Interferons Coordinate a Multifaceted Defense

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While interferons help kill virally infected cells, they can also promote systemic immune responses in distant tissues. In this issue of *Cell Host & Microbe*, Sun et al. (2015) demonstrate that type I interferon induces intestinal epithelial proliferation. This may help maintain a healthy gut and promote recovery from viral gastroenteritis.

Let us view the human immune system as a national department of defense. At its best, the body's defense system utilizes a multifaceted approach to fend off enemies by identifying and disarming evildoers, building a strong army, and maintaining secure borders. When interferons were first described in the 1950s, they were noted to promote immunity by disabling cells in the direct vicinity of virally infected cells. By inducing the release of exosomes to neutralize viruses and triggering apoptosis of host cells, interferons can coordinate the assassination of infected cells and create a perimeter around infected areas (Li et al., 2013). Thus, in the defense system, interferons became well known for their role in killing cells at the primary site of infection. Recently, however, interferons have also been shown to activate systemic immune responses at sites distant from the infection itself.

Indeed, new research indicates that interferons also have a role in building immunological armies and securing the body's defensive borders.

In recent experiments, types I and II IFN have been shown to affect proliferation of hematopoietic stem cells (HSCs) (Essers et al., 2009; Baldridge et al., 2010). IFN stimulation leads to increased proliferation and differentiation of hematopoietic progenitors, suggesting a role for stem cells in building the army of immune cells needed to respond to microbial invasion and injury (Matatall et al., 2014). Unlike the antiviral state in the affected tissue, these interferon responses occur remote from the site of infection and are not associated with immediate apoptosis or induction of cytotoxic responses.

In this issue of *Cell Host & Microbe*, Stappenbeck and colleagues report yet another mechanism of IFN-mediated immunity at the systemic level: strengthening borders in the intestinal epithelium (Sun et al., 2015; summarized in Figure 1). Trillions of microbiota colonize our gut, and the intestinal lining is a critical barrier to infection. Sun et al. (2015) show that some types of viral infection potentiate intestinal epithelial proliferation and repair, even if the infection is located distant from the gut. Further, using mice with chronically elevated IFN levels (*Irgm1*$^{-/-}$ knockout mice), Sun et al. (2015) find that type I IFNs play a vital role in the repair of epithelial injury by stimulating proliferation of cells in the epithelial tissue, including stem cells at the crypt base and transit-amplifying cells in the upper crypt.

The work by Sun et al. (2015) underscores the growing appreciation of direct interactions between the human body and its microbiome to maintain health. The mammalian body has evolved alongside microbes for millions of years, resulting in a complex ecosystem in which the health of the host depends on microbes for nutritional factors such as vitamin K and maintenance of other physiologic processes. As early as the 1960s, studies described abnormalities such as gross and microscopic intestinal differences, slow epithelial turnover, and altered immune responses to antigenic stimuli in germ-free mice (Gordon and Pesti, 1971). Fecal transplants or defined microbe introduction to these mice allowed normalization of at least some of these aberrations. Similar abnormalities have been described in antibiotic-treated mice, further supporting the role of microbes in maintenance of the basal or physiologic inflammatory state. In a recent report by Kernbauer et al. (2014), epithelial turnover was found to be impaired in wild-type (WT) mice treated with antibiotics, with reversal of the phenotype upon infection with murine norovirus in an IFNα-dependent manner. Interestingly, *Ifnar1*$^{-/-}$ single knockout mice did not exhibit impaired wound healing or notably aberrant epithelial proliferation at baseline; however, antibiotic treatment of *Ifnar1*$^{-/-}$ mice did lead to abnormal intestinal morphology, suggesting that other inflammatory mediators, likely derived from the interplay between intestinal flora and the mucosa, may also be involved in enhancing epithelial turnover.

Sun et al. (2015) show that IFNα sensing is required on macrophages, but not epithelial cells for enhanced wound repair. Notably, in the hematopoietic system, macrophages have been reported to serve an anti-inflammatory role to protect stem cell self-renewal (Winkler et al., 2010). The work by Sun et al. (2015) suggests that similar mechanisms may be at play in the intestine, with macrophages serving a sentinel role to promote intestinal turnover in the setting of systemic infection. Using coculture techniques, macrophages were shown to signal to epithelial cells in *trans* by release of apolipoprotein Apol9a, induced during type I IFN responses, and induction of ERK activation. While WNT signaling has been the major focus of study in understanding intestinal epithelial turnover and proliferation, ERK signaling has also been shown to promote cell proliferation in the intestinal epithelium. Although crosstalk between the ERK and WNT pathways has been reported in other models of epithelial repair, Apol9a did not strengthen or substitute for WNT signaling in this injury model.

