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REVIEW ARTICLE

THE ROLE OF PROINFLAMMATORY CYTOKINES IL-6 AND IL-17A AND ANTI-INFLAMMATORY CYTOKINE IL-10 IN COLORECTAL CANCER

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Colorectal cancer (CRC) remains the leading cause of cancer-related mortality worldwide, with chronic inflammation recognized as a critical factor in its pathogenesis. This review focuses on the roles of pro-inflammatory cytokines interleukin-6 (IL-6) and interleukin-17A (IL-17A), alongside the anti-inflammatory cytokine interleukin-10 (IL-10), in the development and progression of CRC. The reason we chose these cytokines among others is that we found a certain number of similar studies in recently published literature for comparison, given that this topic is quite rare. Elevated levels of IL-6 and IL-17A have been linked to enhanced tumor proliferation, survival, invasion, and metastasis, highlighting their contribution to a tumor-promoting microenvironment. Conversely, IL-10 exhibits a dual role by suppressing inflammation yet potentially facilitating immune evasion and tumor progression in certain contexts. Understanding the complex interplay and signalling pathways of these cytokines may improve the CRC risk assessment, diagnosis, prognosis, and offer new avenues for targeted therapies. This review synthesizes current evidence from recent literature to elucidate the molecular mechanisms and clinical implications of IL-6, IL-17A, and IL-10 in colorectal cancer.

Keywords: colorectal cancer, interleukin-6 (IL-6), interleukin-17A (IL-17A), interleukin-10 (IL-10), inflammation

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INTRODUCTION

Colorectal cancer (CRC) represents one of the leading causes of cancer-related mortality worldwide (1). The pathogenesis of CRC involves several key genetic alterations, including mutations in tumor protein 53 (TP53), adenomatous polyposis coli (APC), Kirsten rat sarcoma viral oncogene homolog (KRAS), and genes responsible for DNA mismatch repair (2). Mutations in TP53 are frequently linked to tumor progression and poor prognosis, whereas mutations in APC constitute early events triggering malignant transformation of intestinal epithelial cells (2,3). KRAS mutations are also common and vary according to tumor stage and patient population (4–7).

Chronic inflammation plays a pivotal role in CRC carcinogenesis. Patients suffering from inflammatory bowel diseases (IBD), such as ulcerative colitis and Crohn's disease, are at a significantly increased risk of CRC (8). Persistent inflammation drives continuous regeneration and repair of the intestinal mucosa, potentially leading to the accumulation of genetic and epigenetic alterations that favor malignancy (9–13). Moreover, inflammation shapes a tumor-supportive microenvironment by stimulating epithelial proliferation, angiogenesis, and recruitment of immune cells, further promoting genetic instability (10).

Inflammation mediators such as tumor necrosis factor-alpha (TNF-α), IL-6, and interleukin-1 beta (IL-1β) activate signalling pathways like NF-κB and STAT3, which enhance tumor proliferation, survival, invasion, and metastasis (14–17). Systemic inflammation, influenced by lifestyle factors including obesity, smoking, and alcohol use, correlates closely with CRC risk and progression (18–20). Conversely, physical activity and diets rich in anti-inflammatory components (fruits, vegetables, omega-3 fatty acids) may reduce systemic inflammation and CRC risk (2,14,15,21,22).

Despite advances, many aspects of cytokines' complex roles in CRC tumor biology remain to be elucidated. This study aims to investigate the roles of pro-inflammatory cytokines IL-6 and IL-17A, as well as the anti-inflammatory cytokine IL-10, in the CRC pathogenesis and progression. Understanding the circulating and tissue levels of these cytokines may improve CRC prevention, diagnosis, and personalized therapy.

METHODS

This work is a narrative literature review with elements of a systematic approach, aimed at synthesizing the current knowledge on the roles of the pro-inflammatory cytokines IL-6 and interleukin-17A (IL-17A), as well as the anti-inflammatory cytokine interleukin-10 (IL-10), in the pathogenesis and progression of CRC. The review summarizes key molecular mechanisms, biological functions, and the clinical relevance of these cytokines in relation to CRC development and progression. The included studies involved human subjects diagnosed with CRC, spanning various disease stages and treatment settings. Extracted data were qualitatively analyzed and thematically organized, with an emphasis on molecular pathways involving IL-6, IL-17A, and IL-10, their influence on tumor biology, and their potential roles as diagnostic or prognostic biomarkers and therapeutic targets.

A comprehensive literature search was conducted using three major electronic databases: PubMed, Scopus, and Web of Science. The search strategy combined relevant keywords and Medical Subject Headings (MeSH) terms, including "IL-6," "IL-17A," "IL-10," "colorectal cancer," and "cytokines." The search was restricted to articles published in English between January 2010 and April 2024.

Inclusion criteria encompassed original research articles, systematic reviews, and meta-analyses that addressed the roles of IL-6, IL-17A, and IL-10 in CRC etiology, progression, diagnosis, or treatment. Studies were excluded if they were unavailable in full text, not published in English, or presented as conference abstracts, case reports, editorials, or articles not directly related to cytokine involvement in CRC.

Study selection was conducted independently by two reviewers who screened titles and abstracts for relevance. Full-text articles of potentially eligible studies were retrieved and reviewed. Disagreements were resolved through discussion or consultation with a third reviewer. Extracted data included study design, population characteristics, cytokine measurement methods, key findings, and clinical implications.

