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Review

Innate Lymphoid Cell-Epithelial Cell Modules Sustain Intestinal Homeostasis

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The intestines have the essential but challenging mission of absorbing nutrients, restricting damage from food-derived toxins, promoting colonization by symbionts, and expelling pathogens. These processes are often incompatible with each other and must therefore be prioritized in view of the most crucial contemporary needs of the host. Recent work has shown that tissue-resident innate lymphoid cells (ILCs) constitute a central sensory module allowing adaptation of intestinal organ function to changing environmental input. Here, we propose a conceptual framework positing that the various types of ILC act in distinct modules with intestinal epithelial cells, collectively safeguarding organ function. Such homeostasis-promoting circuitry has high potential to be plumbed for new therapeutic approaches to the treatment of immune-mediated inflammatory diseases.

Recent years have witnessed several paradigm shifts in our understanding of multicellular organisms. First, we have come to fully appreciate that living organisms continuously adjust to biotic (e.g., viruses, bacteria, fungi, and parasites colonizing barrier surfaces and collectively referred to as the microbiota) and vital abiotic (e.g., nutrients, light, etc.) factors that they encounter at border surfaces with the environment. Host cells exploit beneficial environmental components and aim to eliminate environmental threats. The ability to carry out this complicated task relies on the capacity of specialized host cells to act as a sensory apparatus for environmental "input," thereby continuously adapting the organism to changes in the environment. This complex sensory apparatus is formed by a collection of different cell types that can communicate with one another. While historically, the detection of abiotic factors was thought to rely almost exclusively on epithelial cells and neurons, and that of biotic factors was perceived to depend solely on immune cells, we now know that these lines are blurry: non-hematopoietic cells, including epithelial cells, do take part in the detection of and response to biotic entities, and immune cell function does partially rely on sensation of abiotic cues.

The second major thread of new insight came from data revealing roles for the immune system in the development and function of tissues and organs. Circulating immune cells had long been considered transient inhabitants of organs and tissues, relevant only in settings of immune challenge. We now know that some immune cell types display a fairly sedentary lifestyle in organs and tissues (Fan and Rudensky, 2016). These cells are often deposited into tissues during prenatal development, and they are deeply integrated into the fabric of an organ or tissue, fulfilling tasks that support organ function (Branzk et al., 2018; Vivier et al., 2018). This conceptualization of components of the immune system as integral constituents of barrier organs has led to the exploration of the role played by immune cells in terms of organ function, tissue homeostasis, tissue growth, and repair.

Given that we now appreciate that both the immunological and homeostatic functions of an organ depend on both immune and non-immune cells, as well as on environmental cues (such as those from the microbiota), an integrative understanding of the "multicellular meta-organism" is the task of the time (Bosch and McFall-Ngai, 2011). This perspective has had wide ramifications for research informing our understanding of tissue biology. Foremost, the view that epithelial function is regulated solely by epithelial cell-intrinsic signaling circuits has been abandoned. Organ homeostasis and adaptation to components of the environment is maintained by regulatory loops that work similarly to homeostatic circuits. Such a concept entails that environmental factors are continuously sensed by host cells (outside-in signals), and those respond by producing an output signal (inside-out signal) that allows for adaptation of the organ to environmental challenges (Branzk et al., 2018). This integrated concept of organ and tissue biology has been, in part, fueled by the advent of single cell technologies that enable the recording of changes in all cells of an organ in the context of various types of infractions to homeostasis (Potter, 2018).

Here, we review the current understanding of the mechanisms that underlie immune-epithelial cell interactions, with a focus on the intestines, the largest barrier organ exposed to the most diverse environmental input. We discuss the building blocks of the intestinal epithelial barrier and integrate recent insights into epithelial and immune cell communication, diversity, and function. We propose that tissue-resident immune cells, in particular, innate lymphoid cells (ILCs), act within immune-epithelial cell modules that maintain barrier organ function at steady state and shape the response to changing environmental input. The design principles of the intestine have parallels to other barrier organs like the lung and skin, suggesting that a response

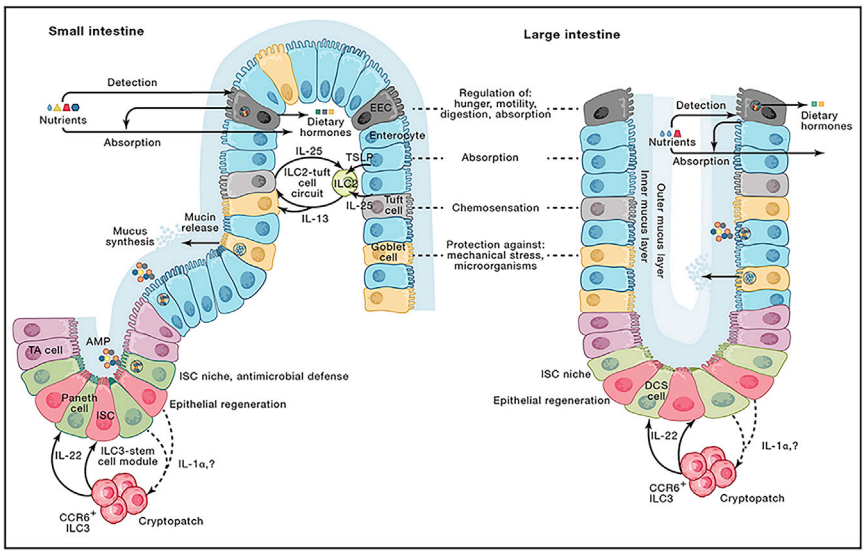

Figure 1. The Intestinal Organ

The intestinal lining consists of one single layer of intestinal epithelial cells (IECs) separating the environment (i.e., microbiota, dietary components) from the lamina propria, which is densely populated by immune cells. All IEC lineages originate from crypt-resident intestinal stem cells (ISCs) and their highly proliferative progeny, transit-amplifying (TA) cells. The small intestinal crypt is also home to Paneth cells, which produce and secrete large amounts of antimicrobial proteins (AMPs) that limit microbial colonization and protect ISCs and IECs against microbial insults. In addition, Paneth cells provide ISCs with signals crucial for their maintenance ("niche signals"). It is believed that Paneth cells are absent from the large intestine, where, in the same location, an obscure epithelial cell subset known as "deep crypt secretory cells" is found. The fundamental role of enterocytes, the most frequent IEC subset, is the absorption of ingested nutrients and water. In addition, enterocytes secrete AMPs into the intestinal lumen. Goblet cells secrete gel-forming mucins, which assemble in the lumen into a single (small intestine) or a double (large intestine) layer of mucus, which is crucial for protection of IECs from mechanical stress and from gut microorganisms. Tuft cells and EECs are rare IEC subsets that specialize in chemosensation of luminal contents. EECs are equipped with a large array of nutrient sensors and communicate the luminal nutrient composition to other cell types and other organs by secreting dietary hormones and neurotransmitters, thus orchestrating the response to feeding and fasting in terms of hunger and satiety, intestinal contractility, secretion of digestive enzymes, and, ultimately, absorptive capacity. It has recently become clear that ISCs also interact with tissue-resident immune cells of the intestinal lamina propria. Relevant immune-epithelial modules are indicated. ILC, innate lymphoid cell; ISC, intestinal stem cell; TA, transit amplifying; EEC, enteroendocrine cell; AMP, antimicrobial peptide; DCS, deep crypt secretory.

framework based on immune-epithelial cell modules is relevant in other tissues.

