Allergic Inflammation—Innately Homeostatic

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Allergic inflammation is associated closely with parasite infection but also asthma and other common allergic diseases. Despite the engagement of similar immunologic pathways, parasitized individuals often show no outward manifestations of allergic disease. In this perspective, we present the thesis that allergic inflammatory responses play a primary role in regulating circadian and environmental inputs involved with tissue homeostasis and metabolic needs. Parasites feed into these pathways and thus engage allergic inflammation to sustain aspects of the parasitic life cycle. In response to parasite infection, an adaptive and regulated immune response is layered on the host effector response, but in the setting of allergy, the effector response remains unregulated, thus leading to the cardinal features of disease. Further understanding of the homeostatic pressures driving allergic inflammation holds promise to further our understanding of human health and the treatment of these common afflictions.

Buoyed by the successes of prophylactic immunization against toxins at the turn of the 20th century, Portier and Richet began studies with hypotoxin from the cnidarian, *Physalia physalis*, commonly known as the Portuguese man o' war, and a related toxin from the sea anemones, *Actinia equina* and *Anemonia sulcata*. These investigations led to the paradoxical discovery of immediate hypersensitivity reactions and even death among some immunized animals by a process termed “anaphylaxis” (Richet 1913). Recognized by a Nobel Prize, these seminal findings underpinned the modern field of allergy and led to the eventual identification

of the transferable nature of the activating agent in serum, first noted by Richet, as immunoglobulin E (IgE) (Ishizaka et al. 1966). The rapid advances in molecular biology, genetics, and genomics from 1970 to 2000 elucidated the central role for cytokines, particularly the duplicated genes for interleukin (IL)-4, IL-13, IL-5, and IL-9, in mediating the effector functions of allergic immunity. Although initial studies fueled by the discoveries of helper T-cell subsets focused on T cells, designated Th2 cells, as sources of these cytokines, recent findings have increasingly highlighted the role of innate cells in allergic immunity. These discoveries have

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raised hopes that insights regarding the initiation and/or maintenance of tissue pathology mediated by interactions between innate and adaptive cells might translate to new therapeutic modalities for diseases underpinned by type 2 immunity.

PREVALENCE OF TYPE 2 IMMUNE MANIFESTATIONS AND THE PARADOX OF ALLERGY

Clinical manifestations of type 2 immune responses are commonplace worldwide in association with parasite infections and allergic diseases. It is estimated that 2–4 billion people worldwide harbor parasitic infections with the vast majority concentrated in developing nations (Chan 1997). Despite the paucity of parasitic infections in developed countries, type 2 immunity significantly impacts human health in the form of allergic diseases, including IgE-mediated anaphylaxis, allergic rhinitis, asthma, atopic dermatitis, eosinophilic gastrointestinal diseases, and food allergies. Worldwide, it is estimated that 300 million people have asthma and 400 million have allergic rhinitis (WHO 2007). In the United States, annual asthma costs approximate 56 billion dollars (CDC 2011).

In humans, “normal” values for IgE and eosinophils are defined using populations from developed countries where elevated levels are associated with pathologic states. In less developed countries, however, parasitic infestation is more widespread, and IgE levels and eosinophils are high. Indeed, hypereosinophilia was the commonest criteria underlying exclusion of healthy Uganda volunteers for vaccine trials (Eller et al. 2008). Although data collection is imperfect, the consensus view is that allergic diseases such as asthma are less prevalent in underdeveloped countries (Godfrey 1975; ISAAC 1998; Eller et al. 2008). In considering nonhuman vertebrates, domestic dogs have IgE levels 100 times greater than that in humans, and populations of Scandinavian wolves and a variety of horses show even higher levels (Ledin et al. 2006, 2008; Wagner 2009). As in humans from less developed countries, elevated IgE and

eosinophils in feral vertebrates are associated with widespread parasitism, particularly intestinal helminths (usually multiple species) and ectoparasites, such as mites and ticks. Crocodiles, Antarctic petrels, Icelandic minke whales, penguins, and arctic mammals including bears, wolves, and cervids all show evidence of ecto- and endoparasitism (Jones 1988; Frenot et al. 2001; Lavikainen et al. 2011; La Grange et al. 2013; Olafsdottir and Shinn 2013). Taken together, these data suggest that manifestations of allergic inflammation are universal in non-human vertebrate populations in association with high levels of parasitism but there is little evidence for pathology associated with human allergic disease.