As important as inflammation is for pathogen clearance and healing, too much inflammation is harmful, as evidenced by autoimmune disorders and

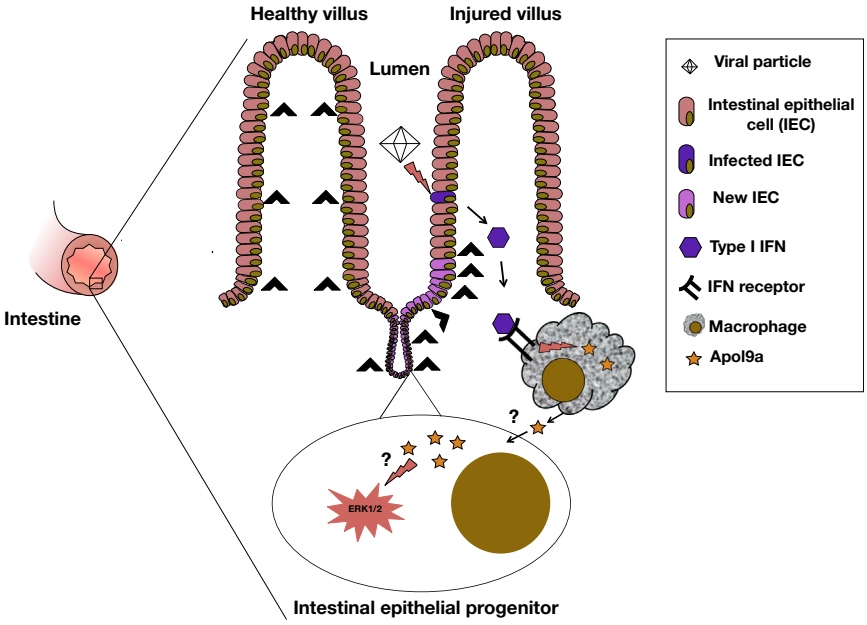

Figure 1. Summary of the Process of Intestinal Epithelial Response to Injury as Described by Sun et al. (2015)

Type I IFN produced by intestinal epithelial cell infected by virus, or by other stimulus on tissue, in turn stimulates macrophage to produce Apol9a. Apol9a is released from macrophage and may be directly taken up by intestinal epithelial progenitor or cause Apol9a production by the progenitor cell by other means. Downstream activation of the ERK pathway occurs, leading to increased proliferation of the intestinal epithelial progenitor cells, allowing rapid regeneration of the intestinal epithelium in response to injury.

processes such as acute respiratory distress syndrome. Use of the Irgm1-deficient mice to model an inflammatory state highlights both the power and the potential weaknesses of this model. We previously reported that Irgm1-deficient mice have high IFNγ levels (King et al., 2011), whereas the Sun et al. (2015) study reports elevated IFNα. In mice with abnormal macrophage function, these differences may reflect inconsistencies in environmental housing conditions and host/microbe interactions, which in turn may impact a variety of phenotypes. These differences demonstrate the need for new standards for microbial colonization as the field of microbiome/host interactions expands. Why the Irgm1-deficient mice do not display signs of autoimmune disease also presents a conundrum for further study. In the hematopoietic system, proliferative responses to IFN are carefully regulated to conserve the stem cell pool and/or reduce the risk of malignancy-inducing DNA copy errors (King et al., 2011; Pietras et al., 2014). Further investigation of these regulatory mechanisms is likely to yield important insights into how to prevent and treat autoimmune conditions.

Despite these caveats, use of the Irgm1 model has enabled characterization of the role of IFNα signaling in intestinal epithelial homeostasis and wound repair. Amazingly, Irgm1-deficient mice showed more rapid wound healing after chemically induced ulcer formation in the intestine. While Sun et al. (2015) have identified Apol9a as an IFN-inducible mediator of intestinal epithelial proliferation, it remains to be determined if exogenous expression of Apol9a at sites of injury can accelerate wound healing. This work would enable the exciting opportunity to explore the therapeutic potential of Apol9a to mediate wound healing without inducing the harmful systemic effects of interferon-mediated inflammation.

Sun et al. (2015) have made important progress in clarifying the process by which the intestinal epithelium responds to viral infection and heals mucosal injury. Interferons, though small and primitive, continue to impress as coordinators of a multifaceted defense system—powerfully protecting the body through coordinated responses ranging from targeted killings to building armies and strengthening borders.

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