Building Blocks of the Intestinal Epithelial Barrier

The gut's single-layered epithelial barrier performs a complex and somewhat paradoxical mission: it must show nutrients the "way in" (i.e., it must absorb them), a task requiring close contact with food components. On the other hand, pathogens and toxins—often co-ingested with nutrients—should be shown the "way out," while commensals, which are crucial for optimal fulfilment of both absorption and defense, should be kept in the "corridor" (the lumen). The ability to distinguish between beneficial and harmful components and the occasional need to embark on an all-out war against intestinal pathogens (at the expense of reduced food absorption and damage to intestinal symbiotic microbial communities) depend on highly regulated, multicellular processes that are only partially understood.

The intestinal epithelium consists of invaginations, called "crypts," and, in the small intestine, finger-like protrusions, or "villi," which dramatically increase the surface area for absorption (Figure 1). Given the constant mechanical, chemical, and microbial insults encountered by the gut epithelium (Gehart and Clevers, 2019), its turnover is rapid, with an average lifetime of 3–5 days per cell for most differentiated intestinal epithelial cell (IEC) subsets (Darwich et al., 2014). Renewal is driven by the constitutive proliferation of crypt-base columnar (CBC) intestinal epithelial stem cells (ISCs) located at the bottom of the crypts (Barker et al., 2007) and by their differentiation into the mid-crypt-located transit-amplifying (TA) cells, which are highly proliferative precursors on the road toward terminal differentiation into the various IEC types. Two principal subsets of mature IECs can be discriminated: absorptive enterocytes and cells of the secretory lineage.

Enterocytes are the most abundant and most fundamental IEC subset: the raison d'être of the intestines is to acquire nutrients and water from the environment, and enterocytes are the IEC subset in charge of absorption. For this task, they are equipped with a plethora of nutrient-digesting enzymes and nutrient transporters. However, the biology of enterocytes is not limited to absorption, as they can participate in fortification of the epithelial barrier, e.g., by secretion of cytokines and antimicrobial peptides (AMPs) (Allaire et al., 2018). The small intestine comprises four other prominent IEC subsets, all of which are referred to as "secretory cells": Paneth cells, goblet cells, enteroendocrine cells (EECs), and tuft cells. Importantly, the large intestinal epithelium contains the latter three, but it normally lacks Paneth cells (Allaire et al., 2018).

Paneth cells, which reside at the crypt base intercalated between CBC, are currently primarily assigned two roles: they can secrete AMP to help protect against microorganisms, and, in addition, they secrete or present factors (WNT, Notch ligands, and EGF) that maintain small intestinal ISCs (Clevers and Bevins, 2013; Sato et al., 2011). Importantly, in the large intestine, ISC maintenance seems to require, instead, signals from the poorly characterized REG4$^+$ deep crypt secretory cells (Sasaki et al., 2016) (Figure 1). Each Paneth cell is filled with secretory granules containing AMP (and other antimicrobial proteins); release of these granules insulates stem-cell-containing crypts against microbe-related damage (Clevers and Bevins, 2013). Another important function of the Paneth cell-ISC module is dynamic adaptation to nutritional changes. Under conditions of caloric restriction, Paneth cells act to assure ISC maintenance, at the expense of reduced differentiation into mature IECs (Yilmaz et al., 2012).

The primary function of intestinal goblet cells is the secretion of mucins in order to form protective mucus layers on top of the

single-cell layer of epithelial cells (Johansson and Hansson, 2016; Pelaseyed et al., 2014). It helps in preventing microorganisms from reaching the epithelial barrier, in ''flushing'' away pathogens, and in reducing the mechanical stress that the gut epithelium is exposed to (Anthony et al., 2007; Johansson and Hansson, 2016; Johansson et al., 2013). In the small intestine, the mucus is single-layered and rather porous, thus allowing efficient nutrient absorption at the price of an increased risk for bacterial invasion (Johansson and Hansson, 2016; Pelaseyed et al., 2014). In the large intestine, whose role in nutrient absorption is more limited, a double mucus layer overlays the epithelium, with a porous outer layer and a dense inner layer (Johansson and Hansson, 2016; Sicard et al., 2017) (Figure 1). The outer mucus layer is the habitat of most of the microbiota (Sicard et al., 2017). The inner layer, on the other hand, is normally impenetrable to microbes, creating a region right above the epithelium that is practically devoid of bacteria (Johansson et al., 2008). Mucus is not a static entity, and intestinal microbial communities actively shape mucus density and composition. For example, in the colon, a specialized goblet cell type, termed ''sentinel goblet cell,'' can, upon pathogen sensing, elicit compound exocytosis of mucins from nearby conventional goblet cells, thus aiding in pathogen expulsion (Birchenough et al., 2016; Wlodarska et al., 2014). Goblet-cell-associated antigen passages were identified as a pathway delivering luminal antigens to underlying lamina propria dendritic cells in the steady state to promote oral tolerance (Knoop et al., 2017; Kulkarni et al., 2019; Kulkarni et al., 2018).

EECs are a chemosensory epithelial cell type dispersed throughout the entire intestine. While EECs are infrequent (~1% of the epithelium), their absolute number renders them the largest endocrine system in the body (Worthington et al., 2018). Intestinal EECs are the gut epithelium's ''specialists'' in all that relates to communicating the nutritional status: they are equipped with a large array of nutrient receptors and can detect the quantity and quality of nutrients in the intestinal lumen. Subsequently, these cells produce hormones and other mediators that inform other cell types—both in their vicinity and in distant organs (including the CNS)—of the nutritional state in the gut, thus affecting digestion, absorption, systemic metabolism, and satiety (Posovszky and Wabitsch, 2015). Classically, EECs were subdivided into at least 8 distinct subclasses, based on subset-exclusive production of at least one gut hormone. Two single-cell RNA-seq surveys of the small intestinal epithelium revealed more complexity (Gehart et al., 2019; Haber et al., 2017), discovering several different EEC progenitors and numerous EEC subsets, several of which are capable of expressing two or more hormones (or neurotransmitters) whose expression in a single given cell was once thought to be mutually exclusive. EECs also affect and are affected by immune-related challenges in the gut, as will be discussed in detail in later sections.

