structure and promoting its translation [3]. Concurrently, IL-17 induces RNA-binding proteins such as Arid5a and HuR as positively regulated factors by assisting inflammatory-related mRNAs to enter the polyribosomal system. In contrast, another negative regulatory factor, Regnase-1, is responsible for recognizing and degrading actively translating mRNAs, thereby switching the activation and attenuation of the inflammatory signal at different stages. This dynamic mRNA regulatory network provides high temporal regulation and cell specificity to the IL-17 signalling and also becomes an important basis for regulating its tumor function.

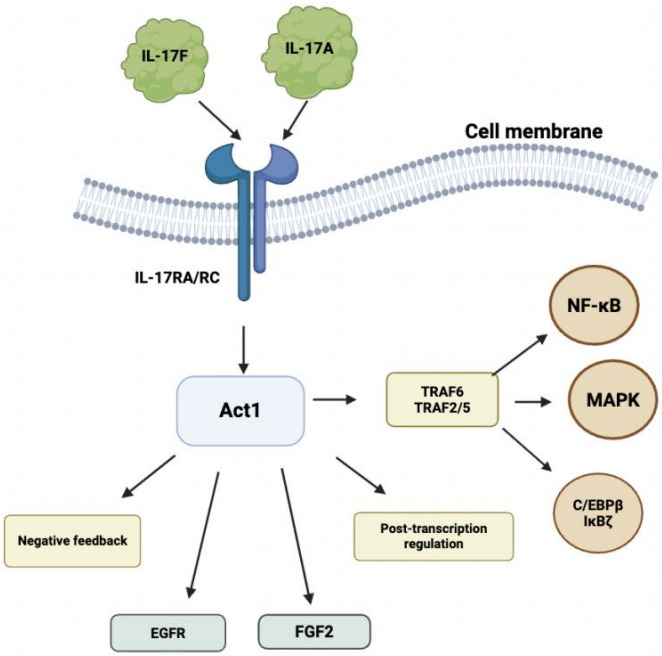

Figure 1. Schematic diagram of the IL-17A and IL-17F signaling pathway

The IL-17 signal can also cross-collaborate with other receptor pathways, especially in epithelial cells and within tumor microenvironments. For instance, IL-17A can engage the epidermal growth factor receptor (EGFR) through the Act1-TRAF4 axis, activating the non-classical ERK5 pathway to promote the migration and proliferation of skin stem cells, which play a crucial role in wound healing and the occurrence of skin tumours [3]. In colon epithelial cells, IL-17 collaborates with fibroblast growth factor 2 (FGF2) to stimulate ERK1/2 activation, then enhance the proliferative potential and epithelial repair ability of intestinal stem cells, and this process may also become a potential driving factor for intestinal tumor development [7]. These findings indicate that IL-17 is not merely an inflammatory factor but can also participate in cell proliferation, migration, and tumor-promoting signaling across different tissue contexts.

Although the pro-inflammatory role of the IL-17 signaling axis in autoimmune diseases is well established, its role in cancer shows a significant dualistic. In certain tumors, such as breast cancer and colorectal cancer, activation of the IL-17 receptor promotes the recruitment of MDSCs, immune evasion, angiogenesis, and extracellular matrix remodeling. In other cases (such as when suppressing inflammatory tumors early), it may produce anti-tumor effects by promoting neutrophil killing or T cell activation. Furthermore, IL-17F has been linked to improved prognosis in several cancer types, indicating that members of the IL-17 family do not universally promote tumor progression but rather have context-dependent and even opposite effects [7]. Consequently, a thorough analysis of receptor pairing pattern, downstream signaling regulation, and tissue-specific expression is not only crucial for understanding its multiple roles in cancer progression but also provides a theoretical basis for targeted intervention.

