Review

CellPress

Chronic inflammation and the development of malignancy in the GI tract

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The role of immunologic factors in the development of gastrointestinal (GI) neoplasia, made evident from the high degree of association of chronic intestinal or gastric inflammation with the development of cancer, has attracted much attention because it promises new ways of treating disease. Here we develop the idea that immunologic factors influence the appearance of GI cancer on two levels: (i) a basic and initiating level during which the epithelial cell is induced to undergo pre-cancerous molecular changes that render it prone to further cancer progression; and (ii) a secondary level that builds on this vulnerability and drives the cell into frank malignancy. This secondary level is uniquely dependent on a single epithelial cell signaling pathway centered on STAT3, and it is this pathway upon which stimulation of mucosal cytokine production and microbiota effects converge.

Introduction

The concept that chronic inflammation is often associated with the development of neoplasia, first introduced over a century ago by Virchow, is now very well established [1]. This association applies with special force to the GI tract inasmuch as this organ is juxtaposed to proinflammatory factors of the gut microbiome that cause a constant state of low-level inflammation in the GI mucosa. However, it would be incorrect to assume that tumor development occurring under the influence of inflammation is radically different from that characterizing sporadic disease. A more realistic view is that inflammation-associated neoplastic transformation is essentially similar to that occurring in sporadic disease, but that inflammatory factors can both initiate and accelerate the sequence of oncogenic events that characterize the sporadic disease. This view is compatible with and indeed encourages the idea that sporadic disease is also influenced by immunologic factors, albeit in a less intense and more inconspicuous fashion.

We discuss these accelerating immunologic factors and put their effects in the context of the mucosal immunity. Whereas the discussion herein is limited mainly to inflammation associated neoplasia occurring in the colon, similar principles apply to *Helicobacter pylori*-associated gastric cancer and esophageal cancer (Barrett's esophagus).

Stages of inflammation-associated GI neoplastic development

In organizing our discussion of the influence of inflammation on the development of gastrointestinal epithelial cell neoplasia it is useful to assume that such influence is exerted in a discontinuous fashion reflective of two major stages. The first stage is a stealthy stage in which the cells are subjected to largely silent mutational 'hits', whereas the second stage is a more obvious stage in which the initial hits are exploited to cause more frankly neoplastic changes, possibly in conjunction with new hits. In the first stage, the initial mutations do not lead to the generation of macroscopic benign and/or invasive tumors in most instances because they initiate cellular processes (such as apoptotic cell death) that, at least for a time, result in the elimination of the potentially cancerous cell. In the second stage, however, this elimination process is undermined by inflammation-associated epithelial cell signaling that, in effect, rescues the epithelial cells bearing a pro-oncogenic change from elimination, and thereby renders the cell susceptible to further tumor progression. The development of intestinal tumors during chronic inflammation *de novo*, such as those occurring in patients with inflammatory bowel disease or in mice with interleukin IL-10 deficiency, experience both the first and second stages of tumor development because in these instances no oncogenic factor is initially present other than the inflammation itself. By contrast, intestinal tumors in mice exposed to a potentially oncogenic agent such as azoxymethane (AOM) and then to inflammation, in effect, experience only the second stage because in this case the epithelial cells have already sustained initial oncogenic changes that are now allowed to develop into frank tumors by pro-oncogenic signaling. It should be noted, however, that inflammation-dependent second-stage events are occurring in, and are necessary for, all tumors that develop during inflammation, and may in fact be operative in human tumors that are not ordinarily thought to be associated with inflammation.

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First-stage effects of inflammation on neoplastic development

As discussed above, first-stage pro-oncogenic effects of inflammation cause pre-neoplastic cellular changes that render the cell vulnerable to further neoplastic transformation. These changes are in fact similar to those that occur during sporadic epithelial cell malignancy, with the possible exception of the sequence of the neoplastic mutations [e.g., adenomatous polyposis coli (Apc) mutations tend to occur earlier in sporadic colorectal cancer than in inflammation-associated malignancy], and thus can ultimately lead to malignancy in the absence or inflammation or in the presence of very low grade local inflammation usually inapparent in sporadic malignancy [2,3]. In the discussion below they are characterized as frankly pro-oncogenic events, albeit ones that are influenced by the presence of chronic inflammation. However, in the two-stage formulation they do not actually cause malignancy until cells are subject to further signaling during the second stage. In this sense they are also a feature of the second phase.

In some cases first-stage oncogenic events consist of 'upstream' factors that exert both cytokine-independent and -dependent effects – such as factors associated with the gut microbiome that act on cells via Toll-like receptors (TLR) and other innate immunity receptors to induce cytokines and growth factors. In other cases these consist of downstream factors induced by soluble factors such as reactive oxygen or nitrogen species and eicosanoids. In either case, the net effect of these cytokine-related and -unrelated factors is to induce stepwise genetic and epigenetic changes in epithelial cells that have the potential to eventuate in frank malignancy (Figure 1).

Cytokines implicated in inflammation-associated malignant transformation of cells are the same as those mediating the inflammation itself, such as IL-1β, tumor necrosis factor α (TNF-α) and IL-6 [4]. In general, these cytokines support oncogenesis by activation of well-known proinflammatory mechanisms involving the activation of the nuclear factor κB (NF-κB) and mitogen-activated protein kinase (MAPK) pathways, and by downstream effects of the latter such as the induction of growth factors, the inhibition of apoptosis, and the enhancement of reactive oxygen species (ROS) production [5]. However, as we shall see, IL-6 and other cytokines that activate signal transducer and activator of transcription 3 (STAT3) have a particularly important role in malignant transformation of epithelial cells.

