Review

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The therapeutic value of targeting inflammation in gastrointestinal cancers

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Inflammation has been implicated in the initiation and progression of gastrointestinal (GI) cancers. Inflammation also plays important roles in subverting immune tolerance, escape from immune surveillance, and conferring resistance to chemotherapeutic agents. Targeting key regulators and mediators of inflammation represents an attractive strategy for GI cancer prevention and treatment. However, the targeting of inflammation in GI cancer is not straightforward and sometimes inflammation may contribute to tumor regression. We discuss the origins and effects of inflammation in GI cancer and how to target it successfully.

Inflammation in GI cancer

GI malignancies, including colorectal, gastric, liver, and pancreatic cancers, are the most frequently diagnosed cancers and the leading causes of cancer-related deaths worldwide [1]. The general organismal response to GI cancers is tightly associated with inflammation and wound healing. In fact, an association between inflammation and cancer was first suggested by Virchow in 1863, based on his observations that tumors usually arose at sites of chronic inflammation and that inflammatory cells were present in most tumors [2]. A large body of evidence indicates that inflammation exerts multiple effects on tumorigenesis, yet not all of the underlying mechanisms have been fully elucidated. In certain GI cancers, localized inflammation exists before the malignancy appears. Most notable examples for such inflammatory conditions and subsequent tumors include ulcerative colitis and colitis-associated colorectal cancer (CAC), *Helicobacter pylori* infection and gastric cancer, and HBV or HCV infections or nonalcoholic steatohepatitis (NASH), and hepatocellular carcinoma (HCC). However, inflammation is also a consequence of initial neoplastic changes in most cancers, even those that are not linked to pre-existing infection or inflammatory disease. Most notable examples are sporadic and familiar colorectal cancers (CRCs), and pancreatic ductal adenocarcinoma (PDAC), both of which contain profound inflammatory infiltrates and activated stroma. Increasing evidence suggests critical roles for the intestinal microbiome and microbial products in colorectal tumorigenesis, tumor immunity, and response to therapy [3,4]. Microbiome studies have identified a few candidate species that may be involved in human CRCs [5]. In addition to tumor promotion, altered host–microbiome interactions (dysbiosis) may also modulate the response to anticancer drugs.

The presence of inflammatory cells and inflammatory mediators, including cytokines, chemokines, and prostaglandins, in tumors and the associated processes of tissue remodeling, fibrosis, and angiogenesis are key aspects of cancer-related inflammation [6]. Although inflammation often contributes to tumor initiation and promotion, growth, invasion, metastasis, and immune evasion, under certain circumstances it can also lead to tumor regression. Inflammation is a key component of host defense, where it assists in the killing of pathogens, clearance of tissue damage, and regeneration [7,8]. Acute inflammation, if properly resolved, does not interfere with maintenance of homeostasis and leads to tissue repair and healing. Nevertheless, chronic inflammation caused by either infections with pathogens that avoid immune clearance or autoimmune disease can result in oncogenesis. Chronic inflammation is characterized by increased abundance of active inflammatory myeloid and lymphoid cells (macrophages, neutrophils, mast cells, myeloid-derived suppressor cells, dendritic cells, natural killer cells, natural killer T cells, activated or effector T and B lymphocytes) within tissues [7]. It has been documented that almost 20% of human cancers are related to chronic inflammation caused by infections, exposure to irritants, or autoimmune disease [9]. Clearly, persistent inflammation is an important driving force in the journey from tissue injury to cancer. Thus, understanding the signaling pathways involved in both positive and negative regulation of cancer-related inflammation could enable the development of new treatments or improve the efficacy of existing therapeutics. This review primarily focuses on the role of inflammation in the initiation and progression of GI cancer and how to target cancer-associated inflammation in a successful and productive manner.

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Inflammation in GI cancer initiation and progression

Oncogenic mutations occurring either in differentiated cells undergoing dedifferentiation or in tissue progenitors/adult stem cells lead to the initiation of malignant tumors (Figure 1). It is generally agreed that an inflammatory microenvironment is associated with genomic instability, high mutation rates, and rapid proliferation of mutated cells [7]. Inflammation may also activate regenerative pathways that lead to dedifferentiation and reprogramming of terminally differentiated cells, which otherwise cannot contribute to tumor initiation. Activated inflammatory cells, including neutrophils, dendritic cells, macrophages, eosinophils, and mast cells, as well as effector T and B lymphocytes, potentiate tumor initiation by releasing reactive oxygen species (ROS), reactive nitrogen intermediates (RNIs), serine and cysteine proteases, matrix metalloproteinases (MMPs), cytokines, growth factors, and other inflammatory mediators that enhance the accumulation of cancer progenitors harboring oncogenic mutations [10,11]. Chronic inflammation results in oxidative stress, oxidative damage, and lipid peroxidation (LPO), thereby generating excess ROS and RNIs within the affected cell [12]. Oxidative damage is involved in all stages of the cancer process. 8-Oxo-7,8-dihydro-2-deoxyguanosine (8oxodG), a specific oxidative DNA modification, can exert mutagenic effects on the host and thus contribute to oncogenesis. In addition to classical mutations, DNA damage can result in gene copy number changes, gene fusions, and can even affect epigenetic modifications. Several transcription factors, such as nuclear factor-κB (NF-κB), adaptor protein-1 (AP-1), signal transducer and activator of transcription 3 (STAT3), p53, hypoxia-inducible factor-1α (HIF-1α), peroxisome proliferator-activated receptor-γ (PPAR-γ), β-catenin, Notch, and nuclear factor erythroid-2 related factor 2 (NRF2), are activated by oxidative stress and inflammatory stimuli, and can contribute to elevated expression of genes encoding growth factors, inflammatory cytokines, chemokines, antiapoptotic proteins, and cell cycle regulators that contribute to early tumor promotion [13,14]. In addition, some of these transcription factors can trigger regenerative responses that entail the reprogramming of terminally differentiated cells to more proliferative and multipotential progenitor cells that can contribute to tumor initiation. However, the primary mechanism responsible for tumor initiation is genomic instability and accumulation of inheritable genetic changes [15]. A key molecule that contributes to this process and whose expression is elevated in inflammatory bowel disease (IBD) is inducible nitric oxide synthase (iNOS) [16].