3. Mechanisms of IL-17–Mediated Cancer Progression

3.1. Promote the formation of chronic inflammation and tumor-promoting immune environment

Through persistent activation of signaling pathways such as NF-κB and MAPK, IL-17 drives the sustained production of pro-inflammatory mediators—including IL-6, CXCL1, and G-CSF. This chronic signaling contributes to the formation of an inflammatory tumor niche that favors immunosuppression by recruiting M2-polarized macrophages and Th2 cells. As a result, the tumor microenvironment becomes more permissive to survival and expansion. In addition, IL-17A enhances tumor immune evasion by activating the STAT3 pathway and upregulating immunosuppressive

cytokines, which collectively dampen effector immune functions. These mechanisms not only support tumor progression but may also impair the efficacy of conventional immunotherapies. Therefore, targeting IL-17-mediated signaling represents a promising strategy to modulate the tumor microenvironment and restore anti-tumor immunity.

3.2. Induction of Angiogenesis

IL-17 plays a crucial role in tumor angiogenesis, promoting the formation of new blood vessels and providing conditions for the continuous growth of tumors. This angiogenic effect mainly relies on the upregulation of various vascular regulatory factors, including the most central VEGF, as well as signaling molecules such as angiopoietin-2 and CXCL8. By enhancing the expression of these factors, IL-17 not only improves the oxygen and nutrient supply in tumor tissues but also induces the formation of disordered and immature vascular networks. These abnormal blood vessels, on the one hand, maintain the proliferation of tumor cells, and on the other hand, provide a convenient channel for their entry into the bloodstream and spread, accelerating the metastasis process. In terms of the molecular mechanism, Rex et al. demonstrated that IL-17A can significantly promote tumor vascularization through the ACT1—TRAF6 signaling pathway. This pathway serves as an important molecular bridge between IL-17 receptor activation and the downstream angiogenic process, further highlighting the core role of IL-17 in promoting tumor expansion and progression. Thus, it can be seen that IL-17, by inducing angiogenesis, once again demonstrates its multiple roles in the tumor microenvironment and also suggests that it may be an important target for anti-angiogenic therapy.

3.3. Remodeling of the Tumor Microenvironment

The IL-17 signaling pathway is recognized as a central force in establishing an immunosuppressive tumor microenvironment. It drives the expansion and infiltration of myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), which in turn compromise the cytotoxic responses of $CD8^+$ T cells and natural killer (NK) cells, thereby weakening anti-tumor immunity. At the same time, IL-17 promotes PD-L1 expression in both tumor and stromal cells and induces the secretion of chemokines such as CCL2 and CXCL5, facilitating the recruitment of additional inhibitory immune subsets. Through these mechanisms, tumors gain a protective niche that supports immune evasion and long-term survival. Regarding cellular origin, Th17 cells are the primary source of IL-17. Nevertheless, innate immune populations, including γδ T cells and type 3 innate lymphoid cells (ILC3s), also provide significant contributions. What makes IL-17 particularly distinctive is its dual role as a mediator between innate and adaptive immunity. Beyond amplifying inflammatory cascades, it actively participates in extracellular matrix remodeling and orchestrates the positioning and migration of immune cells within the tumor site. Clinically, increased IL-17 expression has been repeatedly linked to more advanced disease stages, greater metastatic capacity, and worse patient outcomes. Collectively, these observations define IL-17 as both an indicator of poor prognosis and a promising therapeutic target for future immuno-oncology strategies [9].

Beyond its role in immune evasion, IL-17 also significantly influences cancer stem cell (CSC) biology. CSCs represent a subpopulation of tumor cells with enhanced self-renewal capacity, differentiation potential, and inherent resistance to conventional therapies. These properties drive not only tumor initiation and progression but also contribute to relapses following treatment. Growing evidence implies IL-17 in maintaining the CSC phenotype. For example, in breast cancer, IL-17A activates the mTOR-p70S6K pathway, expanding the $CD44^+CD24^-$ stem cell population and increasing sphere formation and tumor initiation [8]. IL-17 also supports CSC survival and stemness by activating STAT3 and upregulating genes such as Nanog, Sox2, and Oct4. These mechanisms enhance resistance to apoptosis and chemotherapy, promoting tumor recurrence. Targeting IL-17 signaling may therefore offer a promising strategy to disrupt CSC maintenance and improve therapeutic outcomes.