Intestinal tuft cells (named for their characteristic ''tuft'' of microvilli projecting into the lumen) are another chemosensory type of IEC, and they are enriched for proteins participating in taste-sensing pathways (e.g., α-gustducin and the Ca^{2+}-activated monovalent cation channel TRPM5) (Bezençon et al., 2008; Howitt et al., 2016). Like EECs, they too are relatively rare and can be activated by detection of metabolites. The roles of intestinal tuft cells were obscure up until recently. We now appreciate that tuft cells are an important component in type 2 immunity (Figure 1), as will be discussed in detail below. Unsupervised clustering of small intestinal tuft cells based on single-cell transcriptomes revealed two clusters of mature tuft cells, termed ''tuft-1'' and ''tuft-2'' (Haber et al., 2017). While the transcript signature of the ''tuft-1'' subset was mostly associated with neuronal development, that of ''tuft-2'' was strongly linked to immunity.

ILC Are an Integral Part of the Intestinal Organ

The epithelial lining at barrier surfaces is interspersed and underpinned by a large variety of immune cells collectively referred to as the mucosal immune system. In large parts, research on the mucosal immune system has focused on its roles in pathogen defense, in inflammatory and allergic diseases, and in maintaining a ''truce'' with environmental components, which can in principle arouse immune responses. Only more recently, it has become clear that mucosal immune cells directly alter epithelial cell function, thereby adapting organ function to changing needs. These insights have been in large parts driven by the discovery of ILC (Spits et al., 2013). There are three recognized subsets of ILC—ILC1, ILC2, and ILC3—with transcriptional engines and effector programs that mirror those of Th1, Th2, and Th17 cells, respectively. While the parallels to Th cell subsets have attracted considerable attention, eye-opening findings came from studies that linked ILC to functions not usually associated with the immune system. In particular, the various types of ILC seem to form distinct modules with IEC subsets, thereby supporting adaptation of the intestinal organ to changing needs. Such unusual function of ILC is based on various unique attributes of these cells that make them perfectly equipped for such tasks.

ILC seed the intestinal organ during fetal development, and they show an extreme tissue sedentary lifestyle and are likely maintained in the tissue lifelong (Bando et al., 2015; Hoyler et al., 2012; Kanamori et al., 1996; Klose et al., 2014; Sawa et al., 2010). Parabiosis experiments revealed that while intestinal B, T, and NK cells are continuously replenished by circulating cells, ILC are not (Gasteiger et al., 2015). While ILC2 can expand robustly during worm infections, it is mostly explained by expansion of tissue-resident ILC2 or ILC2 progenitors (Bando et al., 2015; Gasteiger et al., 2015).

Another unique feature that separates ILC from T cells is that at steady state, they continuously produce their characteristic cytokines and other soluble factors, many of which can directly affect epithelial cell function. While this is true for various cytokines and growth factors produced by ILC, the epitome of such activity has been interleukin (IL)-22, a cytokine that can be produced on demand by T cells but which is tonically produced by ILC3 (Sanos et al., 2009; Savage et al., 2017). The levels of IL-22 available in the gut are tuned by the microbiota (Sanos et al., 2009; Satoh-Takayama et al., 2008) via regulation of epithelial cytokines like IL-1α (Hernández et al., 2015) and IL-25 (Sawa et al., 2011) (Figure 1). IL-22 is a remarkable cytokine, as its receptor is expressed selectively by non-hematopoietic cells like epithelial and stromal cells (Wolk et al., 2004). Given its conservation (Hernández et al., 2018b), the

ILC3-IL-22-IEC axis is an important paradigm for how immune cells can alter the function of the intestinal organ.

From the above points of view, it may not be surprising that exciting new data have emerged that identify ILC as central sensors of tissue and nutritional status. Thus, ILC have been linked to a variety of non-prototypical functions like tissue regeneration, tissue growth, and epithelial differentiation. We will focus this review on the unique crosstalk between ILC and epithelial cells as part of the adaptation machinery of the intestinal organ. We will discuss the role of ILC-IEC crosstalk for adapting the intestinal organ to postnatal life, explain how ILC affect the major function of the intestine (nutrient absorption), and, finally, portray ILC-IEC modules involved in protecting the intestinal barrier against continuous infractions to its integrity.

ILC3-Derived Signals Adapt the Intestinal Epithelial Barrier to Postnatal Life

The fetal and newborn gut is dominated by innate immune cells like ILC and macrophages (Bain et al., 2014; Eberl et al., 2004). In addition, the transition from the sterile environment before birth to postnatal life is characterized by the influx of microbiota and a rather sudden exposure to a storm of antigens that lead to expansion of T and B cells and gradual shaping of adaptive immunity (Al Nabhani et al., 2019; Mora et al., 2003). Recent work has explored the impact of ILC on IEC in newborns and revealed an important T-cell-mediated regulation of gut ILC3 function in neonates. Newborn mice showed remarkably high levels of phosphorylated (p-)STAT3 in IECs, peaking at 4 weeks after birth. High IEC p-STAT3 levels were directed by ILC3-derived IL-22. During this time, segmented filamentous bacteria (SFB; a commensal in intimate contact with small intestinal epithelial cells) start colonizing the host (Ivanov et al., 2009). SFB were previously implicated in activating ILC3 (Sano et al., 2015) and SFB expansion in the postnatal period, and their detection by monocytes led to increased IL-23 expression, which led to IL-22 release from ILC3 and consecutive upregulation of antimicrobial molecules like REG3 proteins that insulate the barrier from bacteria (Mao et al., 2018). SFB-induced production of IL-22 by ILC3 also induced epithelial serum amyloid A protein (SAA), which promoted intestinal IL-17A expression in T cells, adding an additional layer of protection against the microbial challenge (Sano et al., 2015). Thus, high ILC3 activity early during life supervises colonization with the commensal microbiota and avoids unwanted microbial damage.

Normally, toward 9 weeks of age, mouse IEC p-STAT3 levels decline, a process linked to the emergence in the intestinal organ of T cells—specifically, regulatory T cells (Treg) and SFB-specific Th17 cells (Mao et al., 2018). Various mechanisms were suggested to underlie T cell regulation of ILC3 function (Korn et al., 2014). Cua and colleagues demonstrated that Treg cells specifically restrain IL-23 and IL-1β production by gut-resident macrophages (Bauche et al., 2018). This suppressive effect required cell-cell contact and LAG3 expression by Treg. In addition to T cells, IECs also contributed to the negative regulation of ILC3 function after birth. The increasingly complex intestinal microbiota induced the expression of IL-25 by epithelial cells, which suppressed ILC3 function (Sawa et al., 2011).

