Procarcinogenic regulatory T cells in microbial-induced colon cancer

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Colorectal cancer (CRC) is the third leading cause of cancer-related deaths worldwide. Though most cases of CRC are the result of spontaneous mutagenesis, a fraction of CRC cases are epidemiologically linked to chronic inflammation. Indeed, the risk of developing CRC is significantly increased in patients with either ulcerative colitis or Crohn’s disease. These inflammatory bowel diseases (IBD) are associated with a disturbance of the intestinal microbiota, or dysbiosis, so identifying possible microbial causes of IBD and CRC is of great public interest.

Our lab previously uncovered the carcinogenic potential of one such microbe, ETBF, a virulent toxin-producing bacterium that profoundly disrupts the colonic microenvironment. Colonization of ApcMin mice with ETBF rapidly promoted colon tumorigenesis that was dependent upon a robust IL-17-dominant in the presence of Tregs to robustly IFNγ-dominating in the absence of Tregs. We further showed that reduced tumorigenesis in the absence of Tregs was not dependent on the potent antitumor cytokine IFNγ. Elucidating the mechanisms underlying Treg-dependent ETBF tumorigenesis, we established that Tregs in the ETBF-induced inflammatory environment limit excess IL-2 that commonly inhibits IL-17 production. Thus, because IL-17-mediated inflammation was pro-tumorigenic and overt IFNγ was not, the importance of the quality of inflammation over its quantity was underscored.

Although we unveiled a novel mechanism whereby microbial-triggered Tregs drive carcinogenic immunity in the colon, several uncertainties remain. First, how does ETBF promote Treg accumulation in the colonic lamina propria? It is possible, and perhaps likely, that B. fragilis toxin (BFT)-stimulated epithelial cells relay, as yet undetermined, messages that influence lamina propria-resident T cells. The very positioning of colonic epithelium at the interface between the immune-dense lamina propria and microbiota-rich lumen makes these cells the perfect sentinel to relay such messages (e.g., production of IL-33 upon epithelial assault). Alternatively, the disruption of the intestinal barrier during ETBF-triggered colitis may allow the direct stimulation of Tregs by ETBF via pattern recognition receptors (e.g., Toll-like receptors).

Second, what is the antigenic specificity of these Treg and Th17 cells? Cognate antigen-T cell receptor (TCR) stimulation in the context of TGF-β and IL-2 can induce Treg differentiation and clonal expansion in situ; nonetheless, while direct interactions between ETBF (or BFT) and colonic epithelial cells have been identified, no B. fragilis-specific TCRs have been isolated to date. Third, does the immune-suppressive capacity of Tregs that accumulate in response to pathogens toward, which Th17 immunity is most effective, differ from that of Tregs that accumulate during immune responses to pathogens best targeted by Th1 immunity? That is, perhaps timing of Treg accumulation in anti-viral immunity is delayed so that Th1 responses prevail, but it is possible that the very nature of those Tregs differs from that of Tregs responding to ETBF. For example, some investigators have demonstrated that RORyt+ IL-17-producing Tregs, certainly more prevalent in the storm of Th17 immune responses, are themselves carcinogenic. Furthermore, transcription factors (i.e., Gata-3, Tbet or Stat3) expressed by Treg are critical for
the suppression of various subsets of T cell subsets (i.e., Th2, Th1 and Th17, respectively). Despite the broadly interesting perspective, it is yet unclear whether Tregs arising from two inflammatory conditions differ in any meaningful way or merely represent a fluid continuum of Treg plasticity that is appropriate for any particular condition. Fourth, how is IL-17 pro-carcinogenic (?-4 in Fig. 1)? While IL-17 is a potent recruiter of neutrophils, which have their own carcinogenic potential, our own [unpublished] investigations have failed to elucidate a prominent role for reactive oxygen and nitrogen species in ETBF-induced tumorigenesis. We are currently studying how ETBF-induced IL-17 directly impacts the colonic epithelium, and other investigators have demonstrated the carcinogenic potential of IL-17, independent of ETBF, directly on the colonic epithelium. Thus, it is reasonable to propose a positive-feedback loop, whereby BFT triggers the release of pro-inflammatory Treg/Th17-driving signals by the colonic epithelium, and in turn trigger additional pro-inflammatory and survival pathways in the epithelium, ultimately leading to their cancerous transformation.

These questions are merely the tip of the iceberg with respect to Tregs, inflammation and microbial cancer biology, and it is without a doubt that the response to these questions will profoundly dissect the dogma of Tregs as purely guardians of mucosal immune homeostasis.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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