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AUTHOR'S VIEW



Transmissible inflammation-induced colorectal cancer in inflammasome-deficient mice

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ABSTRACT

The microbiota is pivotal in orchestrating the pathogenesis of IBD-associated colorectal cancer (CRC). We recently demonstrated that altered elements in the microbiota of inflammasome-deficient mice drive transmissible inflammation-induced CRC. This microbiota-mediated effect is dependent upon microbiome-induced CCL5-driven inflammation, which, in turn, promotes epithelial cell proliferation through local activation of the IL-6 pathway, leading to cancer development.

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Environmental factors are considered major risk factors for many cancers.¹ Chronic infection, obesity, toxic agents, and autoimmune response are among the various environmental aspects that have been shown to contribute to carcinogenesis. One fundamental common process to all these factors is chronic inflammation, which is manifested in an abnormally hyperactive or dysregulated immune response. Of these environmental factors, interaction between the host and a number of pathogenic microbes was shown to play a causative role in various stages of carcinogenesis. Noteworthy examples are *Helicobacter Pylori*, considered a direct cause of gastric cancer, and *Salmonella enterica* contributing to development of gallbladder cancer.^{2,3} In both cases, inflammation triggered by host-pathogen interactions was shown to drive tumorigenesis. However, the association between commensal bacteria and cancer, which was suggested already during the 19th century, has been mostly rejected by scientists and physicians and therefore, neglected for years.

The gastrointestinal (GI) tract is the organ most extensively inhabited by commensal microbes. The number of commensal bacteria in the human intestine is approximated to be 1×10^{14} , exceeding the number eukaryotic cells by a factor of 10, with microbial genes outnumbering the human genes by a factor of 100. In recent years, the influence of bacterial factors on host physiology and pathophysiology, including their contribution to carcinogenesis, has gained much attention. Indeed, recent research reveals the involvement of commensal bacteria in promoting cancer in the GI tract. A few mechanisms underlying these functions have been proposed: first, microbiota-derived factors, such as genotoxins and metabolites, could directly promote tumor initiation, neoplastic cell survival or proliferation. For example, bacterial-derived genotoxins, such as cytolethal distending toxin (CDT), that causes direct DNA damage and

bacterial-derived metabolites, such as short chain fatty acids (SCFAs) which demonstrate beneficial effect on carcinogenesis as appose to nitroso and phenol compounds that have pro-carcinogenic influence.^{2,3} In addition, microbiota-derived pathogen-associated molecular patterns (PAMPs) or an altered microbiota composition (dysbiosis) could also drive local inflammation to promote tumorigenesis through alterations induced in the host immune response. For example, direct penetration of microbial products into tumors as a result of diminished intestinal-barrier integrity in mice has been shown to trigger-elicited inflammation which in turn drives tumor growth.^{4,5} We recently demonstrated that altered elements in the microbiota of inflammasome-deficient mice drives transmissible inflammation induced CRC, and suggested that alterations in the microbiome ecosystem be added to factors regulating tumorigenesis and in particular in the inflammatory setting.⁶

We focused in our work on the Nod-like receptor (NLR) family of immune sensors. The NLR family is a group of cytosolic receptor proteins that can be activated by a large variety of both endogenous and exogenous triggers.⁷ Some NLRs (NLRP1, NLRP3, NLRP6, NLRP6, NLRC4), and the PYHIN (pyrin and HIN domain-containing protein) family member absent in melanoma 2 (AIM2) and IFI16 are capable of forming, under tightly regulated conditions, a multi-protein complex named the inflammasome. Once formed, mature inflammasomes recruit and activate pro-inflammatory caspases, mediating the activation by cleavage of the cytokines IL-1 β and IL-18, as well as promote a state of controlled cell death named pyroptosis.⁷

Emerging evidence points to the involvement of inflammasome signaling in multiple physiological and patho-physiological processes, including regulation of infection, inflammation,

metabolism, and cancer.⁸ Recent data from our groups and others have demonstrated important roles for inflammasomes in intestinal inflammation and associated tumor development.^{9,10,7,8} Results linking several NLR and inflammasome components to auto-inflammation and associated cancer remain conflicting. Some studies point toward deficiency in caspase-1, ASC, and NLRP3 in mice as being associated with an enhanced severity of chemically induced colitis, while others reported an ameliorated severity of colitis in NLRP3^{-/-} mice in the same DSS induced colitis model.^{7,8} We recently offered a mechanistic explanation to these conflicting and even opposing results, by suggesting that NLRs such as the newly recognized NLRP6 may act as regulators of the gut microbiota and/or the host response toward different components of the microbiota.¹¹ As such, the effects noted with deficiency in these molecular components may in fact be dependent upon the general surrounding configuration of the native microbiota.

