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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

The STING That Tames Pro-inflammatory T-cells

The ability to generate rapid robust immune responses to a wide variety of targets enables mammalian survival in a world teeming with microbes. Yet, keeping such responses in check is essential for avoiding chronic inflammatory diseases. This dichotomy is exemplified by the function of the intestinal immune system, which is charged with detecting and clearing pathogens without responding excessively to the large microbial ecosystem that normally inhabits this organ in a mutually beneficial manner. Intestinal CD4+ T cells are integral for mediating host homeostasis. However, when unchecked, these cells drive and sustain chronic immune-mediated inflammatory diseases, particularly inflammatory bowel disease (IBD).[1] CD4+ T cells are functionally grouped as effector and regulatory cells (Treg). Intestinal CD4+ effector T cells such as Th1 produce proinflammatory cytokine interferon (IFN)-γ to protect host against pathogens, whereas T-reg generate anti-inflammatory cytokines to prevent excessive inflammation that might otherwise lead to IBD.[2] Regulation of IFN-γ secreting Th1 (IFN-γ+Th1) cells is tightly controlled both intrinsic and extrinsic. Extrinsically, T-reg and myeloid cells are keys to suppressing Th1 by producing interleukin (IL)-10.[3] However, environmental cues that control the intrinsic switching from IFN-γ+Th1 to IL-10+IFN-γ+Th1 cells during Th1 lineage differentiation remain poorly understood.

A report by Cong and colleagues in this issue of *Cellular and Molecular Gastroenterology and Hepatology* reports that the stimulator of interferon genes (STING) protein plays a key role in reducing the pro-inflammatory activity of Th1 cells.[4] Specifically, their work demonstrates that activation of STING causes Th1 cells to reduce their production of pro-inflammatory cytokines such as IL-6 and tumor necrosis factor (TNF)-a while initiating production of the anti-inflammatory cytokine IL-10. The critical importance of IL-10 in preventing chronic inflammation has long been appreciated, as evidenced by development of chronic colitis and early onset respectively, in mice or humans with genetic defects that cause inability to produce or respond to this cytokine.[5] Yet, the notion that Th1 cells might be another source of IL-10 is relatively recent, in that research on IL-10 production has largely focused on antigen-presenting and T-reg cells.[6] Furthermore, mechanisms that govern Th1 cells to switch from a purely effector function to a dual effector/regulatory function had not been well-defined. Although the converting of IFN-γ+Th1 to IL-10+IFN-γ+Th1 cells was seen in response to pharmacologic STING activators, the physiologic importance of this pathway was seen in STING-deficient mice, which, in multiple models of colitis, exhibited exacerbated gut inflammation, accompanied by lack of IL-10 production by Th1 cells, which was not accompanied by altered development of other populations of T-cells.

STING-elicited production of Th1 cell IL-10 appears to proceed by previously established signaling cascades, involving type I interferon, STAT3 and Blimp-1, known to be activated by STING.[7] In contrast, how STING is activated during colitis is not clear, but STING is known to sense DNA, and one can imagine a range of scenarios whereby host and/or microbial DNA is released as inflammation progresses, which might be a reasonably appropriate signal that curtailment of Th1 responsiveness is warranted. Interestingly, high doses of STING activators did not induce Th1 cells to produce IL-10 but rather led these cells to enter cell death pathways, thus suggesting that STING activation may not only nudge Th1 cells to shift from inflammation to resolution but can also give them an immediate order to cease and desist.

The discovery of a new off switch for inflammation, particularly one on Th1 cells, begs the question of whether it can be harnessed to treat IBD. In support of this possibility, STING is indeed present on Th1 cells isolated from inflamed human biopsies, and furthermore, its pharmacologic activation induces Th1 cells to produce less pro-inflammatory cytokines (TNF-a and IL-6) and more IL-10. That expression of both STING and IL-10 are already both elevated in ulcerative colitis suggests these pathways are not defective in IBD per se but rather are already functioning to tamp down inflammation. Nonetheless, it is possible that further activation of STING, particularly if it could be achieved in a Th1 cell-specific manner, may have therapeutic value in this disorder.

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Conflicts of interest
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