By extrapolation, it is likely that human evolution was marked by a higher “set point” for the cells and effector molecules, such as eosinophils and IgE, which are now associated with allergic manifestations that remain unusual or infrequent in wild and indigenous vertebrates. A number of possibilities have been considered to explain this apparent paradox. First, as a variant of the hygiene hypothesis, exposure to pathogens during critical developmental periods may be necessary to entrain the immune system to focus on exogenous organisms rather than innocuous allergens. Mechanisms proposed to underlie such “training” include induction of regulatory T cells or blocking antibodies that function to establish tolerance to antigens acquired later through food or inhalation. The data underlying such explanations have been reviewed elsewhere (Soyer et al. 2013). Such a mechanism may also underlie the dysregulated inflammatory responses that accompany many diseases of developed countries, including atherosclerosis, dementia, and obesity. A variant of this possibility, based on increasing information regarding immune cells that develop during fetal but not adult hematopoiesis (e.g., Langerhans cells and microglia) (Ginhoux et al. 2010; Mold et al. 2010; Hoeffel et al. 2012), is that certain cells in tissues may function in “anticipatory” roles, awaiting terminal differentiation by developmental or environmental signals, such as microbes and food, that the organism encounters postbirth. Alter-

ations in these environmental signals during early developmental periods may bypass windows of differentiation that leave the organism more prone to inflammatory states in later life, whether or not accompanied by excesses of Th1- or Th2-associated pathology (Mold et al. 2010). A final possibility considered here is that intestinal helminths and ectoparasites elicit immune responses that mimic homeostatic responses used by the vertebrate host, but to facilitate aspects of the differentiation or development of the parasite. By this scenario, parasites have evolved to elicit tissue reactions that promote their own parasitism. Although the advantages of such evolution are not always readily apparent, the consideration is warranted owing to the extreme penetrance of parasitic infestation on the vertebrate immune system and the relatively small impact of these infections on survival through the reproductive age.

COMPONENTS OF THE ALLERGIC MODULE IN HOST DEFENSE AND ALLERGIC DISEASE

Studies in humans as well as model organisms have detailed the immunologic constituents of allergic inflammation. Here, we summarize recent insights regarding the functions of these various components (Fig. 1).

IgE, Mast Cells, and Basophils

IgE is the least represented serum immunoglobulin, consistent with a short serum half-life and distribution within peripheral tissues (Gould and Sutton 2008). Isotype switching of B cells to IgE requires IL-4-producing T follicular helper (T_{FH}) cells (Reinhardt et al. 2009; Crotty 2011). T-cell–B-cell collaboration is likely short-lived because IgE-switched B cells egress rapidly from germinal centers to become plas-

Figure 1. Constituents of allergic inflammation. Allergic inflammatory responses involve the coordinated response of (1) tissue-resident cells (dendritic cells, innate lymphoid cell [ILC]2, mast cells, and macrophages), (2) expansion of antigen-specific T cells and B cells in the draining lymph node, and (3) recruited cells from the blood (Th2/Th9 cells, basophils, and eosinophils). On allergen exposure or parasite infection, epithelial sensors evoke the release/production of epithelial cytokines (TSLP, IL-25, and IL-33), which in turn drive dendritic cells to migrate to lymph nodes and facilitate IgE production by B cells. Mast cells can be activated through IgE–antigen interactions as well as epithelial cytokines and modulate vascular tone through the release of granules. ILC2s, recruited basophils, and Th2/Th9 are activated by antigen and/or epithelial cytokines, and all three are significant producers of various type 2 cytokines. The sum total of this response includes alternatively activated macrophage (AAM) differentiation, modulation of smooth muscle and epithelial cell function, and further recruitment of effector cells.

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ma cells resident in extrafollicular regions of the lymph node (Talay et al. 2012; Yang et al. 2012). Clarification is needed to explain how allergen-specific IgE antibodies develop extensive hypermutation consistent with their high-affinity states (Davies et al. 2013), whether arising from previously mutated IgG1 germinal center B cells or through some unknown process driving extensively hypermutated antibodies during chronic antigen exposure, as revealed by studies of neutralizing HIV antibodies (Zhou et al. 2010). IgE disseminates through the bloodstream, where free IgE is stabilized on the surface of cells bearing the high-affinity IgE receptor, FcεRI. Unlike other immunoglobulin isotypes, IgE effector function is related almost entirely to its capacity to bind to FcεRI before antigen recognition. In mice, mast cells and basophils constitutively express FcεRI, and is inducible on some dendritic cell populations (Grayson et al. 2007). In humans, FcεRI is also constitutively expressed on mast cells and basophils, but is more widely expressed, including on dendritic cell populations (Gould and Sutton 2008).

