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Inflammation Plays Multiple Roles in Colorectal Cancer

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Inflammation is a critical process in the generation of neoplasms. It causes genomic instability, which allows cells to acquire the functional properties of a cancer cell or the "hallmarks of cancer" [1]. Epidemiological observations highlight the utility of colorectal cancer as a paradigm for inflammation associated cancer and recent research has demonstrated multiple roles for inflammation in neoplastic transformation [2]. People with inflammatory bowel diseases, which are characterized by chronic intestinal inflammation, have a dramatically increased life-time risk of developing colorectal cancer [3]. Moreover, risk of disease increases with severity and duration of inflammation reaching as high as 40% in people diagnosed with pan colitis before 15 years of age [3]. The assumption thus far has been that inflammation leads to the production of reactive oxygen species that cause DNA damage and neoplastic transformation. While this is correct, recent work has highlighted additional, specific roles for inflammation in cancer development. This commentary will focus on insights provided by mechanistic studies in pre-clinical models of colorectal cancer that have shed light on new roles for inflammation in the development of colorectal cancer.

In 2009, Wu et al. reported that a specific bacterium, enterotoxigenic *Bacteroides fragilis* (ETBF), which expresses *B. fragilis* toxin, was a potent inducer of colonic tumors [4]. For these studies, they colonized Min mice (multiple intestinal neoplasia mice that are defective in the *Apc* gene), which typically develop multiple ileal polyps and colonic adenomas, with a single bacterium (monocolonization). By comparing tumour development in mice monocolonized with *B. fragilis* that expressed or did not express the toxin, they were able to conclude that the toxin is sufficient to drive inflammation and tumorigenesis. Mechanistically, they demonstrated that ETBF drives a specific immune response characterized by infiltration of Th17 cells. The pro- inflammatory cytokine, IL-23, supports Th17 cell development and Th17 cells produce IL-17, a potent inflammatory cytokine that exacerbates inflammation by inducing chemokine production, which leads to the infiltration of additional IL-23-producing monocytes as well as neutrophils. Blockade of either IL-23 or IL-17 was sufficient to block ETBF-induced colonic inflammation and tumour formation [4]. These data are consistent with observations made in human colorectal cancer in which a Th1 response correlates with a cytotoxic and protective anti-tumour effect caused by tumour immune surveillance [5]; whereas a Th17 dominated response correlates with a dramatic decrease in disease-free survival [6]. Furthermore, carriage rates of *B. fragilis* that express the enterotoxin are significantly higher in people with colorectal cancer compared to control subjects. Taken together, these studies suggest a possible role for colonization with a specific toxin-expressing bacterium in driving pathogenic inflammation that leads to the development of colorectal cancer.

A second role for inflammation in colorectal cancer is the disruption of the epithelial barrier. This enables intestinal microbes to access the tumour microenvironment promoting localized inflammation and genetic instability. Givennikov et al. also used APC/Min mice to demonstrate that bacterial colonization and IL-23 signalling are required for colorectal cancer development in these mice [7]. They further demonstrated that there was a loss of polarized expression of epithelial cell junctional proteins, JAM-A and B, in murine adenomas. They extended their observations investigating these phenomena in early human ademonas and showed a direct correlation between the disruption of tight junction proteins and high pathogenic IL-23 and IL-17 levels [6,7]. These studies suggest that inflammation leads to barrier disruption that acts in a positive feedback loop to drive inflammation and colorectal cancer.

A notable common theme in studies discussed thus far is the requirement for intestinal microbes in initiating tumorigenic inflammatory responses. Recent work by Arthur et al. suggests that inflammation actually shapes the microbial community, which, in turn, influences cancer development [8]. IL-10 deficient mice (*il10-/-*) develop spontaneous colonic inflammation and colon tumors. Jobin's group previously demonstrated that tumour development in the *il10-/-* mice is significantly reduced in a germ-free environment compared to conventionally housed mice, which harbour a standard microbiota [9]. This observation sparked the idea that there may be a bacterially-driven oncogenic environment in colorectal cancer. By comparing the microbiota from wild type mice with that from *il10-/-* mice that were untreated or treated with the carcinogen azoxymethane, they demonstrated that inflammation, rather than cancer development, causes a shift in microbial composition, which is also known as dysbiosis [8]. Intriguingly, monocolonization of *il10-/-* mice with a specific *Escherichia coli* strain (NC101) enriched by the inflammatory environment, promoted the development of invasive carcinomas when mice were treated with azoxymethane. Increased tumorigenesis was dependent on bacterial expression of the polyketide synthase (*pks*) island, which encodes the genotoxin Colibactin [8]. In addition, the genotoxic effects of *pks+ E. coli* require bacteria-host cell contact [10] suggesting that the aforementioned inflammation induced barrier disruption may also play a critical role in this model. Correlative data from human studies has demonstrated an association between colonization with adherent and invasive *E. coli* and colorectal cancer suggesting that these bacteria may play a direct role in development of colorectal tumours in humans [11]. Recent work has also demonstrated increased prevalence of *E. coli* producing genotoxin in subjects with colon cancer compared to control subjects [12]. These studies highlight a novel role for inflammation in shaping a carcinogenic microbiome that may drive inflammation associated colon cancer.

Inflammation has been implicated in development of colorectal cancer and its role has been validated by many excellent epidemiological studies. Recent work in pre-clinical models suggests that this association is not simply attributable to production of DNA-damaging reactive oxygen species but rather, that the role of inflammation in colorectal neoplasia is multi-faceted and complex. Figure 1 summarizes the multiple roles that inflammation plays in murine

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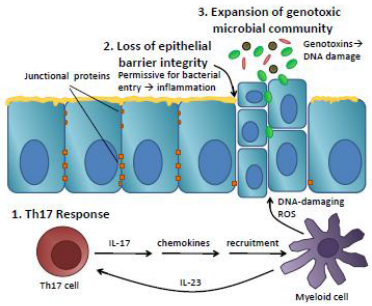

Figure 1: Inflammation plays multiple roles in the development of colorectal neoplasms.

1. The inflammatory response is directed toward an auto-amplifying Th17 response, which contributes to DNA damage in epithelial cells by production of reactive oxygen species (ROS). 2. DNA damage leads to dysfunction in epithelial cell junctional proteins creating a "leaky gut" which permits close association between inflammation-inducing microorganisms and epithelial cells. 3. Inflammation leads to selection and expansion of specific members of the microbial community, some of which have genotoxic capabilities that contribute to DNA damage in epithelial cells.

models of tumorigenesis. In step 1, inflammation is skewed away from protective Th1-mediated tumour surveillance to a Th17 response that auto-amplifies the inflammatory response by recruiting additional inflammatory cells to sites of inflammation. In step 2, inflammation has direct effects on epithelial barrier cell proteins and barrier function that is proportional to damaging inflammatory responses and permits close association between intestinal microorganisms and epithelial cells. Finally, in step 3, inflammation skews the microbial community, which may permit the selection and expansion of microorganisms harbouring genotoxic abilities. Furthermore, evidence suggests that these seemingly disparate roles for inflammation in colorectal cancer may cooperate to create the "perfect storm" permitting neoplastic transformation and the development of colorectal cancer. Importantly, all of these phenomena have been observed in human subjects with colorectal cancer suggesting that the lessons that we have learned from animal models may be directly relevant to human disease. Insight from these studies may lead to the development of novel strategies to prevent colorectal cancer that target inflammation directly, or its effects on epithelial barrier or the intestinal microbiota.

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