4. IL-17 in Specific Cancer Types

4.1. Colorectal Cancer

In microsatellite-stable colorectal cancer (MSS-CRC), high IL-17A expression has been consistently associated with resistance to immunotherapy and poorer clinical outcomes [10]. By promoting the accumulation of myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), while simultaneously upregulating immune checkpoint molecules, IL-17A creates an immunosuppressive niche that undermines anti-PD-1 efficacy. Preclinical mouse studies further confirm that IL-17A blockade enhances the therapeutic benefit of anti-PD-1 antibodies, emphasizing its central role in tumor immune escape. Importantly, IL-17A is not restricted to tumor-promoting activities. Under certain conditions, it may also trigger tumor-inhibitory pathways. One such mechanism involves the induction of mitochondrial stress, which activates the NLRP3/caspase-4/GSDMD axis and leads to pyroptosis, a form of programmed cell death with strong immunogenic potential [11]. This lytic process is coupled with the release of inflammatory mediators such as IL-1β and IL-18, which heighten tumor antigenicity and stimulate adaptive immune responses. In addition, inhibition of IL-17A has been linked to increased infiltration of $CD8^+$ T cells, suggesting that its ultimate effect depends on the immune landscape and regulatory cues within the tumor microenvironment.

Therefore, in colorectal cancer, IL-17A exhibits a "dual attribute". On one hand, it promotes tumor immune escape by shaping an immunosuppressive microenvironment and weakens the efficacy of anti-PD-1 therapy; on the other hand, it may exert anti-tumor effects by inducing pyroptosis and enhancing the infiltration of effector cells [11]. These differences are often closely related to the patient's immune background, the expression pattern of IL-17 receptor subunits, and the cross-regulation of other cytokines. Thus, IL-17A is not only an important tumor-promoting factor in CRC, but also potentially a potential immune-activating factor. If precise stratification and targeted intervention based on patient-specific factors can be achieved in the future, IL-17A-related treatments are expected to bring new breakthroughs in the immunotherapy of colorectal cancer.

4.2. Breast Cancer

IL-17 cytokines play multifaceted and often opposing roles in breast cancer, influenced by the biological context and disease stage. Increased IL-17A levels are commonly detected in breast tumor samples and are strongly associated with advanced disease characteristics such as larger tumor dimensions, lymph node involvement, and inferior survival rates [12]. The pro-tumor mechanisms of IL-17A operate through three synergistic pathways: It first stimulates major signaling networks—ERK1/2, STAT3, and NF-κB—to boost cancer cell growth, diminish apoptotic sensitivity, and increase therapy resistance. Second, it elevates the production of VEGF and matrix-degrading enzymes (MMPs), which enhance blood vessel formation and breakdown of extracellular matrix, supporting both local invasion and metastatic dissemination. Third, IL-17A aids in establishing an immunosuppressive niche via the recruitment of neutrophils and MDSCs. These cells secrete soluble factors like IL-6 and CCL20, perpetuating chronic inflammation and immune dysfunction that favor tumor adaptation and progression. Given these pleiotropic effects, IL-17A represents not only a central driver of breast cancer malignancy but also a compelling candidate for targeted therapy, especially in combination approaches aimed at disrupting both tumor-intrinsic and immune-extrinsic pathways.

