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Review article

INFLAMMATORY MECHANISMS IN COLORECTAL CANCER: THE ROLE OF CYTOKINES AND DIETARY INFLAMMATORY INDEX - A REVIEW

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Abstract: Colorectal cancer is one of the most common malignant tumors, with numerous studies highlighting the role of inflammation in its onset and progression. Cytokines such as IL-6 and TNF-α play a crucial role in sustaining inflammation, contributing to the malignant transformation of cells. The dietary inflammatory index, which reflects the intake of pro-inflammatory nutrients, is associated with an increased risk of developing colorectal cancer. Serum cytokine concentrations may serve as biomarkers for risk assessment, while dietary modifications aimed at reducing inflammation can significantly impact both prevention and therapy. This knowledge opens possibilities for a personalized approach to the treatment and prevention of colorectal cancer.

Keywords: Colorectal Neoplasms, Inflammation, Cytokines, Feeding Behavior.

INTRODUCTION

Colorectal cancer (CRC) is one of the leading causes of cancer-related mortality worldwide, with genetic, epigenetic, and environmental factors playing a significant role in its prevalence (1). Key genes involved in CRC pathogenesis include *Tumor Protein 53* (*TP53*), *Adenomatous Polyposis Coli* (*APC*), *Kirsten Rat Sarcoma Viral Oncogene Homolog* (*KRAS*), and those responsible for DNA mismatch repair, such as *Mismatch Repair* (*MMR*) genes (2). Mutations in *TP53* are frequently associated with tumor progression, whereas mutations in *APC* constitute one of the initial steps in CRC development, triggering a cascade of genetic changes that may lead to the malignant transformation of intestinal cells (2, 3). Similarly, mutations in *KRAS* occur in a substantial number of cases, with their detection holding prognostic significance (4, 5). The frequency of these mutations varies among patients, underscoring the importance of advanced diagnostic techniques for their identification and classification. These advancements pave the way for a more personalized approach to CRC treatment (6, 7).

Inflammation plays a critical role in carcinogenesis, including CRC. Inflammatory bowel diseases, such as ulcerative colitis and Crohn's disease, are significant risk factors associated with an increased likelihood of CRC development (8). In these conditions, chronic inflammation drives continuous regeneration of damaged cells and tissues, potentially leading to mutations and changes that promote malignant transformation (9–13). Additionally, inflammation contributes to the creation of a microenvironment that stimulates epithelial cell proliferation in the colon, fosters angiogenesis, and recruits immune cells, which may further damage surrounding tissues and promote mutations (10).

Moreover, inflammation induces the release of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (*TNF-α*), interleukin-6 (*IL-6*), and interleukin-1 beta (*IL-1β*), which activate signaling pathways associated with tumor cell proliferation, survival, and migration (14–17). Systemic inflammation, triggered by factors such as obesity, smoking, and alcohol consumption, is also linked to CRC, as it amplifies the body's pro-inflammatory response (18, 19, 20). Conversely, factors such as regular physical activity and a diet rich in anti-inflammatory components

(e.g., fruits, vegetables, omega-3 fatty acids) help reduce inflammation, thereby exerting a protective effect against CRC (2, 14, 15, 21). While the roles of cytokines, inflammatory processes, and dietary patterns are well-documented, many aspects of their interplay and precise impact on carcinogenesis and disease prognosis remain unclear (14, 15, 17).

Although advanced diagnostic methods have improved the understanding of genetic mutations in *TP53*, *APC*, and *KRAS*, further research is required to enable personalized therapeutic approaches, particularly concerning the role of inflammation at various stages of the disease (22). Additionally, growing evidence highlights the importance of dietary factors and physical activity in regulating inflammation and reducing CRC risk. However, the lack of consensus regarding optimal dietary and physical activity regimens warrants further investigation (2, 14, 15, 21).

The aim of this study is to examine the significance and interconnection between cytokines, inflammatory responses, and specific dietary patterns in the context of CRC by analyzing existing evidence. This analysis seeks to elucidate the mechanisms underlying these complex interactions. Furthermore, the study aims to contribute to the understanding of how these relationships can inform the prevention, diagnosis, and therapy of CRC, thereby advancing the development of personalized treatment strategies.

CYTOKINES AND THEIR ROLE IN CRC

Cytokines are soluble proteins that act as mediators in numerous immune and inflammatory reactions. Although predominantly secreted by leukocytes, particularly macrophages and T lymphocytes, cytokines can also be produced by other cells in the body (23). Cytokines, especially interleukins as a subgroup, significantly influence various cell types, including leukocytes and other body cells, promoting malignant transformation and becoming key contributors to the development and progression of pathological conditions such as carcinoma (24). Tumor cells can activate oncogenic signaling pathways through cytokine secretion, thereby supporting tumor growth (25).

