REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

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The Gastrointestinal Tumor Microenvironment

MICHAEL QUANTE,[1,*] JULIA VARGA,[2,*] TIMOTHY C. WANG,[3] and FLORIAN R. GRETEN[2,4]

[1]*II. Medizinische Klinik and* [2]*Institut für Molekulare Immunologie, Klinikum rechts der Isar, Technische Universität München, München, Germany;* [3]*Department of Medicine and Irving Cancer Research Center, Columbia University Medical Center, New York, New York; and* [4]*German Cancer Consortium and German Cancer Research Center, Heidelberg, Germany*

Over the past decade, the microenvironment of gastrointestinal tumors has gained increasing attention because it is required for tumor initiation, progression, and metastasis. The tumor microenvironment has many components and has been recognized as one of the major hallmarks of epithelial cancers. Although therapeutic strategies for gastrointestinal cancer have previously focused on the epithelial cell compartment, there is increasing interest in reagents that alter the microenvironment, based on reported interactions among gastrointestinal epithelial, stromal, and immune cells during gastrointestinal carcinogenesis. We review the different cellular components of the gastrointestinal tumor microenvironment and their functions in carcinogenesis and discuss how improving our understanding of the complex stromal network could lead to new therapeutic strategies.

Digestive cancers are a significant health care burden worldwide. In the United States in 2008, it was estimated that more than 270,000 patients were diagnosed with and more than 135,000 died of cancers of the digestive system.[1] Most of the research and treatment strategies for patients with gastrointestinal (GI) cancers have focused on cell-autonomous mechanisms in the epithelial compartment. However, there is accumulating in vivo evidence that epithelial cells respond to their microenvironment, comprising mesenchymal cells and immune cells, the enteric nervous system, and matrix. The luminal content, particularly the microbiome, is another important feature of this complex network; its effects on immunity and tumorigenesis are only beginning to be understood.[2]

Many tumors of the digestive system arise under conditions of chronic inflammation (Figure 1*A*), including esophageal adenocarcinoma (from Barrett's esophagus), gastric cancer (from *Helicobacter pylori*–associated gastritis), hepatocellular cancer (from viral hepatitis), colon cancer (from inflammatory bowel disease), and perhaps even pancreatic cancer (from chronic pancreatitis).[3] Furthermore, eradication of infectious agents (such as *H pylori*) and treatment with anti-inflammatory therapies (such as prostaglandin synthase inhibitors or mesalazine) prevent cancer.[4,5] Tumorigenesis under conditions of chronic inflammation is likely to be mediated by immune cells and the factors they produce, which alter the microenvironment to support tumor formation and progression.[6] Importantly, sporadic tumors, which do not develop as a direct consequence of chronic inflammation, are also characterized by an inflammatory microenvironment.

Not all tumor-associated inflammation supports tumor formation; the adaptive immune response has effective roles in immune surveillance and tumor suppression.[7] Nevertheless, it appears that chronic overt and/or low-level inflammation more commonly stimulates tumorigenesis than prevents it. Cytokines and growth factors can promote tumor cell proliferation, inhibit apoptosis, and suppress antitumor immunity; matrix metalloproteases (MMPs) and angiogenic factors contribute to invasion, metastasis, and tumor blood vessel formation. Thus, it appears that an altered epithelium itself alters the surrounding stroma and with it the mediators that ultimately create a tumorigenic microenvironment. To design better surveillance strategies and therapeutics, it is important to understand the function and contribution of diverse stromal cell types to the tumor microenvironment.

Cell Types in the Tumor Microenvironment

Although it is not clear whether inflammation precedes or is activated by tumorigenesis, the stroma of GI

*Authors share co-first authorship.

Abbreviations used in this paper: CAC, colitis-associated cancer; CAF, cancer-associated fibroblast; CRC, colorectal cancer; CSC, colorectal cancer stem cell; DC, dendritic cell; EMT, epithelial-mesenchymal transition; GI, gastrointestinal; HGF, hepatocyte growth factor; IFN, interferon; IL, interleukin; IL22BP, interleukin-22 binding protein; ISC, intestinal stem cell; iMC, immature myeloid cell; MAPK, mitogen-activated protein kinase; MC, mast cell; MDSC, myeloid-derived suppressor cell; MMP, matrix metalloprotease; MSC, mesenchymal stem cell; NF-κB, nuclear factor κB; TAM, tumor-associated macrophage; TGF, transforming growth factor; Th, T-helper; TLR, Toll-like receptor; TNF, tumor necrosis factor; Treg, T regulatory; VEGF, vascular endothelial growth factor.

