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Review article

Interleukin-17 acts as double-edged sword in anti-tumor immunity and tumorigenesis

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ABSTRACT

Interleukin-17 (IL-17), a proinflammatory cytokine, mainly produced by Th17 cells, participates in both innate and adaptive immune responses and is involved in various diseases, including infectious diseases, autoimmune disorders and cancer. Emerging evidence indicates that IL-17 not only has an oncogenic role in tumorigenesis by regulating tumor angiogenesis and enhancing tumor immune evasion but also exerts anti-tumor functions by enhancing natural killer (NK) cells and cytotoxic T lymphocytes (CTLs) activation and through the recruitment of neutrophils, NK cells and $CD4^+$ and $CD8^+$ T cells to tumor tissue. In this review, we provide an overview on the basic biology of IL-17 and recent findings regarding its enigmatic double-edged features in tumorigenesis, with special attention to the roles of IL-17 produced by tumor cells interacting with other factors in the tumor microenvironment.

Contents

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1. Introduction

In 1863, Virchow proposed a possible link between chronic inflammation and cancer, based on the origin of cancer at sites of chronic inflammation and inflammatory cell infiltration into neoplastic tissues [1]. Chronic inflammation can create an environment that is conducive to carcinogenesis. Tumor cells produce various cytokines and chemokines to attract multiple leukocyte populations including neutrophils, dendritic cells (DCs), macrophages, mast cells and lymphocytes, all of which are able to produce an array of cytokines and other cytotoxic mediators to participate in tumor immunity [1].

Interleukin-17 (IL-17) is primarily produced by T helper 17 (Th17) cells, which are known as a subset of T helper cells that are different from the classic T helper 1 (Th1) and 2 (Th2) cells. IL-17 recognizes target genes that mediate autoimmunity and chronic infections through the direct or non-direct induction of a variety of cytokines, chemokines, inflammatory effectors and antimicrobial proteins [2]. Recently, it has been found that IL-17 has an intimate relationship with tumorigenesis, with growing evidence revealing that IL-17 can both enhance natural killer (NK) cells and cytotoxic T lymphocytes (CTLs) activity to generate antitumor effects and promote tumor growth by inducing tumor angiogenesis, although the unambiguous effect of this cytokine in tumorigenesis has not been determined yet.

2. The basic biology and expression of IL-17 and IL-17 receptors

IL-17 was originally designated as cytotoxic T lymphocyte antigen 8 (CTLA-8) when it was first isolated and cloned from a murine T lymphocyte hybridoma cDNA library [3]. Subsequently, the gene encoding human IL-17 homologue was cloned from a $CD4^+$ T lymphocyte cDNA library. The human IL-17 protein has a 155 amino acid sequence containing an N-terminal signal peptide [4]. The IL-17 family has six members, including IL-17A (previously named as IL-17), IL-17B, IL-17C, IL-17D, IL-17E (IL-25) and IL-17F [2]. IL-17A is expressed regionally and was originally thought to be produced by Th17 cells [5]. Now, it is known to be secreted by several other cell types including macrophages [6–8], DCs, γδ-T cells [9,10], nature killer T (NKT) cells [11,12], $CD8^+$ T cells [13–16], regulatory T cells (Tregs) [17,18], neutrophils [19,20], mast cells [20–22], myeloid-derived suppressor cells (MDSCs) [23] and lymphoid tissue inducer (LTi) cells [24]. Currently, several lines of evidence indicate that γδ-T cells are the predominate source of IL-17 in some tumors [10,25–28]. Increasing evidence demonstrates that epithelial cells, pericytes, smooth muscle cells and tumor cells are other sources of IL-17 [29–34], although the mechanism is still not clear.

IL-17 signals through interacting with its transmembrane receptor. To date, five members of the human IL-17 receptor family have been identified, designated as IL-17RA, IL-17RB, IL-17RC, IL-17RD and IL-17RE [2]. The gene encoding IL-17RA is located on chromosome 22, and the others encoding IL-17RB, -17RC, -17RD and -17RE cluster on chromosome 3. The IL-17R is a single-pass transmembrane protein consisting of a 27 amino acid N-terminal signal peptide, a 293 amino acid extracellular domain, a 21 amino acid transmembrane domain and an unusually long cytoplasmic tail of 525 amino acids [2]. IL-17RA is ubiquitously expressed in various tissues and normal cells, including in tumor cells [35,36]. It is generally accepted that IL-17 binds to a receptor composed of at least two IL-17RA subunits and one IL-17RC subunit [37].

3. The oncogenic role of IL-17 in both human and mouse systems

Many studies have shown that IL-17 is highly expressed in tumor tissues of gastric carcinoma [21,38,39], medulloblastoma [40], ovarian cancer [41], colorectal carcinoma [42], non-small-cell lung cancer (NSCLC) [43], breast cancer[6], mycosis fungoides and Sezary syndrome [44], with the levels of IL-17 expression positively correlating with the aggressiveness of the malignancy. Although the details remain unclear, accumulating evidence has demonstrated that IL-17 might play an oncogenic role by inhibiting tumor cell apoptosis, impairing antitumor responses, promoting tumor angiogenesis and promoting tumor metastasis and invasion (Fig. 1).

3.1. Inhibiting tumor apoptosis and promoting tumor proliferation

Several independent studies have demonstrated that IL-17 inhibits tumor apoptosis and promotes tumor proliferation. Knockdown of the IL-17 receptor ($IL\text{-}17R^{-/-}$) in 4T1 mouse mammary cancer cells enhances apoptosis and decreases tumor growth in vivo [45], whereas in another study, the number of apoptotic cells observed significantly increases in $IL\text{-}17R^{-/-}$ lymphoma tumor mice, with proliferating cells significantly reduced in $IL\text{-}17R^{-/-}$ mice when compared with wild-type mice [46], suggesting that the deficiency in IL-17R inhibits tumor cell proliferation and enhances apoptosis. Moreover, IL-17 was shown to be able to increase tumor cell proliferation and reduce apoptosis in tumor

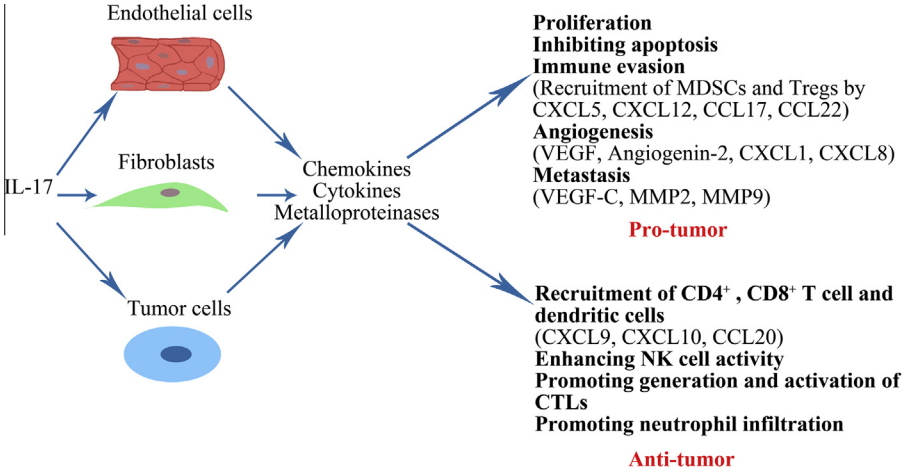

Fig. 1. The double-edged sword of interleukin (IL)-17 in tumorigenesis.

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