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Commentary

Molecular Cancer Research

IMPlicating Mesenchymal Imp1 in Colitis-Associated Cancer

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Abstract

Chronic inflammation and associated pathways are significant facilitators of many disease states, including malignancies. In the context of cancer, fibroblasts can actively regulate both inflammation and carcinogenesis. In this issue, Hamilton and colleagues describe a fibroblast-specific role of the RNA binding protein Imp1 in suppression of intestinal inflammatory responses and development of colitis-associated cancer. *Mol Cancer Res; 13(11); 1452–4. ©2015 AACR.*

See related article by Hamilton et al., p. 1478

Commentary

The tumor microenvironment (TME) is increasingly recognized as one of the critical components of cancer development and progression. The non-neoplastic immune, vascular, and stromal cells often represent a significant fraction of the bulk mass of the tumor. These cells have well-established roles as key "tumor infrastructure" constituents, and they are also recognized to play an active role in tumor development, such as by producing signaling factors that support tumor growth and progression (1).

Cancer-associated fibroblasts (CAF), in particular, have long been implicated in tumor growth via variety of mechanisms, including the ability to provide tissue-protective and proliferation-inducing factors, induce angiogenesis, provide nutrients to cancer cells, and induce an immunosuppressive TME. Because cancers frequently manifest features of chronic injury and repair (i.e., "wounds that never heal"), the functions of CAFs are likely to resemble in many ways some of the evolutionary conserved roles of "normal" fibroblasts. Tissue injury and continuous regeneration are especially prominent in cancers, whose development is preceded by chronic inflammation, such as colitis-associated colon cancers (CAC) in patients with inflammatory bowel diseases (2). Notably, the expression profiles of "naïve/homeostatic" fibroblasts are quite different from CAFs or those participating in wound healing, but the mechanisms underlying differential gene expression programs of fibroblasts in different tissue contexts remain incompletely understood.

In this issue of *Molecular Cancer Research*, Hamilton and colleagues (3) address the function of the Imp1 (Igf2bp1) protein within the Dermo1/Twist2^{+} cells of mesodermal origin (including embryonic tissue macrophages and fibroblasts), in a mouse model of CAC induced by the carcinogen azoxymethane (AOM) and repetitive colonic injury with dextran sulfate sodium (DSS). Imp1 is an inducible protein, with the capacity to bind and regulate the stability and translation of multiple mRNAs, some of which encode known oncogenes, such as c-Myc and others. Indeed, prior work from the Rustgi laboratory demonstrated that in a spontaneous intestinal tumorigenesis mouse model (APC^{Min} mice), Imp1 deficiency in epithelial cells substantially inhibited intestinal tumorigenesis, suggesting a protumorigenic role for Imp1 in the epithelial compartment (4). These prior studies in a mouse model were consistent with data indicating that increased Imp1 levels are often seen in a variety of cancers and that increased Imp1 expression often correlates with poor prognosis (4). However, many primary tumor expression analyses often do not specifically distinguish gene expression in the neoplastic (e.g., epithelial) cell compartment from expression in other cell populations present in the primary tumor. In addition, the function of key regulators in different cell types and contexts may be very different. As such, it was not possible to predict *a priori* the role of Imp1-regulated gene expression in fibroblasts and how altered Imp1 function might affect colitis and CAC.

Hamilton and colleagues demonstrated that mice lacking Imp1 expression in Dermo1^{+} cells (Dermo-Imp1 mice) do not exhibit any abnormalities under homeostatic conditions. However, colitis-induced tumorigenesis in these mice was markedly enhanced, with increased tumor numbers, tumor size, and incidence of adenocarcinomas (3). These data showing that protumorigenic effects following loss of Imp1 expression in fibroblasts were well correlated with increased inflammation, neutrophilia, stromal involvement, and fibrosis in the tissues of Dermo-Imp1 mice at the late stages of AOM/DSS model led the authors to hypothesize that Imp1 in the mesenchymal compartment is required to quickly and efficiently heal the tissue during chronic inflammation.