The relationship between IBD and CRC risk has been argued since 1925 [17]. IBD patients are at a very high risk of progression from dysplasia to CAC, which accounts for 10–15% of deaths in this disease [17]. A more comprehensive analysis of the impact of anticytokine drugs used in IBD treatment on CAC risk is needed to assess whether a reduction in colonic inflammation truly reduces cancer risk [18]. A recent study has shown that IBD and CRC patients

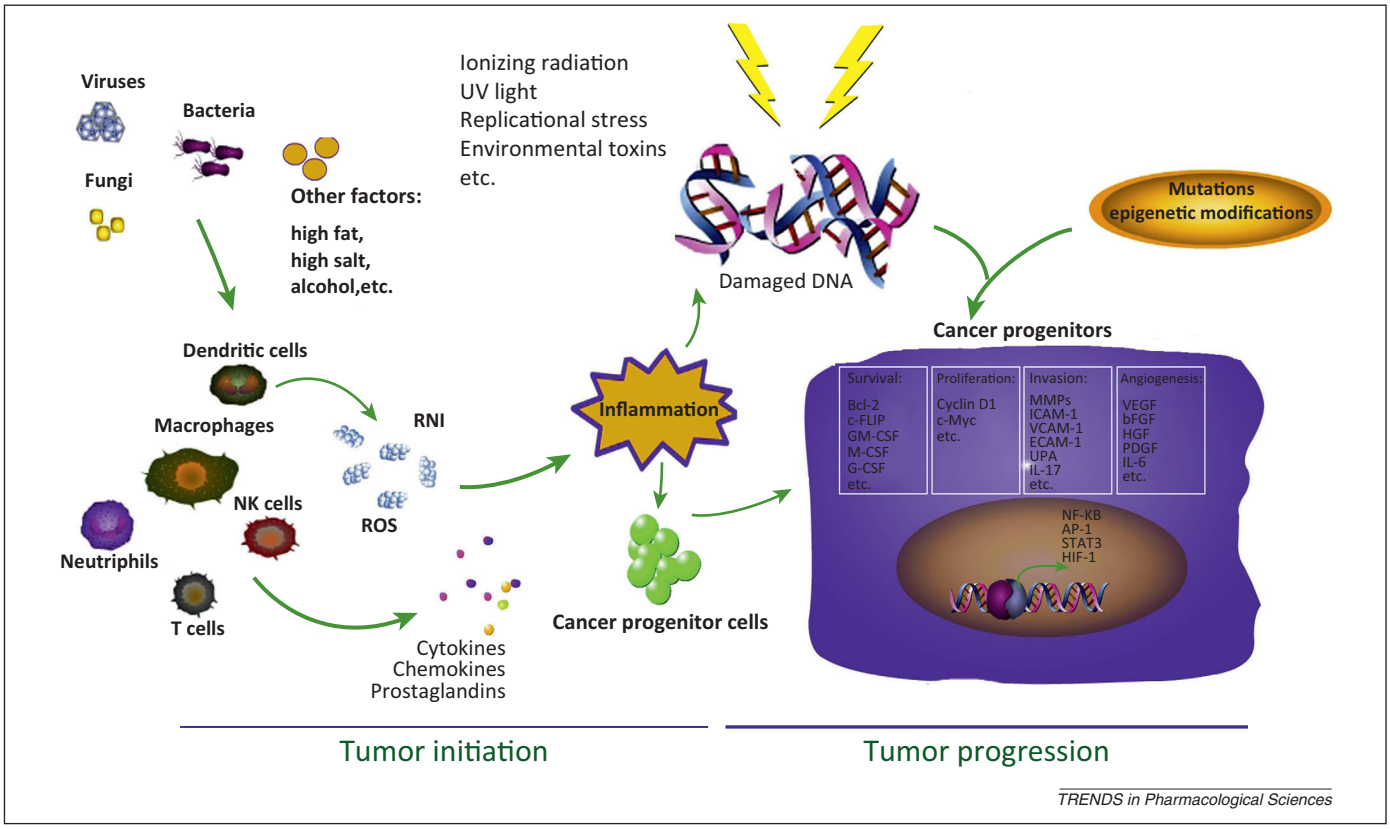

Figure 1. Role of inflammation in tumor initiation and progression. Inflammation can result in mutations and epigenetic changes that favor tumor initiation. Reactive oxygen species (ROS) and reactive nitrogen intermediates (RNIs) produced by activated inflammatory/immune cells, and DNA damaging toxins produced by carcinogenic pathogens, induce mutations and genomic alterations resulting in appearance of premalignant cells that proliferate and survive in response to cytokines produced by inflammatory immune cells.