Beyond IL-17A, IL-17B and its receptor IL-17RB are frequently overexpressed in triple-negative breast cancer (TNBC), where they correlate with chemotherapy resistance, increased invasiveness, and unfavorable clinical outcomes [12]. The IL-17B/IL-17RB axis activates ERK1/2 and NF-κB pathways to support cancer cell survival and migration, while also promoting the infiltration of tumor-associated macrophages, which further dampens anti-tumor immunity. This signaling pathway is thus considered a key contributor to treatment resistance and immune evasion in breast cancer. In contrast, IL-17E (IL-25) exhibits context-dependent effects. It can induce caspase-dependent apoptosis via the

IL-17RA/IL-17RB complex, thereby inhibiting tumor growth. However, under certain conditions, IL-17E may also participate in pro-inflammatory processes and promote tumor progression, influenced by local receptor expression and cytokine milieus.

Th17 cells, a major producer of IL-17, also contribute significantly to breast cancer metastasis. Shibabaw et al. demonstrated that Th17-derived IL-17 enhances cancer cell migration and epithelial–mesenchymal transition (EMT), facilitating distant metastasis to sites such as the lungs and bones [13]. Clinically, elevated Th17 cell or IL-17 levels in peripheral blood and tumor tissues are associated with increased metastatic risk and worse prognosis, highlighting the Th17/IL-17 axis as a critical regulator of metastasis and a potential prognostic biomarker. Furthermore, IL-17 expression correlates positively with PD-L1, suggesting an additional role in promoting immune escape.

In breast cancer, the IL-17 family plays various roles. IL-17A and IL-17B generally act as oncogenic factors, promoting tumor proliferation, invasion, metastasis, immunosuppression, and drug resistance; IL-17E may have anti-tumor effects, but its function is heterogeneous and influenced by the tumor microenvironment and receptor expression, while the Th17/IL-17 axis directly participates in the metastasis process of breast cancer and is closely related to prognosis. Therefore, targeting IL-17 or its receptors, especially IL-17A and IL-17RB, may provide new therapeutic ideas for breast cancer, especially triple-negative breast cancer, and show potential clinical value in future combined applications with immune checkpoint inhibitors.

4.3. Lung Cancer

IL-17 is increasingly recognized as a pivotal factor in lung cancer pathogenesis, immune modulation, and disease progression. Its dual role as a detectable biomarker and a therapeutic target offers significant clinical potential. For example, in non-small cell lung cancer (NSCLC), elevated IL-17 levels in exhaled breath condensate correlate positively with VEGF and exhaled nitric oxide (FeNO), indicating that a combined assay of these markers could serve as a non-invasive tool for early diagnosis and treatment response monitoring by capturing both inflammatory and angiogenic activities [14]. Mechanistically, IL-17 activates pro-survival and metastatic pathways such as STAT3, NF-κB, and ERK1/2, which collectively enhance tumor cell resistance to apoptosis. It also upregulates MMP-2, MMP-9, and EMT-related transcription factors to promote invasion and metastasis. Moreover, through the CXCL1/5/8–CXCR2 axis, IL-17 stimulates angiogenesis and neutrophil infiltration, while simultaneously recruiting immunosuppressive populations including MDSCs and M2-type TAMs. These actions synergize to establish an immunosuppressive tumor microenvironment that supports immune evasion [15]. Given these multifaceted roles, IL-17 represents both a prognostic indicator and a promising target for intervention. Future therapeutic approaches may include IL-17 inhibition in combination with anti-VEGF agents, immune checkpoint blockers, or pathway-specific inhibitors targeting CXCR2 and STAT3, opening new possibilities for combinatorial treatment in lung cancer.

IL-17 is also closely associated with smoking-induced chronic inflammation. Smoking can lead to persistent neutrophilic inflammation and airway remodeling, and this process is highly dependent on IL-17A/F stimulating airway epithelial and stromal cells through the IL-17RA/RC complex. Specifically, IL-17 upregulates inflammatory factors such as CXCL1, CXCL5, and CXCL8, as well as IL-6 and IL-1, driving neutrophil homing and chronic inflammatory responses; animal experiments also show that knocking out IL-17A or its receptor can significantly alleviate airway inflammation and structural damage associated with smoke exposure [16]. At the oncogenesis level, long-term IL-17-driven inflammation not only induces reactive oxygen species (ROS) and DNA damage but also accelerates extracellular matrix remodeling, angiogenesis, lymph angiogenesis, and interacts with immunosuppression to significantly increase the risk of lung cancer occurrence and development. Moreover, epidemiological studies have shown that smokers with IL-17 gene polymorphisms (such as -152G>A) have a significantly increased risk of lung cancer, and mouse models also indicate that deletion of IL-17 can reduce the incidence and metastasis ability of K-ras-driven lung cancer [15].