Imp1-null mesenchymal cells isolated from chronically inflamed AOM/DSS-treated colons demonstrated upregulation of several cytokines and chemokines, including IL6, IL1β, IL22, and MCP1 (3), all of which have been implicated in CAC tumorigenesis (2). Similarly, increased levels of HGF were observed. HGF is a well-known growth factor for colonic and cancer stem cells implicated into activation of c-Met and Wnt/β-catenin signaling pathways in colorectal cancer development. Indeed, *in vivo* CAC tumors from Dermo-Imp1 mice

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demonstrated enhanced protein processing and the presence of an active form of HGF (3). It is possible that *in vivo* levels of HGF rise indirectly in response to enhanced injury during acute and chronic colitis (Fig. 1). However, the authors demonstrated that there may be a direct cell autonomous connection between Imp1 and HGF, because shRNA-mediated knockdown of Imp1 in fibroblast cells led to an increase in HGF protein but not in mRNA, implicating Imp1-regulated HGF posttranscription/translation/protein stability. To what extent the increased inflammation in the absence of Imp1 in fibroblasts can be generally attributed to the heightened levels of acute and chronic colitis versus the specific involvement of HGF remains to be determined, but the authors indeed documented increased inflammatory infiltrates at later stages in the AOM/DSS model.

Imp1 expression in normal colonic mesenchyme is very low or undetectable. It is not clear what factors and mechanisms lead to Imp1 induction in the setting of colitis, and the full range of Imp1 roles in the response to colitis is unclear. However, following stresses and inflammatory insults, Imp1 levels do increase. It is possible that microbial and cytokine signals control Igf2bp (Impl) expression via activation of NF-kB and Lin28 and repression of