Mast cells are tissue-resident cells found near blood vessels in a perivascular distribution. This positioning allows mast cells to extend cellular processes across the endothelial barrier to acquire circulating IgE as well as to control vascular tone and permeability (Galli and Tsai 2010; Cheng et al. 2013). On activation, mast cells release preformed and synthesized mediators, including histamine, lipid mediators, and cytokines. In the skin, the clinical manifestations of this reaction include the “wheal and flare” seen in urticaria. The evolutionary benefit of these rapidly activated responses may be to mitigate threats from insects or noxious substances by promoting resolution of the threat or alerting the host to establish avoidance behavior (Palm et al. 2012). In the gut, these mediators also lead to neural stimulation and intestinal smooth muscle hypermotility, which might function to clear ingested toxins via emesis and diarrhea.

Although commonly associated with allergic conditions, mast cells also participate in host defense to bacterial pathogens (Malaviya et al. 1996; McLachlan et al. 2003). As during allergy, these nonallergic stimulants promote changes

in vascular permeability, activate antigen-presenting cells to mature and migrate to draining lymph nodes, and engage components of adaptive immunity (Shelburne et al. 2009). Because mast cells are tissue-resident cells capable of sensing a variety of inputs associated with disparate inflammatory modules, these cells may have evolved the capacity to acquire IgE to broaden functional capacity and respond to environmental insults.

Basophils are closely related to mast cells as revealed by developmental similarities driven by common transcription factor modules (Qi et al. 2013). Basophils also bind IgE but, unlike mast cells, circulate in blood with a half-life similar to other circulating myeloid cells (Voehringer 2013). The scarcest of all circulating leukocytes, basophils degranulate after FcεRI-mediated activation, but unlike mast cells, contribute little to anaphylaxis (Ohnmacht et al. 2010). During migratory helminth infection, basophils enter involved tissues and interact closely with CD4 T cells, which mediate contact-dependent and IL-3-dependent IL-4 release from basophils; antigen-specific IgE enhances basophil IL-4 production (Sullivan et al. 2011). Basophils also promote eosinophil entry into skin models of chronic allergic inflammation and induce the differentiation of recruited monocytes to alternatively activated macrophages in tissues (see below).

CD4 T Cells: Th2 Cells, Th9 Cells, and T Regulatory Cells (Tregs)

Activation of helper T cells in allergy is dependent on dendritic cells (DCs), although the precise signals and surface phenotype of type 2-inducing DCs may differ in response to different stimuli or within different tissues (Pulendran et al. 2010). A gradient defined by integration of T-cell receptor (TCR) signal strength, T-cell precursor frequency, and antigen abundance underlies the proclivity of some cells to enter follicles and become IL-4-expressing T_{FH} cells (typically higher-affinity TCRs) or activate more extensive patterns of type 2 cytokine expression and leave lymph nodes to enter peripheral tissues as Th2 cells (Tubo et al. 2013). Tissue

Th2 cells show a range of cytokine patterns, including single and multiple combinations of IL-4, IL-5, IL-9, and IL-13. As shown most convincingly using knockout mice in models of helminth and allergic immune challenges, these cytokines have both unique and redundant functions in type 2 immunity (Fallon et al. 2002; Nath et al. 2007); importantly, absence of all of these attenuates most of the manifestations of allergy, in part owing to the inevitable outgrowth of effector T cells expressing inflammatory cytokines. Further information is needed to understand fully the distribution and life span of allergic memory cells to ascertain whether long-term tissue reservoirs exist for these cells as shown for other memory-effector T cells (Shin and Iwasaki 2013).

A second area of much importance and in need of clarification is the relationship of allergic immunity with Treg induction. Infants born with *FOXP3* mutations, and thus lacking Treg, suffer from a multisystem inflammatory disorder termed immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX). Although patients suffer from a wide range of inflammatory disease, allergic manifestations with severe eczema, elevated IgE, and eosinophilia are prominent (Ozcan et al. 2008). Other T-cell immunodeficiencies, including Wiskott-Aldrich and Omenn's syndromes, show inflammatory disorders that are characterized by unrestrained allergic inflammation with clinical features including increased IgE and eosinophils and eczematous skin conditions. Both disorders are accompanied by Treg deficiency and/or dysfunction to which the allergic manifestations have been attributed (Ozcan et al. 2008). Mice with defects in extrathymically derived Treg also show systemic allergic inflammation (Josefowicz et al. 2012). Ablation of GATA3, a transcription factor required for Th2 function, in Foxp3-expressing cells leads to uncontrolled allergic inflammation mimicking total Foxp3 gene ablation, thus emphasizing a primary role for these cells in the control of allergic inflammation to environmental antigens (Rudra et al. 2012). Helminth infections have been linked with Treg induction, consistent with resistance to allergy induction in infected mice (Maizels

and Smith 2011), but why environmental allergens fail to induce similarly restraining Tregs in susceptible individuals remains unknown.