Genome-wide transcriptional profiling of ileal tissue revealed that high ILC3 activity and high p-STAT3 levels in epithelial cells of newborn mice had important metabolic and immunological consequences, with increased IEC expression of antimicrobial molecules and reduced IEC expression of key lipid binding and transporter genes (such as *Cd36*, *Npc1l1*, *Fabp1*, and *Fabp2*). Mice lacking all T cells ($Rag^{-/-}$ mice) did not downregulate epithelial p-STAT3 and ILC3-derived IL-22 expression, maintaining the high levels even during adulthood. Consequently, $Rag^{-/-}$ mice were leaner and had lower serum triglyceride and cholesterol levels (Mao et al., 2018). Taken together, these data exemplify how innate and adaptive lymphocytes affect in a time-dependent manner the adaptation of the neonate intestines to the influx of microbes it encounters. It also shows that during the early postnatal phase, the host sacrifices lipid absorption for increased fortification of the epithelial barrier against microbes. This may be an acceptable trade-off, as it specifically affects suckling mice, whose lipid-rich diet may allow them to overcome the reduced efficiency of intestinal lipid absorption (Figure 2A).

An ILC2-Tuft Cell Module for the Adaptation to Commensal and Pathogenic Parasites

The postnatal and weaning phase also leads to shifts in the representation of goblet and tuft cells, which increase in numbers during the first weeks of life. A feed-forward ILC2-tuft cell circuit was discovered in the small intestine, underpinned by the surprising finding (Gerbe et al., 2016; Howitt et al., 2016; von Moltke et al., 2016) that intestinal tuft cells at steady-state are a potent and unique source of IL-25, an epithelia-derived cytokine recognized for enhancing type 2 immunity (Hammad and Lambrecht, 2015) (Figure 2B). This tuft cell-IL-25-ILC2 circuit is enhanced by intestinal worm infections and results in increased IL-13 secretion by ILC2, leading to increased frequencies of tuft and of mucus-producing goblet cells. Goblet cell hyperplasia is characteristic of many intestinal helminth infections and is required for the ''weep-and-sweep response,'' in which increased luminal fluids (weep) and muscle contractility (sweep) are speculated to make the intestinal lumen an inhospitable environment for the helminth parasite (Finkelman et al., 2004; Oeser et al., 2015; von Moltke et al., 2016; Waddell et al., 2019). Importantly, dysfunction of the circuit can result in reduced expulsion of pathogenic helminths (Howitt et al., 2016; Nadjsombati et al., 2018). How exactly IL-13 signaling in ISCs or progenitor cells drives tuft and goblet cell differentiation is not entirely clear, although modulation of Notch signaling may be involved (von Moltke et al., 2016), with Notch signaling as a key checkpoint against differentiation toward the secretory IEC lineage (van Es et al., 2012).

The manner in which parasites are detected by tuft cells to initiate the ILC2-tuft cell circuit remained unknown until recently, when three reports revealed that the ability of intestinal tuft cells to recognize colonization of newborn mice with protists of the *Tritrichomonas* genus depended on *Tritrichomonas* fermentation of dietary fibers into the SCFA succinate, which activates the succinate receptor GPR91 (encoded by *Sucnr1*) on tuft cells, leading to TRPM5-mediated IL-25 secretion, igniting the ILC2-tuft cell circuit (Lei et al., 2018; Nadjsombati et al., 2018; Schneider et al., 2018). *Tritrichomonas* protists are mouse pathobionts, meaning that while they may cause disease under

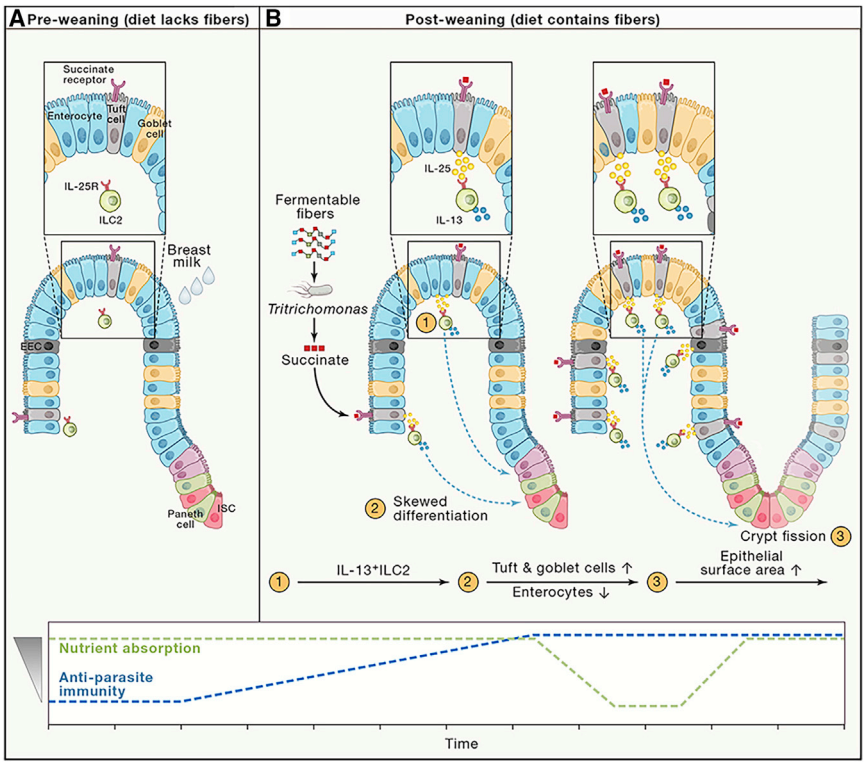

Figure 2. A Nutrient-Tuft Cell-ILC2 Module Leads to Small Intestinal Nutritional Adaptation and Supports Organ Growth

(A) Before weaning, nutrient supply is provided by breast milk, which is devoid of fermentable fibers. (B) Upon weaning (1), the introduction of fermentable fibers to the diet allows intestinal colonization by both pathobiont and pathogenic parasites. One of the genera of pathobionts that, if present in the environment, can now colonize the gut is *Tritrichomonas*. Fermentation-dependent production of succinate by *Tritrichomonas* then ignites the tuft cell-ILC2 circuit: succinate binds its receptor (GPR91) on the surface of small intestinal tuft cells, leading to enhanced tuft cell secretion of IL-25, which, in turn, induces ILC2 proliferation and IL-13 production. ILC2-derived IL-13 then acts on an unknown target (most likely ISCs or TA cells) to increase differentiation toward tuft and goblet cell fates, at the expense of absorptive enterocytes. The resulting increase in tuft cells, goblet cells, and IL-13$^+$ ILC2 protects against future infections by pathogenic parasites ("concomitant immunity"), likely at the price of a reduced nutrient absorption capacity stemming from the decrease in enterocyte frequencies (2). In addition, a process of crypt fission, which would ultimately give rise to additional crypt-villus units, is induced. The induction of crypt fission results, within weeks, in a substantial lengthening of the small intestine in conjunction with normalization of nutrient absorption, likely due to the lengthening-associated increase in absolute enterocyte numbers (3). Anti-parasitic immunity remains optimal. ISC, intestinal stem cell; TA, transit amplifying; EEC, enteroendocrine cell.

certain circumstances, they normally live in symbiosis with the host.

