Effects of Inflammatory Cytokines on the Initiation and Progression of Colorectal Cancer

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Abstract

Chronic intestinal inflammation is a well-established high-risk factor for colorectal cancer (CRC). Patients with long-term inflammatory bowel disease (IBD) carry 5–10 times higher CRC risk than healthy populations. Inflammatory cytokines secreted by intestinal immune cells, epithelial cells and cancer-associated fibroblasts construct a persistent pro-tumor microenvironment, driving adenoma-carcinoma sequence and serrated pathway malignant transformation. This review systematically classifies core pro-tumor and regulatory cytokines involved in CRC, elaborates how TNF-α, IL-6, IL-17, IL-23 promote tumor initiation via NF-κB/STAT3 signaling, and illustrates dual regulatory roles of IL-10 and TGF-β in tumor immunity. We further discuss cytokine-mediated mechanisms including intestinal barrier destruction, cancer stem cell maintenance, angiogenesis and immune evasion, summarize clinical correlations between serum/tissue cytokine levels and CRC staging, metastasis and prognosis, and analyze anti-inflammatory intervention strategies for CRC prevention. Existing research gaps and future translational directions are discussed to clarify the inflammatory cytokine network as potential diagnostic biomarkers and therapeutic targets for CRC.

Key words: colorectal cancer; inflammatory cytokine; chronic inflammation; tumor microenvironment; NF-κB; IBD

1 Introduction

Colorectal cancer ranks third in global tumor incidence and second in mortality, with sporadic CRC and colitis-associated carcinoma (CAC) as

two major subtypes[1]. The inflammation-cancer transformation theory has been fully validated in clinical cohorts: ulcerative colitis patients with over 8-year disease duration show sharply increased colorectal dysplasia and carcinoma risk[2]. Under physiological conditions, intestinal cytokines maintain mucosal barrier homeostasis and coordinate anti-pathogen immune responses; persistent mucosal injury disrupts cytokine balance, shifting the microenvironment toward a sustained pro-oncogenic inflammatory state[3].

Activated macrophages, dendritic cells, Th17 cells and intestinal epithelial cells secrete large quantities of inflammatory cytokines. These molecules act as signaling messengers to trigger DNA damage, inhibit epithelial apoptosis, accelerate abnormal proliferation, remodel extracellular matrix and suppress anti-tumor immunity, covering the full stages of CRC initiation, adenoma progression, invasion and distant metastasis[4]. The core cytokine network includes pro-inflammatory oncogenic factors (TNF-α, IL-1β, IL-6, IL-17A, IL-23) and dual-function immune regulatory cytokines (TGF-β, IL-10). Recent multi-cohort clinical studies confirm elevated circulating IL-6 and TNF-α serve as independent poor prognostic indicators for advanced CRC[5]. This review systematically expounds the multiple carcinogenic effects of inflammatory cytokines on colorectal tumorigenesis.

2 Core Pro-Tumor Inflammatory Cytokines and Their Mechanisms

2.1 TNF-α and IL-1 Family: Initiators of Mucosal Malignant Injury

Tumor necrosis factor-α (TNF-α) is primarily secreted by intestinal macrophages upon mucosal damage. It activates canonical NF-κB signaling in colonic epithelial cells, upregulating cyclooxygenase-2 (COX-2) to produce reactive oxygen species (ROS) and reactive nitrogen species (RNS)[6]. Excess oxidative stress induces DNA strand breaks and gene point mutations in epithelial cells, initiating premalignant dysplasia. TNF-α also disrupts tight junction proteins occludin and claudin-1, destroying intestinal barrier function and allowing gut microbial antigens to infiltrate lamina propria, forming a positive inflammatory feedback loop.

IL-1α and IL-1β are inflammasome-activated cytokines. NLRP3 inflammasome assembly cleaves pro-IL-1β into mature active IL-1β, further amplifying NF-κB activation. IL-1β synergizes TNF-α to upregulate matrix metalloproteinases (MMP2, MMP9), degrading basement membrane and facilitating early adenoma invasive growth[7]. Clinical tissue detection shows significantly higher TNF-α and IL-1β

expression in IBD-dysplasia and CAC specimens than normal mucosa.

2.2 IL-6/STAT3 Axis: Central Driver of Epithelial Malignant Proliferation

IL-6 is the most extensively studied cytokine linking inflammation and CRC. Secreted by monocytes, fibroblasts and tumor cells, IL-6 binds membrane IL-6R to activate JAK2 and STAT3 phosphorylation[8]. Nuclear p-STAT3 upregulates cyclin D1 and c-Myc to accelerate epithelial cell cycle progression, while simultaneously inducing anti-apoptotic Bcl-xL to eliminate damaged cell clearance.

In sporadic CRC and CAC, sustained IL-6 release maintains persistent STAT3 activation, enriching colorectal cancer stem cells (CSCs) with CD133+ phenotype. These stem cells possess strong self-renewal and drug resistance capacity, driving postoperative recurrence[9]. Serum IL-6 concentration positively correlates with tumor TNM stage and liver metastasis incidence, acting as a non-invasive auxiliary prognostic biomarker. Combined STAT3 and NF- κ B inhibition effectively suppresses IL-6-mediated adenoma proliferation in ApcMin mouse models.