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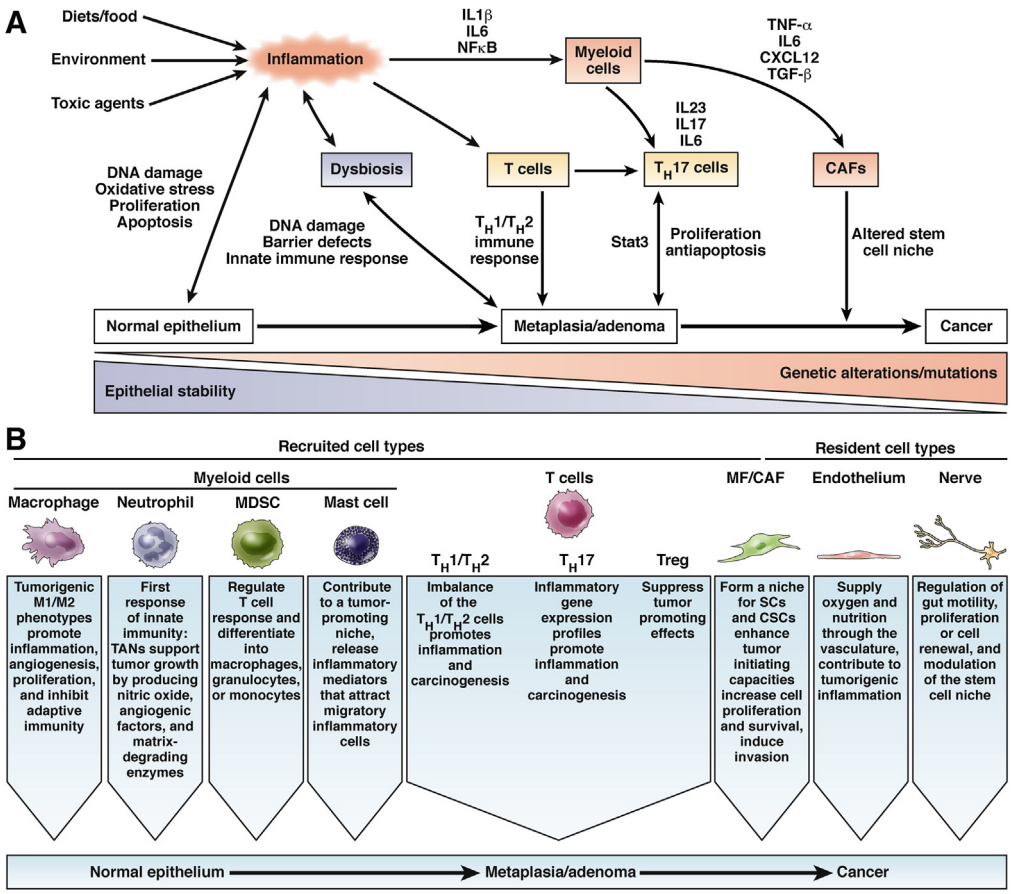

Figure 1. (*A*) Different cellular mechanisms of inflammation-induced carcinogenesis. External and host factors can create an inflammatory environment in the intestine that induces DNA damage and leads to genetic alterations over chronic injury. During carcinogenesis, different myeloid cells, T cells, and CAFs (see Figure 2) are recruited to sites of inflammation and create a microenvironment that promotes epithelial proliferation and prevents apoptosis due to an imbalance of protumorigenic and antitumorigenic factors. A network of multiple cytokines and chemokines generates a niche that enables the appearance and growth of tumor-initiating cells. (*B*) Types of cells that are recruited (myeloid cells, T cells, CAFs) or resident (CAFs, endothelial cells, nerves) in the tumor microenvironment and their tumor-promoting or -inhibiting functionss. The complex network of signaling among these cell types allows progression from normal to metaplastic to dysplastic gastrointestinal epithelium (carcinogenesis).

tumors is infiltrated by a range of bone marrow–derived cells that contribute to an expanding stroma (Figure 1*B*). The inflammatory environment contains cells of the innate immune system such as tumor-associated macrophages (TAMs), neutrophil granulocytes, myeloid-derived suppressor cells (MDSCs) or immature myeloid cells (iMCs), mast cells (MCs), and dendritic cells (DCs). It also contains cells of the adaptive immune system, such as T and B cells[8] (Figure 1*B*). The complex network of immune cells in the tumor stroma affects almost every aspect of tumor biology.

Innate and adaptive immune cells can promote tumorigenesis. Innate immune cells, such as TAMs, MCs, neutrophils, and MDSCs, promote tumor development, whereas subsets of adaptive immune cells, such as T-helper (Th)17 and Th2 cells, also contribute to inflammation and can promote tumorigenesis. The tumorigenic properties of these cells require their production of cytokines, growth factors, enzymes, and angiogenic mediators. Immune cells recruited to the tumors not only promote proliferation and invasion but also are required for antitumor immune responses.

The density and location of T cells in colon tumors are associated with patient outcomes; they could be better prognostic factors than histology-based TNM classification.[9,10] High densities of cytotoxic and memory T cells in the tumor center and at invasion fronts are associated with reduced recurrence of disease and are positive prognostic factors[9] for patients with colon cancer and even those with liver metastases. Moreover, the composition of the immune infiltrate in metastases has been associated with patients' response to therapy.[11]

These observations have led to the idea of an "immune score" that quantifies the intratumor location and density of cytotoxic and memory T cells. Because of its powerful prognostic value, it has been proposed that the immune score could be incorporated into the routine diagnostic and prognostic assessment of patients with tumors.[12] Furthermore, immune-based therapies might be developed that disrupt tumor-induced immune suppression and allow induction of antitumor immune responses.[13] So far, the precise mechanism of differential accumulation of T-cell subsets is only partially understood. However, elucidating the regulation of the adaptive T-cell response would have great therapeutic potential.

TAMs are a heterogeneous and plastic population of immune cells; large numbers of these cells in tumors