Activation of the ILC2-tuft cell module led to a decreased proportion of enterocytes among all IECs (likely because epithelial progenitors are pushed away from the absorptive lineage trajectory and toward a tuft and goblet cell fate) (Figure 2B) and thus can, in the short term, result in reduced ability to absorb ingested nutrients (Figure 2B). However, over time, nutrient absorption is normalized, in conjunction with a substantial lengthening of the small intestine driven by crypt fission (which results in increase in absolute enterocyte number) (Schneider et al., 2018) (Figure 2B). The molecular basis of this ILC2-dependent longitudinal growth of the intestinal organ is unknown. A possible explanation may be that IL-13 produced by ILC2 may increase self-renewal of and β-catenin signaling in ISCs (Zhu et al., 2019). IL-13 directly interacted with IL-13 receptor (IL-13R) expressed on ISCs. IL-13R expression in ISCs was positively regulated by a non-coding and regulatory circular RNA, circPan3. Mice lacking circPan3 in ISCs showed impaired function and maintenance of ISCs (Zhu et al., 2019).

In mice exposed to *Tritrichomonas*, efficient colonization with this pathobiont, and thus activation of the ILC2-tuft cell circuit, occurs only after weaning, a time in which the host begins consuming fermentable fibers that support *Tritrichomonas* colonization of the gut (Schneider et al., 2018). Importantly, weaning is not only the time in which the host starts consuming nutrients that can enable intestinal colonization by certain parasites (including both pathobionts and pathogens) but also a time of great challenges for the intestines in terms of nutrient digestion and absorption (Boudry et al., 2004). The fact that weaning can ignite an ILC2-tuft cell module that eliminates intestinal pathogens while sparing intestinal pathobionts and remodeling the intestinal organ to correct for the initial reduction in nutrient absorption resulting from this defense response is an exemplary case of communication between epithelial and immune cells in the gut that enable balancing the host's immune and nutritional requirements from the intestines (Figure 2).

Trade-Offs between Nutrient Intake and Antimicrobial Defense: the VIP-ILC-Enterocyte Axis

The gut is charged with 3 main tasks: nutrient and water absorption, clearance of pathogens, and maintenance of symbionts. Fulfilling any of these roles can be a double-edged sword, however, because they are often incompatible with each other, at least in the short term (for instance, diarrhea is often necessary for parasite expulsion, but it also results in reduced nutrient absorption and loss of symbionts).

In the intestines, enteric neurons can produce vasoactive intestinal peptide (VIP), a neuropeptide whose secretion is increased upon food consumption and that possesses wide-ranging effects on the ability of the intestines to absorb nutrients and to mount immune responses (Chayvialle et al., 1980; Delgado et al., 2004; Iwasaki et al., 2019; Seillet et al., 2019). Nussbaum et al. were first to report a potential link between VIP, nutrition and gut ILC (Nussbaum et al., 2013). They found that compared with fasted mice, recently fed mice exhibited increased small intestinal frequencies of IL-13$^+$ ILC2. In addition, both VIP receptors—VIPR1 and VIPR2—were highly expressed on gut ILC2, and *ex vivo* incubation of intestinal ILC2 with VIP resulted in increased production of IL-5, another ILC2 cytokine.

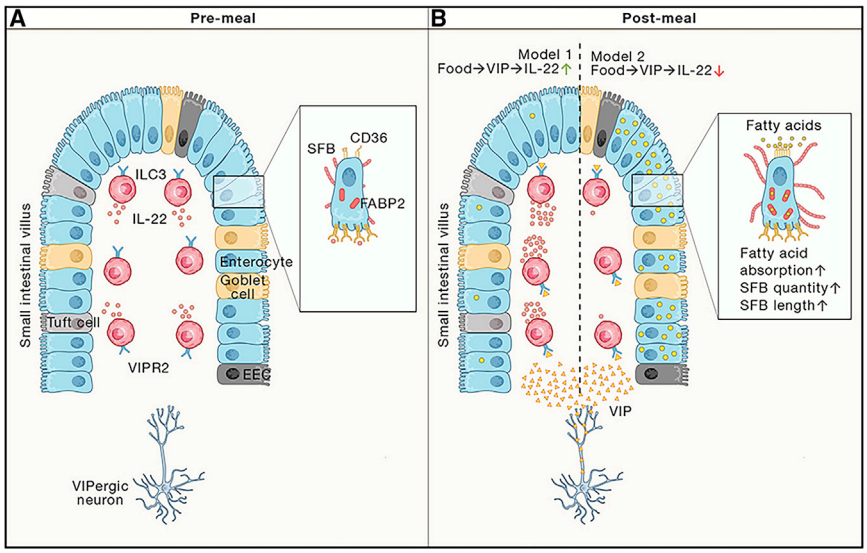

Figure 3. A VIP-ILC3-IEC Module Regulates Intestinal Absorption and Immune Defense Based on Circadian Changes in Feeding

(A) Prior to food ingestion, VIP production by enteric neurons is low. At that time, an intermediate proportion of gut ILC3 produce IL-22, resulting in some degree of control over the growth and morphology of epithelium-associated segmented filamentous bacteria (SFB). In the absence of recent food ingestion, enterocytes express an intermediate level of the genes encoding CD36 and FABP2, proteins involved in uptake and transport of fatty acids by IECs.

(B) Feeding induces enteric neuron secretion of VIP, which binds its receptor VIPR2 on intestinal ILC3 and affects their activity. The nature of this effect, however, is currently debated, with one investigation discovering a VIP-mediated increase in IL-22 (left) and the other reporting a VIP-mediated decrease in IL-22 (right). The reduction in gut IL-22 levels in the model presented to the right leads to increased numbers and length of enterocyte-associated SFB, to enhanced epithelial expression of CD36 and FABP2, and, upon further feeding, to improved lipid absorption. VIP, vasoactive intestinal peptide; VIPR2, vasoactive intestinal peptide receptor 2; ISC, intestinal stem cell; DCS, deep crypt secretory; TA, transit amplifying; EEC, enteroendocrine cell; SFB, segmented filamentous bacteria.