Overall, IL-17 contributes to lung cancer progression through various mechanisms, including angiogenesis, EMT, and immunosuppression, and chronic inflammation induced by smoking. Future strategies could focus on precise patient stratification to identify "IL-17 high-expression" lung cancer and explore the combined therapies targeting the IL-17 pathway with existing immunotherapy and anti-angiogenesis reatments to identify new therapeutic targets for lung cancer clinical treatment.

4.4. Other Cancer

Beyond its roles in colorectal, breast, lung, and hepatocellular cancers, IL-17 signaling has garnered increasing interest due to its context-dependent functions and significant heterogeneity across tumor types. In prostate cancer, elevated expression of IL-17A and IL-17F enhances tumor invasion and metastasis by upregulating matrix metalloproteinases (MMPs) and pro-angiogenic factors. Conversely, IL-17RA deficiency markedly reduces tumor incidence in vivo, highlighting the pivotal role of IL-17 in promoting prostate cancer progression. In melanoma, IL-17A supports immune evasion by recruiting myeloid-derived suppressor cells (MDSCs), inducing immune checkpoint molecules, and stimulating angiogenesis, collectively increasing metastatic potential. Notably, IL-17 expression levels may also affect the efficacy of PD-1 blockade, reflecting its functional duality in cancer immunity [18]. In gastric cancer, polymorphisms in IL-17 genes—such as IL-17A rs2275913 and IL-17F rs763780—are associated with increased tumor risk and advanced disease stage. High IL-17 expression correlates strongly with lymph node metastasis and poorer clinical outcomes [19]. Interestingly, the functional impact of IL-17F appears to be highly tissue-specific: it acts as a tumor suppressor in oral squamous cell carcinoma and pancreatic cancer by inhibiting angiogenesis and slowing tumor growth, whereas in prostate and bladder cancers, it exhibits pro-tumorigenic activities. This suggests that the role of IL-17F is shaped by the unique immune and molecular microenvironment of each cancer type [19].

In summary, the research on the IL-17 family in various types of cancers has continuously revealed the "multifaceted" nature of its functions: it can either act as a driving force in the chain of inflammation-angiogenesis-immune escape or may exhibit anti-tumor potential under specific circumstances. These cross-cancer results of differential outcomes not only reflect the high dependence of IL-17 signaling on the tumor microenvironment but also suggest that future treatment strategies should combine cancer type specificity, receptor subunit expression profiles, and individual immune background to precisely determine the clinical application value of IL-17.

5. Conclusion

The IL-17 family exhibits a significant dual effect on cancer occurrence and progression. On one hand, it accelerates the development of various solid tumors by promoting inflammation, angiogenesis, immune evasion, and tumor cell invasion; on the other hand, in specific tissue contexts or disease stages, especially IL-17F, it may exert tumor-suppressing effects by activating immune cells or inducing tumor cell apoptosis. This difference mainly depends on tumor type, microenvironment composition, expression profile of receptor subunits, and cross-regulation with other signaling pathways. Therefore, IL-17 is not only an important node in cancer research but also provides new ideas for precise tumor immunotherapy. Future research needs to combine the patient's immune background and molecular classification to clarify the functional differences of different IL-17 family members and explore the potential of multi-modal treatment strategies, such as combined immune checkpoint inhibitors and anti-angiogenic drugs, to achieve precise regulation of the IL-17 signal and improve the clinical prognosis of cancer patients.

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