2.3 IL-17/IL-23 Axis: Th17 Cell-Dependent Tumor-Promoting Inflammation

IL-23 secreted by dendritic cells induces naive T cell differentiation into Th17 cells, which produce high levels of IL-17A. IL-17A binds epithelial receptors to activate MAPK and NF-κB cascades, stimulating secretion of CCL20 chemokine to recruit more Th17 and myeloid-derived suppressor cells (MDSCs) to tumor sites[10].

The IL-17/IL-23 axis plays a unique role in serrated pathway CRC, which accounts for 30% of all colorectal malignancies. Serrated adenomas exhibit massive Th17 infiltration and high IL-17 expression, accelerating malignant transformation faster than traditional tubular adenomas. IL-17 also promotes angiogenesis by upregulating VEGF and angiopoietin-2, supplying nutrients for rapidly growing tumor lesions.

3 Dual-Function Regulatory Cytokines in CRC Microenvironment

3.1 TGF-β

Transforming growth factor- β (TGF- β) exhibits stage-dependent bidirectional effects. In early premalignant lesions, TGF- β inhibits normal epithelial proliferation via cell cycle arrest; once APC or SMAD4 mutations occur in adenoma cells, tumor cells lose TGF- β growth inhibition response[11]. At advanced CRC stages, abundant TGF- β

secreted by fibroblasts induces epithelial-mesenchymal transition (EMT), enhancing tumor migration and liver metastatic potential. TGF-β also suppresses CD8+ T cell anti-tumor function to mediate immune escape.

3.2 IL-10

IL-10 is mainly produced by regulatory T cells (Tregs) and M2 macrophages. It inhibits secretion of anti-tumor cytokines IFN-γ and IL-12, suppressing dendritic cell antigen presentation and creating an immune-suppressive microenvironment[12]. High IL-10 in tumor tissue correlates with low lymphocyte infiltration and worse overall survival. However, mild IL-10 elevation alleviates excessive acute mucosal inflammation in mild IBD, reducing early mutation risk, forming context-dependent dual effects.

4 Multi-Dimensional Carcinogenic Effects of Inflammatory Cytokines

4.1 Destroy Intestinal Mucosal Barrier and Amplify Inflammatory Circulation

TNF-α, IL-1β and IL-17 jointly downregulate tight junction proteins, increasing intestinal permeability. Gut bacteria and lipopolysaccharide (LPS) translocate into lamina propria, further stimulating immune cells to release more pro-inflammatory cytokines, forming a self-amplifying inflammatory loop that continuously exposes epithelial cells to mutagenic oxidative stress.

4.2 Maintain Colorectal Cancer Stem Cell Characteristics

IL-6/STAT3 and IL-17 signaling upregulate stemness genes LGR5 and SOX2, sustaining CSC proliferation. CSCs are the source of tumor recurrence and metastasis; blocking cytokine signaling significantly reduces CSC proportion in CRC organoid models[9].

4.3 Promote Angiogenesis and Distant Metastasis

Cytokine network collectively upregulates VEGF, bFGF and MMPs. New blood vessel formation supplies nutrition for primary tumor growth, while MMP-mediated extracellular matrix degradation enables tumor cell invasion into blood and lymphatic vessels, triggering liver and peritoneal metastasis.

4.4 Mediate Tumor Immune Escape

TGF-β and IL-10 inhibit cytotoxic T cell activity; IL-6 and IL-23 recruit MDSCs and Tregs to tumor tissue, eliminating effective anti-tumor immune responses and rendering tumors insensitive to immune checkpoint inhibitors.

5 Clinical Transformation and Intervention Value

Cytokine detection possesses dual clinical value for diagnosis and treatment. Tissue IL-6, TNF-α and IL-17 expression can distinguish benign adenoma from malignant lesions; serum cytokine levels assist metastasis risk stratification[5]. Anti-inflammatory intervention strategies targeting cytokine networks include: (1) traditional NSAIDs inhibiting COX-2 to reduce inflammatory mediator production; (2) monoclonal antibodies neutralizing IL-6 or IL-17 for IBD patients to lower CAC risk; (3) JAK/STAT small molecules blocking downstream cytokine signaling for advanced combined therapy.

6 Existing Challenges and Future Perspectives

Current research limitations include insufficient clarification of cytokine dynamic changes across adenoma-carcinoma stages and lack tissue-specific detection standardization for clinical biomarkers. Future research directions: (1) construct multi-cytokine combined prediction panels for early CRC screening; (2) develop oral cytokine neutralizing agents targeting intestinal local inflammation; (3) combine anti-cytokine therapy with immunotherapy to reverse tumor immune suppression.

7 Conclusion

Persistent imbalance of inflammatory cytokines forms a pro-carcinogenic microenvironment throughout colorectal cancer development. Pro-inflammatory cytokines TNF-α, IL-1β, IL-6, IL-17 drive mucosal injury, abnormal proliferation and metastasis via NF-κB/STAT3/MAPK pathways, while TGF-β and IL-10 mediate immune escape in advanced tumors. Targeting inflammatory cytokine networks provides novel strategies for CRC early prevention, auxiliary diagnosis and comprehensive treatment. Further clinical cohort and translational research will realize the clinical application of cytokine-based intervention approaches.

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