Chronic inflammation, which is commonly observed in the tumor microenvironment, plays a crucial role in cancer progression. In this context, pro-inflammatory cytokines, such as IL-6, Interleukin 17A, Interleukin 17ATumor Necrosis Factor Alpha (TNF-α), and Interferon Gamma (IFN-γ), produced during inflammation, can directly contribute to tumor growth and spread (26). The CRC microenvironment exhibits high concentrations of these cytokines, which enhance the inflammatory response and have the potential to stimulate various oncogenic signaling pathways. For instance, IL-6 is known not only to promote tumor growth but also to increase the tumor's ability to metastasize to other parts of the body (27). TNF-α, associated with advanced disease stages, also plays a significant role in modulating the tumor microenvironment, promoting metaplasia and invasiveness (28, 29).

Conversely, Interleukin-10 (IL-10), often considered an anti-inflammatory cytokine, has a complex role in the tumor microenvironment. While IL-10 reduces the inflammatory response, which can be beneficial in preventing tissue damage, excessive production of this cytokine may suppress an effective immune response to the tumor (30). This effect can contribute to tumor development by reducing the activity of cytotoxic T lymphocytes and macrophages, which are critical for eliminating tumor cells (31, 32). Some studies suggest that elevated levels of IL-10 may be associated with poor prognosis in patients with various cancers, including CRC. In such cases, IL-10 may contribute to immune suppression, allowing tumor cells to survive and spread (29).

However, cytokines such as Interleukin-12 (IL-12), a pro-inflammatory cytokine, have demonstrated anti-tumor activity in various studies (33). IL-12 exerts its effects by activating natural killer (NK) cells and T lymphocytes, enhancing the body's capacity to eliminate tumor cells. Although the effects of IL-12 in the tumor microenvironment are complex, evidence suggests its potential therapeutic application due to its ability to amplify the immune response against tumors. Unfortunately, the therapeutic use of IL-12 remains underdeveloped because of challenges related to its stability and potential side effects (33, 34).

The elevated concentration of pro-inflammatory cytokines in the tumor microenvironment is often used as a biomarker of poor prognosis, as it may indicate accelerated tumor growth and metastasis. Given the complex role of cytokines in tumor biological dynamics, understanding their specific functions could aid in the development of novel therapeutic strategies targeting cytokines and their signaling pathways (35). For instance, cytokine pathway inhibitors may enable selective modulation of the inflammatory response, potentially enhancing the immune response to the tumor and reducing its capacity to spread (36).

DIETARY INFLAMMATORY INDEX AND CRC RISK

The Dietary Inflammatory Index (DII) is an innovative tool designed to quantify the inflammatory potential of a diet and its impact on disease develop-

ment, such as colorectal cancer (CRC). Developed in 2009, the DII synthesizes the effects of dietary components on inflammation in the body, using data from numerous studies linking diet to inflammatory processes (37–40). The index categorizes diets as pro-inflammatory or anti-inflammatory, with a higher DII score indicating a diet that promotes inflammation, while a lower score reflects a diet with reduced inflammatory potential (39, 40, 41).

Consumption of pro-inflammatory foods, such as red and processed meats, has been associated with an increased risk of CRC (37, 42). Conversely, diets rich in fiber and anti-inflammatory components are linked to a reduced risk of CRC (38). Studies have demonstrated a significant correlation between high DII scores and an elevated risk of CRC, while lower DII values indicate a reduced risk (43). These findings suggest that dietary modifications aimed at reducing inflammatory potential could be a crucial strategy for CRC prevention and management (38, 43).

Previous research has analyzed inflammation markers such as C-reactive protein (CRP), IL-6, and TNF-α, showing a positive association between high DII scores and elevated levels of these biomarkers (24, 32, 39). For example, higher DII scores were associated with increased high-sensitivity CRP levels in several studies (41, 44–46). Additionally, elevated DII scores have been linked to a greater risk of other cancers and higher mortality rates from cardiovascular and cancer-specific causes (47–49).

However, there remains a lack of data on the precise relationship between DII scores and cytokine profiles, particularly pro-inflammatory and anti-inflammatory cytokines, in CRC patients. This presents a significant avenue for future research (50, 51, 52). Such investigations could enhance our understanding of the impact of diet on the inflammatory microenvironment in CRC (38, 40). Furthermore, these findings could pave the way for the development of new therapeutic strategies, including immunotherapy and dietary adjustments aimed at reducing inflammation (53).

ASSOCIATION BETWEEN SERUM CYTOKINE LEVELS AND THE DIETARY INFLAMMATORY INDEX

DII serves as a valuable tool for assessing the inflammatory potential of a diet and its impact on systemic inflammation. A higher DII score indicates a pro-inflammatory diet that may elevate levels of pro-inflammatory cytokines, whereas a lower DII score, reflecting an anti-inflammatory diet, is associated with reduced levels of cytokines such as IL-6 and TNF-α (39, 40, 41).

Interestingly, studies have demonstrated a positive correlation between higher DII scores and elevated levels of inflammatory markers such as CRP, IL-6, and TNF-α. This correlation suggests that an inflammatory diet can modulate the body's immune response, potentially contributing to the development or progression of CRC (41, 54, 55). Research indicates that patients with higher DII scores are at increased risk of CRC, with those in the highest DII score quartile showing up to a 40% greater risk compared to those with lower scores (43, 52, 56).