Together with the fact that VIP levels in the intestines are increased by food ingestion, these findings raise the possibility that the feeding-induced activation of gut ILC2 is mediated, at least in part, by feeding-induced VIP secretion.

Two recent reports examined the effects of feeding and VIP on gut ILC3 (Seillet et al., 2019; Talbot et al., 2020). In both reports, feeding and VIP were found to affect intestinal ILC3. However, these reports are at odds with each other in terms of the direction of that effect: Seillet et al. found that feeding and VIP lead to an increase in the frequencies of small intestinal IL-22$^+$ ILC3 (Seillet et al., 2019), while Talbot et al. found that VIP stimulation resulted in a decreased frequency of IL-22$^+$ ILC3 (Talbot et al., 2020) (Figure 3). In both studies, VIP was shown to exert important influences over intestinal inflammation and immune defense: *Vipr2*-deficient mice exhibited a more severe course of DSS-induced colitis (Seillet et al., 2019), whereas in the context of colonic *C. rodentium* infection, pharmacological excitation of VIP-expressing cells (to increase VIP release) leads to increased bacterial burdens and reduced survival, unless the mice are administered with exogenous IL-22 (Talbot et al., 2020) (Figure 3). In addition, the feeding- and VIP-dependent oscillations in IL-22 had a significant impact on the intestinal commensal microbiota and on nutrient absorption. VIP-mediated suppression of IL-22 resulted in increased expression of lipid and fatty acid binding proteins and transporters and in increased lipid absorption by IECs (Figure 3B, right). Moreover, genetic deletion of *Vipr2* in ILC3 led to reduced body weight (Talbot et al., 2020). On the other hand, IL-22 suppression by VIP led to an increase in SFB numbers and length (Figure 3B, right). These data indicate that optimized absorption of lipids during feeding may come with a lowered guard against bacteria. Currently, the discrepancies between the two reports concerning the effects of VIP on ILC3 remain unexplained. One possibility is that regional differences in proximal and distal parts of the intestine in VIP-mediated circuits may underlie these opposite outcomes, but additional work is required to resolve the matter. Another important deteminant of IL-22 production is circadian rhythmicity, and discrepancies in timing of ILC3 analysis may have an impact on the data obtained. Indeed, various reports have shown that ILC3 display circadian oscillation in the expression of clock genes and of cytokines like IL-22 and IL-17A. Disruption of circadian rhythm led to alterations in cytokine release (Godinho-Silva et al., 2019; Teng et al., 2019; Wang et al., 2019; Wang et al., 2017). In addition, further investigations into the trade-offs between nutrient absorption and intestinal immunity are warranted and shall lead to a more complete understanding of the mechanisms affecting immunity specifically in the body's nutrient-absorbing organ.

Another important regulatory program in IECs controlled by ILC3-derived IL-22 is the glycosylation status of IEC proteins. IL-22 controlled epithelial expression of *Fut2,* which catalyzes the fucosylation of IEC proteins. Disruption of fucosylation led to shifts in commensal communities because gut bacteria metabolize fucose from host fucosylated proteins. In addition, IL-22-mediated fucosylation of IEC proteins increased resistance against intestinal infections with *C. rodentium* or *Salmonella typhimurium* (Goto et al., 2014; Pham et al., 2014; Pickard et al., 2014). Collectively, the available data indicate that IL-22 is an important regulatory node in prioritizing conflicting tasks of the intestinal organ, such as nutrient absorption versus antimicrobial defense. The newly described roles of IL-22 for regulating lipid transporters in IECs may inform new strategies for the treatment of metabolic diseases.

Nutrient-EEC-Immune Circuits

How can a balance between the nutritional and immunological needs of the organism be achieved at intestinal barrier surfaces? EECs may be a prime candidate to aid such decision making. Like other IEC subsets, EECs can perform immune-related tasks, but more than any other IEC subset, EEC activity is heavily

influenced by sensing the nutritional status. Thus, reports of links between EECs, gut immunity, and, in some cases, the nutritional status will be described in the following paragraphs.

GI tract inflammation is often associated with hypophagia (reduced food intake) (Faro et al., 2000; Hartman et al., 2009; Ilzarbe et al., 2017; McHugh et al., 1993a; McHugh et al., 1993b). One interesting question is whether there is a qualitative difference in the mechanisms leading to hypophagia between hypophagia induced by infection of the GI tract and that seen upon infection of organs not directly related to food absorption. At least in one scenario, the answer seems to be affirmative: infection of mice with the nematode *Trichinella spiralis* (*T. spiralis*) is characterized by two phases, an intestinal phase and, subsequently, an extraintestinal phase (infection of skeletal muscles). An immune-mediated hypophagia characterizes both phases but with an important distinction: while the hypophagia during the extraintestinal phase seems to be EEC independent, the reduction in food intake seen during the intestinal infection phase is largely elicited by type 2 cytokines, which lead to an increase in EECs producing the anorexigenic (appetite-suppressing) hormone cholecystokinin (CCK) (McDermott et al., 2006; Worthington et al., 2013). Moreover, the hypophagia and resulting weight loss seem to aid in parasite expulsion by reducing the secretion of leptin (which enhances type 1 and suppresses type 2 cytokine production [Conde et al., 2010]), thus enhancing a type 2 immune response needed for parasite clearance.

Colonic infection of mice with *Citrobacter (C.) rodentium* leads to decreased frequencies of serotonin$^+$ EECs (also known as enterochromaffin cells) and somatostatin$^+$ EECs (O'Hara et al., 2006) and to a rapid increase in colonic IL-22 (Tsai et al., 2017), a cytokine capable of reducing EEC frequencies (Zha et al., 2019; Zhang et al., 2019). Interestingly, there seems to be a link between gut IL-22 produced by ILC3, *C. rodentium* infection, and the systemic nutritional status, as *C. rodentium*-induced IL-22 production is impaired in obese mice, while deletion of the IL-22 receptor increases the susceptibility of high-fat-diet-fed mice to metabolic disorders (Wang et al., 2014). The molecular details of this circuit and whether IL-22 directly acts on EECs or whether it skews differentiation from EEC progenitors are not known.