Cytokines and their role in colorectal cancer

Cytokines are secreted proteins that mediate immune and inflammatory responses. Primarily produced by leukocytes (macrophages, T lymphocytes), they influence various cell types, including tumor cells, promoting malignant transformation and tumor progression (23,24). Tumor cells themselves can secrete cytokines to activate oncogenic pathways supporting growth (25). Chronic inflammation involves elevated pro-inflammatory cytokines, such as IL-6, IL-17A, TNF-α, and IFN-γ, which contribute to tumor

growth and metastasis (26). The CRC microenvironment contains increased concentrations of these cytokines; for example, IL-6 not only promotes tumor proliferation but also metastatic potential (27). TNF-α is associated with advanced stages and enhances tumor invasiveness and metaplasia (28,29).

Conversely, the anti-inflammatory cytokine IL-10 has a complex dual role in the tumor microenvironment. While it suppresses inflammation and protects tissue, excessive IL-10 production may inhibit anti-tumor immune responses by dampening cytotoxic T lymphocyte and macrophage activity, facilitating immune evasion by tumors (30–32). Elevated IL-10 levels have been correlated with poor prognosis in CRC and other cancers (29).

Some cytokines, such as IL-12, possess anti-tumor effects by activating NK cells and T lymphocytes but have limited therapeutic use due to stability and potential side effects (33,34). Elevated pro-inflammatory cytokines often reflect aggressive tumor phenotypes and poor prognosis, making cytokine signaling a promising therapeutic target (35,36).

Roles of IL-6, IL-17A (Pro-inflammatory) and IL-10 (Anti-inflammatory) in CRC

Cytokines are classified into pro-inflammatory (e.g., IL-1β, IL-6, IL-17A, TNF-α), anti-inflammatory (e.g., IL-4, IL-10, IL-13), chemokines (e.g., IL-8), and growth factors (e.g., VEGF) (37). The CRC tumor microenvironment is characterized by elevated pro-inflammatory cytokines IL-6, IL-17A, TNF-α, and IFN-γ, as well as anti-inflammatory cytokines like IL-10, which modulate immune responses (38,39).

IL-6, mainly secreted by monocytes and macrophages, plays a multifunctional role by inhibiting apoptosis, promoting tumor cell survival, and regulating reactive oxygen species (ROS) production. Under homeostasis, IL-6 and related cytokines (IL-10, IL-11, IL-23) serve as “alarm” signals resolving inflammation (40-43). IL-1α and IL-1β initiate and amplify local inflammation, while IL-12 and IL-23 drive differentiation of naïve T cells into IFN-γ-producing Th1 cells with antitumor activity (44,45).

IL-10 is an immunosuppressive type 2 cytokine that inhibits type 1 immune responses and host antitumor immunity (46). In advanced CRC, increased serum IL-10 correlates with reduced IL-12 production by stimulated peripheral blood mononuclear cells, promoting immune evasion (46). The role of IL-10 is context-dependent; it may both promote and inhibit tumorigenesis (47), and dysregulated IL-10 expression is implicated in systemic diseases (48).

DISCUSSION

IL-6 has been extensively studied in CRC, with multiple reports confirming elevated serum levels in patients compared to controls. IL-6 enhances tumor progression by promoting proliferation, survival, and differentiation of malignant epithelial cells, thereby facilitating metastasis (49,50). Elevated IL-6 levels correlate positively with tumor size, TNM stage, poor differentiation, and worse prognosis, suggesting its potential as both a diagnostic and prognostic biomarker (50–54). In vitro data support the role of IL-6 in stimulating CRC cell growth (51,52).

IL-10 is crucial for intestinal immune regulation. Therapeutic IL-10 administration in Crohn’s disease demonstrates its ability to suppress excessive immune responses and maintain homeostasis (55). Stanilova et al. reported increased IL-10 gene expression in CRC patients, with higher preoperative IL-10 mRNA levels than postoperative or control levels, suggesting a pro-tumorigenic role (56). Conversely, IL-10 knockout mouse models exhibit increased CRC susceptibility, indicating a protective role in tumor prevention (57). Abtahi et al. highlighted the context-dependent role of IL-10 influenced by the tumor microenvironment (58).

Recent studies identify serum IL-17 as a promising early diagnostic and prognostic biomarker in CRC. Elevated IL-17 correlates with advanced disease and p53 deficiency, reflecting tumor-associated cytokine production and systemic release. Radosavljević et al. confirmed the importance of IL-17 as a potential tumor-specific biomarker in CRC (59). Wang D et al. additionally indicated that the combination of CCL20 and IL-17A could serve as reliable biomarkers for early diagnosis and prognosis (60).

Large-scale multicenter studies should be conducted to further elucidate the importance of measuring inflammatory cytokines in CRC patients and their possible role in CRC diagnosis and prognosis. Future research involving larger targeted studies is necessary to thoroughly understand the mechanisms underlying the increase in de novo cytokines in the serum of CRC patients. Long-term and readily available biomarkers could facilitate matching patients to state-of-the-art therapeutic modalities such as blockade with monoclonal anti-cytokine antibodies. The positive results of this study should only serve as a starting point for additional confirmatory research.

Pro-inflammatory cytokines IL-6 and IL-17A contribute to CRC pathogenesis by promoting tumor growth, survival, and metastasis, while the anti-inflammatory cytokine IL-10 plays a complex, context-dependent role in immune regulation and tumor progression. Understanding these cytokines' dynamics offers opportunities for improved CRC diagnosis, prognosis, and targeted therapy development.

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Authors' Contributions

Conceptualization, investigation, writing – original draft, review & editing, L.S., E.H., A.M.A., S.M., A.M., E.H., S.B., A.K., and R.Š.K. All authors have read and approved the published version of the manuscript.

Statement of Competing Interest

The authors declare no relevant conflicts of interest.

Statement of Data Availability

Not applicable.

Statement of Generative AI Technologies Use

No generative AI was used.

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