Although the link between inflammatory cytokines and DII is well established, limitations exist in current research. Many studies have focused on only one or a few cytokines without evaluating a broader spectrum. Including a wider range of both pro-inflammatory and anti-inflammatory cytokines could provide a more comprehensive understanding of the mechanisms by which diet influences inflammation and CRC progression (50, 51, 52).

Improved insight into this relationship could aid in developing more effective strategies for CRC prevention and treatment. These strategies might include dietary modifications and immunotherapy aimed at reducing inflammation and, consequently, lowering the risk of cancer development (38, 57).

CLINICAL SIGNIFICANCE AND PERSPECTIVES IN THERAPY AND PREVENTION

Understanding the relationship between serum cytokine concentrations, the DII, and CRC development holds significant potential for advancing diagnostics, personalized nutrition, and treatment strategies for patients with this disease (37). Biomarkers such as TNF-α, IL-6, and CRP provide valuable insights into systemic inflammation, a key factor in CRC development and progression (39, 41, 58).

Diagnostics leveraging these biomarkers could enable the identification of patients in the early stages of CRC, when treatment options are most effective and impactful. For instance, elevated levels of inflammatory cytokines, particularly IL-6, have been linked to more aggressive forms of CRC and could serve as indicators of disease progression (39, 41). Additionally, these biomarkers could identify high-risk individuals before the onset of clinical symptoms, facilitating the implementation of preventive measures and earlier interventions (59, 60).

Beyond diagnostics, these biomarkers support personalized approaches to nutrition and treatment. Tailored dietary plans based on specific cytokine levels and DII scores could aim to reduce inflammation and minimize CRC risk. Recommendations for an an-

ti-inflammatory diet rich in fiber, omega-3 fatty acids, and antioxidants may substantially reduce systemic inflammation and, consequently, the risk of CRC development or progression (39, 41). Furthermore, personalized dietary interventions might enhance treatment responses, such as chemotherapy efficacy, by mitigating inflammation, improving therapeutic outcomes, and reducing adverse effects (34).

In the context of therapy, the manipulation of inflammatory cytokines through biological drugs or specific immunotherapies also represents a promising direction. Research indicates that inhibiting specific cytokines, such as TNF-α or IL-6, has the potential to direct therapy towards specific molecular pathways, thereby increasing treatment efficacy and reducing side effects (40, 41). Additionally, research in inflammation-reducing therapies could introduce new approaches to treating patients with CRC, particularly those with high inflammatory scores or advanced stages of the disease (43, 44, 54, 55).

Finally, the significance of biomarkers such as IL-6, TNF-α, and CRP in CRC prevention should not be overlooked. Their integration into routine practice could help identify individuals at high risk and monitor the effectiveness of preventive interventions, such as dietary changes, exercise, and supplementation (24). A healthy lifestyle, which includes reducing inflammation, could be a key factor in lowering CRC incidence, with biomarkers serving as tools for assessing the success of these preventive strategies (39, 41, 57).

CONCLUSION

Our study explored the impact of serum cytokine concentrations and the DII index on the onset and progression of CRC, aiming to identify their significance in the pathogenesis of the disease.

An analysis of data from available medical literature highlighted the significant role of pro-inflammatory cytokines, such as IL-6, TNF-α, and Interleukin-17A, in increasing inflammation and contributing to the onset and progression of CRC. Additionally, the DII index, reflecting both nutritional and inflammatory parameters, proved to be a useful predictive marker in relation to cytokine levels and the prognosis of these patients. Elevated cytokine levels, combined with a higher DII index, contributed to the deterioration of clinical status and poorer prognosis. These findings suggest that targeting inflammatory pathways, along with optimizing nutrition, could have significant therapeutic value in the treatment of CRC. Further research is needed to thoroughly examine the role of diet in modifying inflammatory responses and their connection to serum cytokine levels, which could contribute to the development of personalized therapeutic approaches for CRC patients.

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Sažetak

INFLAMATORNI MEHANIZMI KOD KOLOREKTALNOG KARCINOMA: ULOGA CITOKINA I DIJETALNOG INFLAMATORNOG INDEKSA

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Karcinom debelog creva jedan je od najčešćih zloćudnih tumora, a brojna istraživanja ističu uticaj inflamacije na njegov nastanak i progresiju. Citokini kao što su IL-6 i TNF-α igraju ključnu ulogu u održavanju inflamacije, koja može pridoneti malignoj transformaciji ćelija. Inflamatorni indeks u prehrani, koji se odnosi na unos proinflamatornih nutrijenata, povezan je s povećanim rizikom od razvoja kolorektalnog karcinoma. Koncentracije citokina u serumu mogu poslužiti kao biomarkeri za procenu rizika, dok modifikovane prehrambene navike usmerene na smanjenje inflamacije mogu značajno uticati na prevenciju i terapiju. Ova saznanja otvaraju mogućnosti personalizovanog pristupa u lečenju i prevenciji raka debelog creva.

Ključne reči: kolorektalne neoplazme, inflamacija, citokini, obrasci ishrane.

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