Innate Lymphoid Cell (ILC)2

The identification of innate lymphoid cells, now designated ILC2, as the major source of innate type 2 cytokines has kindled much interest in these cells in studies of allergic immunity (Spits and Cupedo 2012). ILC2 are dispersed throughout the body in most organs, and particularly in barrier tissues like the lung, gastrointestinal tract, and skin (Moro et al. 2010; Neill et al. 2010; Price et al. 2010; Nussbaum et al. 2013). Recent studies show that these cells accumulate in organs in the perinatal period and constitute a relatively long-lived subset of tissue lymphoid cells. As shown using cytokine reporter mice, small numbers of ILC2 in tissues constitutively produce IL-5, thus accounting for basal eosinophilopoiesis (Nussbaum et al. 2013). In response to migratory helminths, ILC2 respond to tissue alarmins, such as IL-33, IL-25, and thymic stromal lymphopoietin (TSLP) (Walker and McKenzie 2013), to express increased amounts and range of type 2 cytokines, including IL-13 and IL-9 but also growth factors, such as amphiregulin, that may contribute to local epithelial repair (Monticelli et al. 2011). As such, activated ILC2 are required to mediate early recruitment of tissue eosinophils from blood and the differentiation of tissue macrophages and recruited monocytes to an alternatively activated macrophage (AAM) phenotype (Molofsky et al. 2013). Although less well studied, activated ILC2 may also play a role in the early attraction of Th2 effectors to tissues, where these cells amplify the cytokine milieu, but also provide growth signals that stimulate the proliferation and/or recruitment of the tissue ILC2 population; some studies suggest a role for IL-9, both from Th2 cells and, in an autocrine fashion, from ILC2 themselves (Wilhelm et al. 2011). Although Th2 cells migrate to involved sites deeper in tissues to mediate local immunity, it remains unclear whether ILC2 migrate from their position near vascular tissues; further study is needed. The ultimate fate of ex-

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panded ILC2 populations in tissue and their ultimate interactions with Th2 memory cells and Treg remain important areas for investigation.

AAMs

Macrophages are constitutive in all tissues and increase in number and change their phenotype during inflammation (Galli et al. 2011; Van Dyken and Locksley 2013). In the setting of type 2 immunity, IL-4 and/or IL-13 promote the coordinate expression of a set of genes that characterize alternatively activated (or M2) macrophages. Under some conditions, AAM differentiation is driven by in situ proliferation of resident tissue macrophages (Jenkins et al. 2011), whereas differentiation of both resident and recruited blood monocytes into AAMs occurs in other situations (Reese et al. 2007). Recent findings that resident tissue macrophages, such as Langerhans cells and microglia, accumulate in tissues from fetal blood precursors emphasize the potential that certain populations of hematopoietic cells may be intimately involved during discrete developmental windows, with implications for tissue integrity based on the capacity to fully renew these populations in response to injury or senescence (Schulz et al. 2012). Along these lines, AAM-like cells are found dispersed throughout the body during embryonic development and peak during periods of growth, remodeling, and organization of developing tissues, such as the kidney (Rae et al. 2007).

The role of AAMs in type 2 immunity has been explored in various systems involving deletion of key elements involved in their differentiation, such as the IL-4R α component of the type 1 and 2 IL-4 receptors. After infection with *Schistosoma mansoni*, mice lacking the capacity to generate IL-4/IL-13-mediated AAM differentiation fail to control intestinal epithelial integrity around trapped eggs and die from sepsis owing to enhanced translocation of intestinal bacteria and their products into the systemic circulation (Herbert et al. 2004). Thus, part of the function of AAMs may involve control of barrier integrity in response to antigens that elicit granulomatous type 2 immunity.