Serotonin and enterochromaffin cells were also tied to enteric worm infections. *T. spiralis* infection, for instance, can alter the frequencies of small intestinal and colonic serotonin$^+$ EECs (Wheatcroft et al., 2005). In addition, infection with the large intestinal nematode *Trichuris muris* (*T. muris*) can lead to an increase in the levels of colonic serotonin and serotonin$^+$ EECs, and these changes seem largely dependent on IL-13, a cytokine that also promotes clearance of *T. muris* (Manocha et al., 2013; Wang et al., 2007). Whether enterochromaffin cells and serotonin take part in the IL-13-dependent clearance of *T. muris* remains, however, unknown. Nevertheless, there is evidence that at least in some circumstances, serotonin can indeed contribute to the immune-related consequences of increased colonic IL-13 levels, with one report finding that colitis induction by DSS results in elevated colonic IL-13 levels and that, compared with DSS-treated wild-type controls, DSS-treated *Il13*$^{-/-}$ mice exhibited reduced colonic serotonin and enterochromaffin cell quantities, as well as diminished inflammation and disease severity, improvements that were partially reversed by administration of a serotonin precursor to IL-13-deficient animals (Shajib et al., 2013).

Taken together, it seems that several intestinal components, such as immune cells, chemosensory IECs (EECs and tuft cells), microbiota, and the ENS, can act together to integrate nutrition- and immunity-related information in order to optimize the capacity of the intestines to carry out their complicated job: keeping pathogens out, letting nutrients in, and cultivating an optimal composition of intestinal microorganismal symbionts. Nevertheless, the extent, circumstances, and outcomes of such coordination are still far from being fully understood, and, thus, future research into this complicated, yet fascinating topic is warranted.

The ILC3-ISC Module, Protecting Stem Cells against Damage

Several lines of investigation have linked ILC-associated cytokines to the function of ISCs. In particular, IL-22 was found to affect small intestinal stem-cell maintenance and differentiation (Lindemans et al., 2015; Zha et al., 2019; Zhang et al., 2019; Zwarycz et al., 2018) and to protect ISCs against genotoxic stress (Gronke et al., 2019).

IL-22 has been linked early on to intestinal epithelial repair following DSS-induced colitis. Mice genetically lacking IL-22 were not more susceptible during treatment with DSS but showed a significantly delayed repair phase when DSS application was stopped (Huber et al., 2012; Sugimoto et al., 2008; Zenewicz et al., 2008). The details of IL-22-controlled circuits are still only partially understood, but a study using intestinal epithelial specific deletion of *Stat3* (the major signal transducer of IL-22 receptor activation) showed a strong reduction in expression of genes associated with tissue repair (Pickert et al., 2009). Similar results were reported for epithelial repair in a mouse model of graft-versus-host disease (GvHD) where graft-derived allogeneic T cells attack intestinal stem cells (Hanash et al., 2012) (Figure 4A). ISCs were shown to express the IL-22 receptor (IL-22R), and mice genetically lacking IL-22 showed a more severe reduction of ISCs following bone marrow transplantation and an aggravated clinical course of GvHD. Mechanistically, IL-22 could induce STAT3 activation in LGR5$^+$ ISCs and controlled expansion of ISCs independent of Paneth cells (Hanash et al., 2012). Treatment with IL-22 or an IL-22 receptor agonist *in vivo* enhanced the recovery of ISCs, increased epithelial regeneration, and reduced intestinal pathology and mortality from GvHD. The molecular regulators of IL-22-controlled ISC expansion are not known (Lindemans et al., 2015).

Epithelial surfaces experience frequent contact with genotoxic compounds. Preservation of genomic integrity is largely mediated by a highly conserved signaling pathway, the DNA damage response (DDR). Mice genetically lacking IL-22 develop a higher colitis-associated cancer burden (Gronke et al., 2019; Huber et al., 2012), which was initially attributed to the more extensive inflammatory response in *Il22*$^{-/-}$ mice (see above) (Huber et al., 2012). To disentangle a potential role of IL-22 on the ISC mutational landscape from inflammation-driven effects, we developed a mouse model allowing for the sporadic deletion of IL-22R on some (but not all) ISCs. IL-22R-deficient ISCs

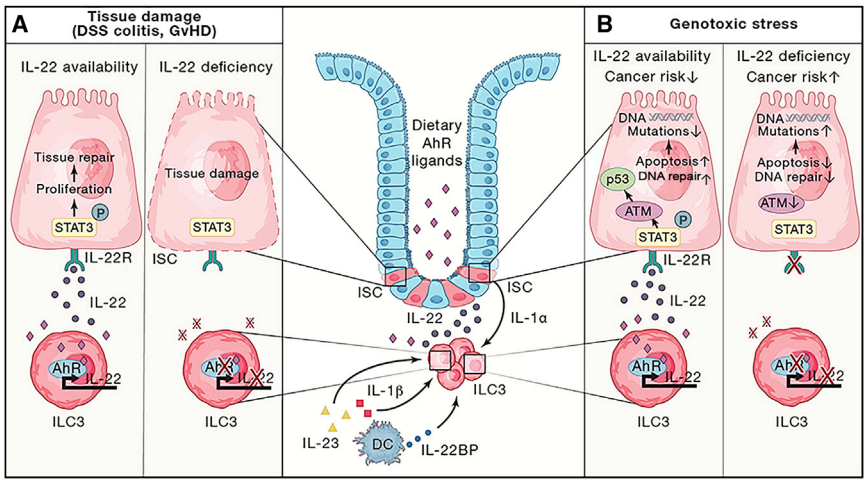

Figure 4. A nutrient-ILC3-ISC Module Supports Adaptation of the Intestinal Organ to Tissue Damage and Genotoxic Stress

(A) GvHD or DSS treatment induce epithelial damage in the colon. ILC3 produce IL-22, a cytokine directly acting on ISCs. In ISCs, IL-22 directs a powerful tissue repair program leading to increased maintenance of epithelial stem cells, increased proliferation, and epithelial repair. Availability of IL-22 is controlled by external and internal factors. Dendritic cells (DCs) produce a soluble form of the IL-22 receptor (referred to as IL-22 binding protein) that binds IL-22 with high affinity and controls the amount of IL-22 available for biological effects. On the other hand, IL-22 production of ILC3 is controlled by myeloid cell-derived cytokines like IL-23 and IL-1β and epithelial cytokines like IL-1α. In addition, dietary components (phytochemicals like glucosinolates) are ligands for the transcription factor aryl hydrocarbon receptor (AhR). Binding of such dietary compounds to the AhR leads to the induction of a battery of genes, including enhanced IL-22 expression. Impairment of IL-22 signaling or availability leads to inadequate STAT3 activation and inability of ISCs to adequately replenish damaged tissue.
(B) IL-22 protects colonic ISCs against genotoxic stress. IL-22 released from CCR6^{+} ILC3 controls the STAT3-dependent expression of ATM, an upstream module of the DNA damage response machinery. ISCs deprived of IL-22 signals had reduced ATM levels, reduced formation of γH2AX, and impaired function of the DNA repair and/or apoptosis machinery downstream of p53. Consequently, ISCs deprived of IL-22 accumulated more mutations following carcinogen challenge and were more likely to progress to colon cancer. Some glucosinolates have genotoxic qualities and boost the DNA damage response machinery in stem cells by AhR-mediated provision of increased IL-22 levels.