NLRP6 is primarily expressed in the non-hematopoietic compartment, including intestinal epithelial cells, and has been implicated in host defense against certain bacteria.⁷ These and other results suggest that NLRP6 may play an important role in regulating the gut microbiota communities and maintaining intestinal tissue homeostasis. In support of this notion, we have recently shown that mice with perturbations in the NLRP6 inflammasome pathway featured a distorted microbiota composition, characterized by multiple microbial aberrations including overrepresentation of several bacterial taxa including *Prevotellaceae* and TM7 and under-representation of *lactobacilli*.¹¹ This state of dysbiosis induced spontaneous intestinal auto-inflammation and enhanced susceptibility to chemically-induced colitis. Furthermore, dysbiosis in the NLRP6 inflammasome-deficiency setting was linked to an enhanced susceptibility to

colorectal tumorigenesis in the AOM-DSS model, by promoting chronic inflammation characterized by IL-6 signaling dependent over-proliferation of intestinal epithelial cells.¹⁰ The dysbiotic microbiota was dominant over the wildtype (WT) microbiota, as it was fully transferable to WT mice horizontally upon prolonged co-habitation or by cross-fostering of newborn pups. This state of competitive dominance over the endogenous microbiota resulted in development of increased inflammation even in cohoused genetically-intact WT mice. Accordingly, enhanced CRC in this model was “infectious” in the sense that it could be fully transferrable to WT mice upon prolonged cohabitation. This interesting phenomenon suggests that at least in some settings, a dysbiotic microbiota may confer susceptibility to cancer in this model. Mechanistically, increased tumorigenesis was dependent on microbiota induced CCL5 (RANTES) driven inflammation, which in turn promoted epithelial IL-6 signaling pathway (Fig. 1). Of note, the bacteria of the family *Prevotellaceae* overrepresented in NLRP6 deficient mice were also found to be expanded in the fecal microbiota in some patients with CRC compared to control subjects, suggesting this family may contain certain pathogenic bacterial species that promote inflammation associated intestinal tumorigenesis.¹²

Altogether, our results demonstrate that altered elements in the microbiota of inflammasome-deficient mice participate in driving inflammation-induced CRC. This work highlights a novel mechanism integrating host and environmental factors as mediators of inflammation-induced CRC in mice. Specifically, the cooperative activity of genetic (inflammasome deficiency) and environmental factors (alterations in the composition of the intestinal microbiota), result in enhanced local colonic inflammation through epithelial reprogramming and induction of CCL5 transcription, which in turn induces

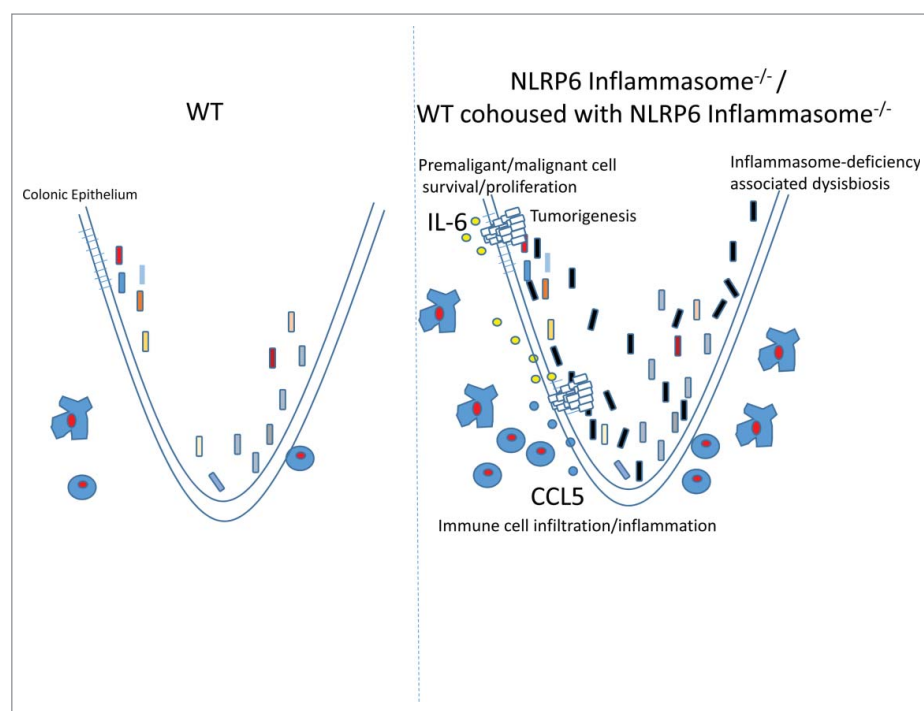


Figure 1. Inflammasome deficiency-associated dysbiosis promote colorectal cancer. Altered elements in the microbiota induce colonic inflammation through epithelial reprogramming and induction of CCL5 transcription. This in turn, results in local induction of IL-6 secretion and resultant proliferative signaling on intestinal epithelial cells culminating in tumor formation.

enhanced epithelial cell proliferation through activation of IL-6 pathway, culminating in tumor formation. Intriguingly, enhanced tumorigenesis can be transferred to cohabitated WT mice, suggesting a contribution of transmissible infectious component in some cases of inflammation-induced cancer. We suggest that alterations in the microbiome ecosystem be added to factors regulating tumorigenesis and in particular in the inflammatory setting. Manipulation of microflora–host interactions may represent novel therapeutic targets for the prevention of IBD-associated CRC. Further studies are needed to characterize components in the altered microbiome in inflammasome-deficient animals that are responsible for transferable inflammation-induced tumorigenesis and the possible implications for human IBD-associated CRC; together these issues merit further investigation in mice and humans.

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Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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