Eosinophils

Elevations of blood and tissue eosinophils are hallmarks of virtually all disorders of type 2 immunity (Rosenberg et al. 2013). Although decades of work highlighted the capacity of eosinophils to mediate parasite damage in various in vitro systems, data supporting a direct role for eosinophils in limiting the initiation or duration of adapted intestinal helminth infection in vivo is modest at best. The widespread prevalence of helminths in feral vertebrates, together with the relatively long life span of adult worms, despite prolonged eosinophilia, is difficult to reconcile with a primary role for these cells in limiting established parasitism. During secondary infections, however, the combination of memory-effector Th2 cells and expanded tissue ILC2 may accelerate and focus eosinophils at sites of larval migration, thus limiting further infection by a process termed “concomitant immunity” (a situation in which immunity against larval forms limits infections despite the presence of living adult parasites in the body that cannot be rejected). An emerging concept that requires further exploration is the inevitable co-accumulation of eosinophils with AAMs, reflecting the stereotyped response of tissues to the presence of activated ILC2 and Th2 that produce type 2 cytokines.

As discussed above, another possibility is that helminths evoke eosinophilia to elicit a tissue response that favors parasitism. After infection with *Trichinella spiralis*, newborn larvae migrate from the intestines to skeletal muscle to complete their development. Larval maturation involves the dedifferentiation of muscle cells to nurse cells, which provide the necessary environment. Although not entirely understood, eosinophils accumulate around nurse cells and are themselves required for continued larval development, presumably owing to their role in sustaining the nurse cell (Gebreselassie et al. 2012). As noted below, aspects of this response resemble that seen during muscle injury, suggesting that *Trichinella* elicits a gene program used by the host for one purpose but co-opts it to establish a developmental niche. Evidence that bacteria can also subvert cellular

gene programs to redirect fundamental pathways of differentiation suggests that further understanding of such highly involved interactions between microbes and hosts may yield fundamental insights into cellular reprogramming that might be applicable to many disease states (Masaki et al. 2013). Such examples offer the possibility that uncovering the basic roles for type 2 immunity in vertebrate homeostasis may lead to enhanced understanding of its stereotyped elicitation by helminths and allergens.

HOMEOSTATIC ROLES FOR COMPONENTS OF ALLERGIC MODULE

As noted above, the majority of studies of type 2 immunity have focused on pathologic associations with parasite infection and allergic diseases. Recent investigations have called attention to potential roles for type 2 immunity in metabolism and tissue homeostasis in response to injury that might suggest pathways by which these responses come to be linked with these two pathologic states (Fig. 2).

Figure 2. An integrated view of allergic inflammation in infection and disease. (A) Innate components of allergic inflammation (ILC2, eosinophils, and AAMs) along with Tregs integrate broad inputs related to circadian patterns and environmental perturbations to drive tissue homeostasis and meet systemic energy needs. (B) During parasite infection, the additional stress on tissue homeostasis and energy needs engages a broader but balanced adaptive immune response, which promotes both host and parasite fitness, and is characterized by a regulatory component. (C) Allergen-specific responses fail to establish this balance, with a lack of Treg activation, resulting in tissue injury and disease.

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Metabolism

A number of studies over the last decade have provided evidence that obesity is accompanied by an inflammatory state, marked by infiltration of activated macrophages and other immune cells into visceral adipose with adverse effects on systemic insulin resistance and lipid metabolism (Mathis 2013). Conversely, lean animals and perhaps humans contain AAMs in white adipose tissue, and deleting these cells in animals results in proclivity to obesity and insulin resistance (Odegaard et al. 2007). AAMs may also play a role in brown adipose tissue by facilitating early production of norepinephrine and the transfer of fat from reservoirs in white to metabolizing brown fat tissue during adaptive thermogenesis (Nguyen et al. 2011). As alluded to above, AAMs in tissue are accompanied by eosinophils and ILC2s, and, indeed, both of these cells are not only present in resting visceral adipose, but their presence is necessary to restrain metabolic abnormalities incurred by challenge with a high-fat diet (Wu et al. 2011; Molofsky et al. 2013). Further evidence for the linkage between these core elements of innate type 2 immunity and Treg cells is the finding that the latter cells are also present in fat and required for the maintenance of metabolic homeostasis (Feuerer et al. 2009). Like ILC2, adipose Treg express GATA-3 and the IL-33 receptor; conversely, ILC2 express CD25, the high-affinity IL-2 receptor. Thus, ILC2 and Treg in adipose tissues share these and additional surface receptors and transcription factors, a finding that may underlie the capacity of these cells to respond to common environmental signals in specialized tissues undergoing cyclic nutrient exchange.