Molecular analysis of individual malignant epithelial cells has disclosed that these cells can contain as many as 100 coding-region mutations including 10–20 that have known oncogenic properties [6]. In addition, these cells exhibit numerous somatic rearrangements and multiple methylated genes that have also been associated with malignancy. Knowledge of the mechanisms by which chronic inflammation creates these genetic changes is only fragmentary. Generally speaking, however, they involve inflammation-associated generation of factors that cause inactivation of tumor-suppressor genes or, conversely, the activation of oncogenes. The most cogent example of tumor-suppressor gene inactivation is that involving tumor protein 53 (*TP53*), a gene that is central to the prevention of malignant transformation as a result of the capacity of *TP53* to bind to sites regulating the cell cycle and responses to DNA damage or oxidative stress; in other

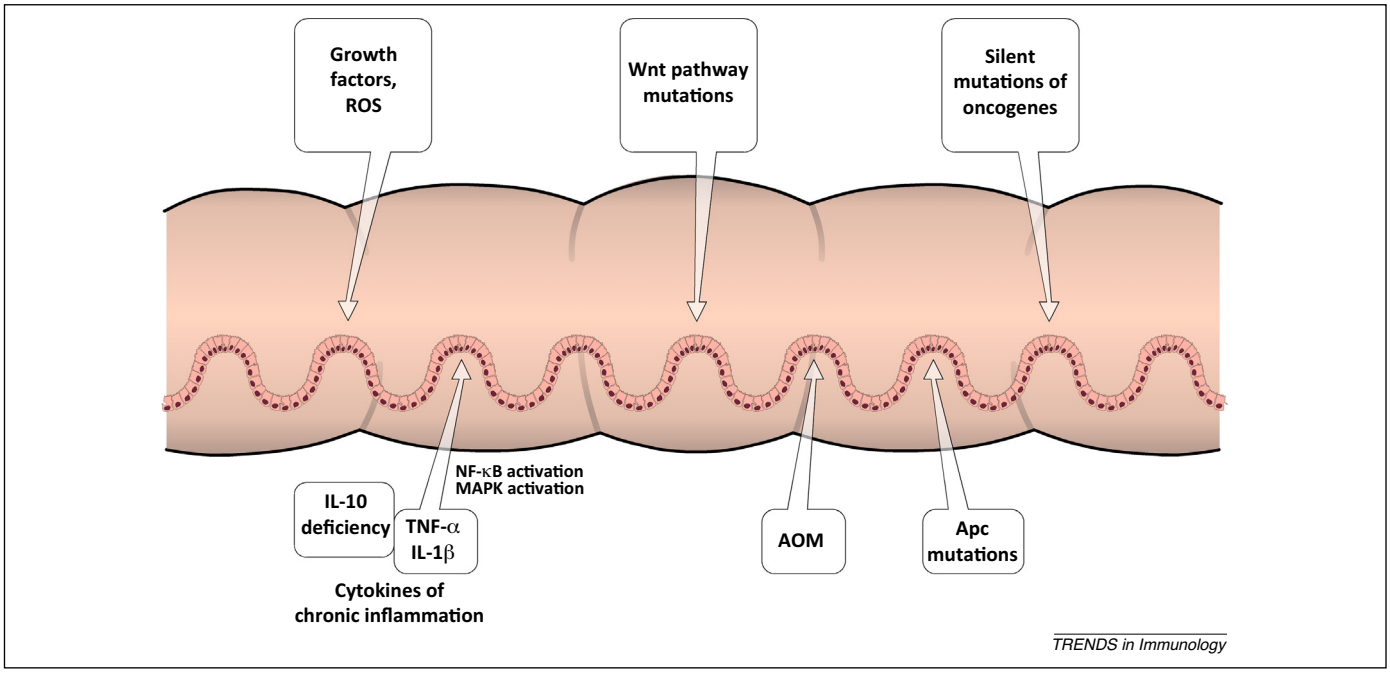

Figure 1. First-stage oncogenic events. The development of malignancy in the gastrointestinal epithelium as a result of chronic intestinal inflammation is usually a two-stage process. The first stage is a 'stealthy' and relatively prolonged process in which factors in the milieu created by chronic inflammation cause oncogenic 'hits' – in other words, molecular changes involving tumor-suppressor genes or pro-oncogenic genes that result in cells vulnerable to immunologic stimulation of signaling pathways that drive frank malignant changes. Inflammatory cytokines such as TNF-α induce downstream factors such as ROS to cause silent mutational changes in oncogenes such *TP53* and *Kras*. These changes render the cell vulnerable to induction of frank neoplastic changes in the second stage of tumor development. The presence of the Apc genetic mutation or the administration of a genotoxic agent such as azoxymethane (AOM) 'short-circuit' this initial phase and allow the rapid progress of oncogenesis by immunologic factors. Abbreviations: *Kras*, Kirsten rat sarcoma viral oncogene homolog; ROS, reactive oxygen species; TNF, tumor necrosis factor; *TP53*, tumor protein 53.