were more likely to give rise to colon cancer than were those that expressed the IL-22R (Gronke et al., 2019). Transcriptional profiling of ISCs deprived of IL-22 signals showed a striking reduction of genes associated with the DDR (e.g., ATM, p53, p21, and PUMA). Upon genotoxic stress, ISCs deprived of IL-22 signals generated a poor DDR with reduced activation of p53 and PUMA and, consequently, reduced apoptosis of damaged ISCs. Accordingly, ISCs from *Il22*$^{-/-}$ mice had a higher mutational load, which may contribute to the increased cancer burden in *Il22*$^{-/-}$ mice (Figure 4B). While IL-22 produced at the steady state is certainly a barrier against tumorigenesis, IL-22 acting on cells that have already lost cell-cycle control may enhance tumor proliferation (Hernandez et al., 2018a; Huber et al., 2012; Kirchberger et al., 2013).

The aryl hydrocarbon receptor (AhR), a ligand-dependent transcription factor (McIntosh et al., 2010), is a key regulator of IL-22 expression in ILC3 (Kiss et al., 2011; Lee et al., 2011; Qiu et al., 2012). An important group of AhR ligands are phytochemicals of the glucosinolate group, which are components of our daily diets, that bind with high affinity to the AhR (Bjeldanes et al., 1991). Interestingly, glucosinolates are genotoxic and induce a full-blown DDR in ISCs when applied to mice (Glatt et al., 2011; Schumacher et al., 2014). These data suggested that the ILC3-IL-22-ISC module may have developed to adapt the host to genotoxic components in our diets (Figure 4B). Indeed, feeding a synthetic, genotoxic AhR ligand led to AhR-mediated enhancement of IL-22 production by intestinal ILC3 (Gronke et al., 2019). Deprivation of mice from nutritional AhR ligands led to diminished expression of IL-22 and a feeble response to genotoxic stress. Taken together, these data reveal a previously unappreciated homeostatic circuit by which on-demand production of IL-22 by ILC3 adapts ISCs to genotoxic compounds contained in our diets.

AhR signaling has emerged as an important regulatory module to protect ISCs against tumor transformation. Sensing of AhR ligands in IECs led to the upregulation of the AhR target gene *Cyp1a1*, which oxygenates AhR ligands, leading to their metabolic clearance and detoxification. Enforced expression of CYP1A1 in IECs resulted in a sharp reduction of AhR ligands available for ILC3 and, consequently, in ILC3 numbers (Schiering et al., 2017), similar to what has been observed in mice lacking AhR expression in ILC3 (Kiss et al., 2011; Li et al., 2011). Thus, IECs serve as gatekeepers for the supply of AhR ligands to the host by regulating their metabolism via CYP1A1. Stockinger and colleagues also identified an important role of AhR signaling within ISCs that protected against inflammation and tumor transformation (Metidji et al., 2018). Mice lacking AhR in ISC developed more tumors in a mouse model of colitis-associated cancer. AhR activation in ISCs prevented tumorigenesis via direct transcriptional regulation of RNF43 and ZNRF3, E3 ubiquitin ligases that inhibit WNT-β-catenin signaling and restrict ISC proliferation. It is intriguing to speculate that such adaptive pathways may be exploited for therapies with a high genotoxic burden. The IL-22-STAT3 axis may be a pathway that could be harnessed for the therapy of diseases or against side effects of therapies with high tissue toxicity, such as bone marrow transplantation, irradiation, or checkpoint blockade. It is worth noting that the effects of IL-22 on epithelial regeneration are not limited to the intestine, with similar data reported for thymic epithelial cells (Dudakov et al., 2012), skin (McGee et al., 2013), and lung (Aujla et al., 2008; Kumar et al., 2013) following an array of insults (chemical, infectious, physical, etc.).

Concluding Remarks

Nutrient acquisition can be viewed as an unavoidable opening of a can of worms (sometimes literally), as an increase in nutrient supply to the body is inherently tied to an increased risk of exposure to pathogens and toxins. Given that the nutritional and immunological roles of the intestines are so inseparable, the recent unravelling of nutrition-related roles played by

gut-resident immune cells and of immune-related roles carried out by the gut epithelium seems only logical. The finding of loops of cooperation between the gut immune and epithelial constituents is important, as they have allowed first insights into the molecular machinery allowing the intestinal organ to prioritize its tasks based on contemporaneous demand. In this review, we have discussed ILC-IEC modules that, among others, allow the intestines to mitigate the cancer-promoting qualities of certain components of our diets, adapt to both the nutritional and immunological challenges brought about by weaning, balance between absorption and immunity on the basis of presence versus absence of food in the lumen, and even promote changes in body fat levels to indirectly optimize immunity against intestinal infections.

Despite the significant advancement in our understanding of cooperative modules of gut immune and epithelial cells, we currently seem to miss two principal components that would be crucial for obtaining a more comprehensive understanding of the intestine's *modus operandi*. First, while we now know of few such circuits, it seems reasonable to suspect that many more exist. Second, and perhaps most importantly, our comprehension of the unique missions that necessitate the existence of such hybrid circuits is very much at its infancy: the rate at which we learn of the existence of cooperative circuits of immune and epithelial cells in the gut far outpaces that at which we learn of the importance of these circuits. Therefore, future investigations into known and yet-unknown immune-epithelial modules in the gut should attempt to understand the real-life task(s) these circuits were evolutionarily developed to carry out. To achieve such understanding, it shall be beneficial to consider that in the gut, it is likely that circuits formed by both immune and epithelial cells act to solve problems that strongly relate to balancing between the immune and nutritional roles assigned to this unique barrier organ.

It is intriguing to view these immune-epithelial cell modules as drivers of adaptation of multicellular organisms to their habitats. A deeper understanding of these evolutionary old circuitry, which likely developed to increase adaptative fitness, is also important on the background of the recent rise in immune-mediated, inflammatory diseases, such as inflammatory bowel diseases, multiple sclerosis, and also metabolic diseases (Bach, 2002). It is believed that changes in our environment (e.g., nutrients, food processing) are drivers of such rapidly increasing diseases (Ananthakrishnan et al., 2018). In the conceptual framework of the highlighted immune-epithelial circuits, inappropriate inflammatory responses at barrier surfaces may be the result of inadequate adaptation to components from the environment. A deeper understanding of both health-promoting immune-epithelial modules as well as of maladaptive processes fueling inflammation may reveal new therapeutic targets for the treatment of inflammatory diseases.

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