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Another Earth: Innate Lymphoid Cells and Intestinal Inflammation

Lin Lin and Jonathan Braun

Department of Pathology and Lab Medicine The UCLA David Geffen School of Medicine Los Angeles, California

In the ever-weird world of immunity, a new category of lymphocytes has emerged, innate lymphoid cells (ILC). Prominent in the intestinal mucosa, they sense environmental rather than antigenic cues and deliver the full scope of inflammatory functions a magnitude faster than adaptive B, CD4⁺, or CD8⁺ T cells. The discovery of functionally diverse ILC subsets suggests the presence of an innate version of cytotoxic, Th1, Th2, Th17, and Th22 immunity. From a distance, these 2 sides of immunity are distinct in detail, but common in function and meaning (Figure 1). We may need to rethink how much immune control occurs at the innate level and the new opportunities this offers for therapeutic manipulation of infection and inflammatory disease.

ILC and What They Do

ILC are a distinct family of lymphocytes from B or T cells, because their developmental pathway is unique and they are equipped environmental sensors rather than antigen-specific receptors. Localized to the mucosa and related stromal tissues, ILC bear a cellular physiology designed for rapid, innate protective responses.¹

The first identified ILC was the natural killer (NK) cell, based on its innate (antigen-receptor independent) detection of virally infected and stressed cells, prompt and potent cytolytic activity, and secrete of Th1 proinflammatory cytokines (notably interferon- γ ; termed conventional NK). Thymic-derived NK cells may exclusively produce Th1 cytokines, and hence have been termed ILC1. The roles of NK cells in gastrointestinal diseases have been widely studied, most notably as potent and early participants in recognition of viral and intracellular pathogen infections.² NK and ILC1 cells are under tight control by the large family of activating and inhibiting killer immunoglobulin-like receptors (KIR), which modulate their responsiveness to mucosal cells bearing cognate KIR ligands (class 1 major histocompatibility complex [MHC] genes), whose display in turn is tuned by environmental cues.³ The activity of NK cells and ILC1 is divergent among individuals, in part because of the exceptional combinatorial genetic polymorphism of KIRs and MHCs between individuals. Hence, resistance to important viral pathogens such as cytomegalovirus, hepatitis C, and human immunodeficiency virus show a strong association with select stimulatory or inhibitory KIRs and their cognate MHC loci.^{3–8}

NK and ILC1 paradoxically seem to be protective in inflammatory bowel disease, but are deleterious in celiac disease. NK cells have reduced cytotoxic activity in IBD patients,⁹ and there is genetic association of KIR and MHC alleles with IBD disease risk.^{10,11} In contrast, NK-like functions are a prominent, disease-associated process in celiac disease, although the relative contributions of NK and ILC1, compared with the innate-like function of adaptive lymphocytes are still being dissected.¹²

Lymphoid tissue inducer (LTi) cells are critical organizers of lymphoid tissue formation and adaptive immunity, through their activation of select stromal cells, chemokine-mediated

recruitment of hemopoietic cells, and B-cell differentiation for immunoglobulin A production.^{13,14} Upon mucosal bacterial infection and attendant mucosal myeloid IL-23, LT α i cells are the major early producers of interleukin (IL)-17 and IL-22, and hence important for protective neutrophil recruitment (IL-17) and epithelial defense and survival mechanisms (IL-22).¹⁵

ILC restricted to production of IL-17 or IL-22 (ILC17 and ILC22, respectively) overlap with LT α i in terms of developmental requirements and anatomic distribution. Indeed, it is possible that, like ILC1 and NK, ILC17 and ILC22 may be alternate differentiation states of the LT α i sublineage. ILC17 accumulate at sites of inflammation in experimental microbial and immune-mediated colitis, and infection-associated IL-23 production stimulates ILC17 to produce large amount of IL-17 and interferon- γ .¹⁶ Human ILC17 cells are overrepresented in the colon and ileum of Crohn's disease patients, are a major source of tissue IL-17, and are critical to pathological outcome.¹⁷

ILC22 are present in intestine, mainly residing in small intestine lamina propria. Like NK and ILC-1 cells, ILC22 development requires IL2 and IL-15 signaling,¹⁸ but they also require microbial flora for differentiation; ILC22 are deficient in germ-free mice, but are elicited after colonization with normal microflora. ILC22 in human also are primarily located in mucosa-associated lymphoid tissue (tonsils and Peyer patches), where they secrete IL-22 and IL-26 in response to IL-23. They are equipped for homing and adherence to epithelial cells, and through this interaction induce epithelial IL-10, a powerful anti-inflammatory cytokine. Thus, human ILC22 seem to be specialized for restoring epithelial recovery after infection.¹⁹

Host protection against parasitic infections is a specialized feature of TH2 adaptive immunity, but the innate immune equivalent was not recognized until the recent discovery of TH2-like ILC (ILC2). Defined by their production IL-5 and IL-13, they reside in mesenteric lymph nodes and adipose tissue ("nuocytes"), as well as in the peritoneal cavity ("natural helper" cells). Upon helminthic infection, mast cell IL-25 and epithelial IL-33 directly activate ILC2 to expand and produce mediators required for early eosinophil recruitment and mucosal processes for worm expulsion.^{20,21}

Issues Ahead

The recognition of ILC has revealed a parallel world of adaptive and innate lymphocytes proficient in each of the immune modes of microbial defense and inflammatory regulation. These 2 worlds share the same activation mechanisms and responsiveness to chemokine and cytokines. So, either may be reflected in genome-wide association studies and targets of current immunologic therapies observed in diseases like viral hepatitis and inflammatory bowel disease. We are thus confronted with conundrums. How much of our thinking about adaptive immunity in disease pathogenesis is instead operating at the innate level? Can we create useful analytic and genetic methods to better distinguish which parallel universe is at play for an individual patients' disease risk and monitor the nature of disease activity? And, can we better define the sensors and regulators for ILC that could provide targets for their therapeutic manipulation? We may not need another earth, but now that we have one, let's embrace the wonder and opportunity.

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Figure 1. Visible Earth. NASA Goddard Space Flight Center images by Reto Stöckli and Robert Simmon. Available at: http://visibleearth.nasa.gov/view_rec.php?id=2429.