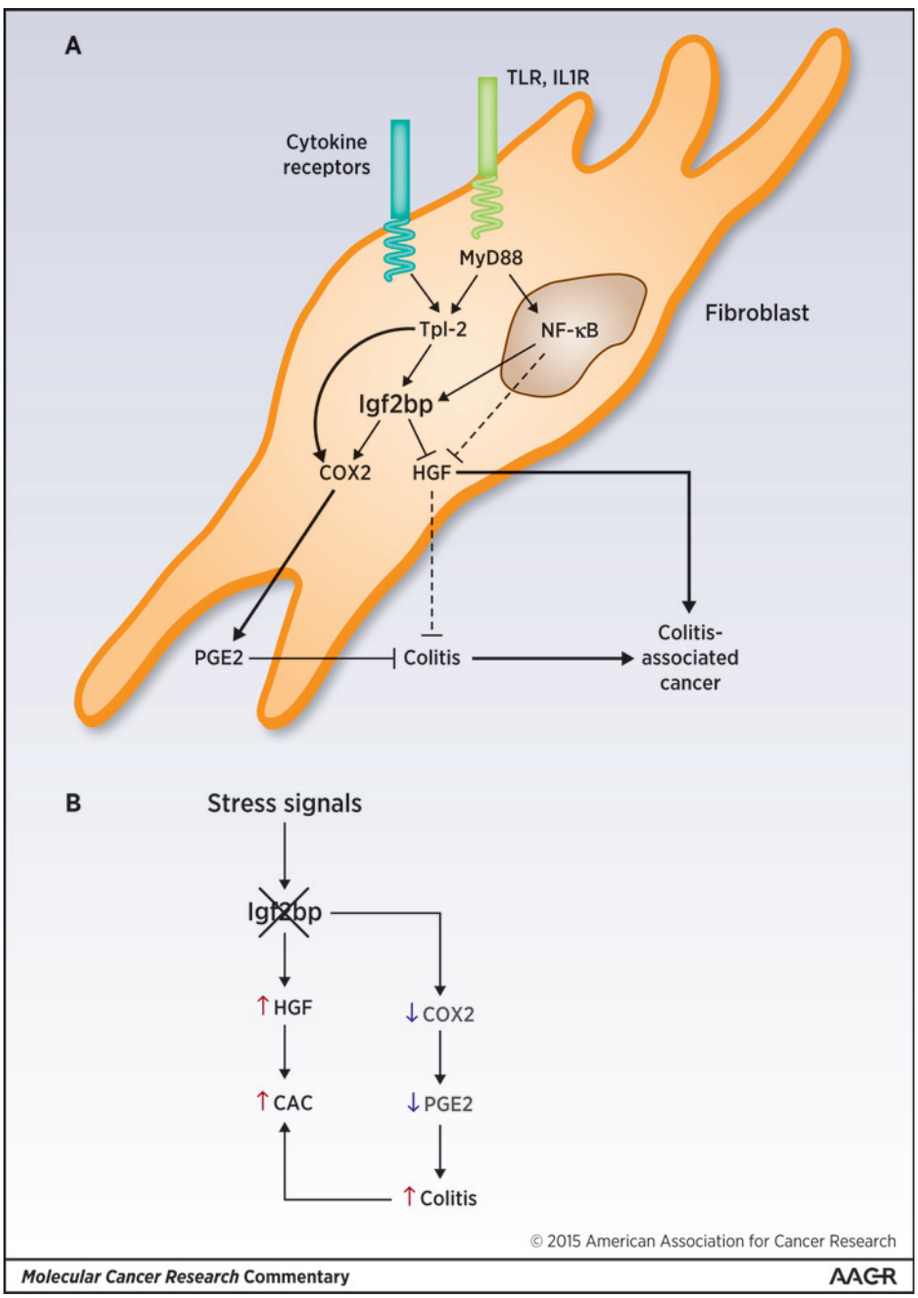

Figure 1.
Induction of Imp1 in fibroblasts and its action during colitis and cancer development. A, pathway for Imp1 in fibroblasts induction and how Imp1 controls COX2 (previous reports) and negatively controls HGF (Hamilton et al., this issue) are shown. Further relationships of these events with the development of colitis and CAC are outlined. B, consequences of Imp1 ablation are shown as a reduction in COX2 and PGE2 (blue arrows) and an increase in HGF (red arrows). Altogether, that results in increased colitis and enhanced CAC tumorigenesis.

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Let-7, which negatively controls Imp1 expression (5). Intriguingly, downstream of Toll-like receptors (TLR), IL1R, and other inflammatory pathways is the protein kinase "tumor progression locus 2" (Tpl2), whose inactivation in intestinal myofibroblasts results in altered Imp1/Igf2bp1 expression (6). Another question is whether the ability of Imp1 in fibroblasts to control the expression of HGF and protumorigenic cytokines fully explains the heightened CAC development in Dermo-Imp1 mice? Other groups have shown that Imp1 in colonic myofibroblasts also promotes the expression of cyclooxygenase 2 (COX2/PTGS2), a rate-limiting enzyme in prostaglandin E2 (PGE2) production, which is a key player in wound healing during colitis (7). Also, it was shown that activation of COX2 expression is MyD88- and Tpl2-dependent (6, 7), just like Imp1 expression is. Moreover, Tpl2 in myofibroblasts regulates HGF levels during the development of CAC (8), and its deficiency also promotes spontaneous colorectal cancer in the APC^{Min} model, albeit there is more involvement of Tpl2 in T cells and other hematopoietic cells (9).

Altogether, as highlighted in Fig. 1, the work from Hamilton and colleagues (3) and others in the field indicates that Imp1 in colonic and cancer-associated fibroblasts is induced by inflammatory stimuli, such as those transmitting their signals via MyD88, Tpl2, and partially NF-kB, leading to increased Imp1 expression. While in the epithelial compartment, Imp1 appears to function as an oncogene; in fibroblasts, Imp1 acts as a tumor suppressor via at least two different mechanisms. First, it suppresses the expression of oncogenic HGF (3; and other protumorigenic cytokines). Second, it induces the tissue-protective COX2-PGE2 pathway which ameliorates colitis, thus inhibiting CAC. In the absence of MyD88, Tpl2, Imp1, or COX2 components of this common pathway, an increased colitis, HGF production, and enhanced CAC tumorigenesis ensue (Fig. 1B). Some of the phenotypes of fibroblast-specific Tpl2 knockout can be rectified by exogenous PGE2 (6). Similarly, it would be interesting to examine whether blockade of HGF reverses the increased tumorigenicity in Dermo-Imp1 mice, or whether exogenous PGE2 supplementation would have similar effects since both of the pathways are seemingly controlled by Imp1. Another important notion is that COX2 and PGE2 suppress colitis and CAC development, but for spontaneous colorectal cancer, these factors are extremely tumor-promoting (10). As demonstrated by Hamilton and colleagues, Imp1 in fibroblasts is an important tumor suppressor in CAC, but its possible involvement into spontaneous colon carcinogenesis remains to be addressed and may be its possible HGF-dependent, hypothetically COX2-independent role will be revealed there.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Writing, review, and/or revision of the manuscript: E.K. Koltsova, S.I. Grivennikov

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): E.K. Koltsova, S.I. Grivennikov

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