Eosinophils display prominent circadian cycling that was shown to be entrained by food intake more than 35 years ago (Pauly et al. 1975). A small percentage of tissue-dispersed ILC2s constitutively secrete IL-5 necessary for reactive eosinophilopoiesis (Nussbaum et al. 2013). Unexpectedly, IL-5 secretion was circadian, thus accounting for the cyclic nature of blood eosinophils, but secretion was enhanced by feeding and depressed by fasting (Nussbaum et al. 2013). Eosinophils, like Treg, are present consti-

tutively in the intestines, particularly the small bowel, and ILC2 in the intestine activated IL-13 secretion in response to nutrient intake. ILC2 also express vasoactive intestinal polypeptide receptor (VPAC)2, the type 2 receptor for the neuronal peptide, vasoactive intestinal peptide (VIP), and activate IL-5 secretion rapidly after activation by VIP or VPAC2 analogs in vitro (Nussbaum et al. 2013). VIP is itself secreted from intestinal neurons in response to feeding, and helps to coordinate pancreatic secretions, smooth muscle contractility, and hepatic metabolic cycles linked with nutrient absorption and disposition (Lelievre et al. 2007). Mice deficient in VIP or VPAC2, both of which are highly expressed in neurons of the suprachiasmatic nucleus (Maywood et al. 2013), lose the ability to coordinate environmental signals with the circadian cycle, and show metabolic dysregulation (Harmar et al. 2002; Colwell et al. 2003). Thus, ILC2 respond to VIP, integrating their activation with central circadian rhythms, although precisely what role recruited eosinophils might play in nutrient acquisition or other aspects of metabolism remains unknown. Type 2 cytokines and Stat6-mediated signaling have been shown to affect primary hepatic metabolism directly as well (Sajic et al. 2013; Stanya et al. 2013).

An additional layer of complexity in metabolic homeostasis is the relationship of intestinal commensal organisms with epithelial and immune cell populations. In mice, key innate lymphoid cells are established after birth during exposure to dietary nutrients via signals sustained through the aryl hydrocarbon receptor (Kiss et al. 2011; Li et al. 2011; Lee et al. 2012). Development of these immune cell populations is constrained to a defined window of time postbirth, suggesting that alterations of this window might have adverse effects on gut homeostasis. Intriguingly, antibiotics, which have long been used to increase body size and fat content in animals farmed for food, have been shown to affect body size and intestinal microbial communities in adult mice, even when given in subtherapeutic levels during the perinatal period (Cho et al. 2012). Antibiotic use in early life has been linked to patterns of obesity at the population level (Trasande et al. 2013). Although causality has

yet to be established, the similarities in a number of the systemic consequences of dysbiotic microbial communities and the absence of AAMs, eosinophils, ILC2s, and/or Tregs raise the possibility that some or each of the components of this type 2 immune module are linked deeply with basal metabolic homeostasis (Fig. 2A).

Wound Healing

Maintenance of barrier integrity is critical for vertebrate survival, particularly at mucosal sites involved with gas exchange and nutrient acquisition in the lungs and bowel, respectively. Animals rendered unable to respond to IL-4/IL-13 signals from immune cells have been shown to suffer adverse epithelial injury against migratory and intestinal helminths in model systems (Gause et al. 2013). Recovery after toxin-mediated muscle injury was also enhanced by eosinophils and an intact type 2 cytokine system by a process linked to proliferation and differentiation of resident pluripotent fibro-/adipogenic precursor cells (FAPs) at the injury site (Heredia et al. 2013). FAPs were implicated in necrotic cell clearance and muscle regeneration; in the absence of IL-4/-13, the FAPs differentiated into adipocytes resulting in fatty degeneration. A similar role for eosinophils and IL-4/-13 was found in liver regeneration, but, in this case, IL-4 promoted hepatocyte proliferation and liver regeneration (Goh et al. 2013). In various skin models involving epicutaneous sensitization, a variety of type 2 immune cells, including basophils, eosinophils, ILC2, and AAMs, have been implicated along with IgE in mediating the manifestations of allergy (Mukai et al. 2005; Egawa et al. 2013). Thus, multiple components of the type 2 immune response have been implicated in barrier injury responses, although the precise molecular mechanisms by which these responses are mediated remain incompletely defined.

CONCLUDING REMARKS: SPECULATIONS AND FUTURE NEEDS

The deep penetrance of allergy prevalence into humans living in developed countries suggests

that environmental alterations have impacted an evolved pathway that is deeply embedded in normal biology. Here, we have summarized recent support for involvement of type 2 immune cells in metabolism and tissue integrity, particularly at barriers. Although much more work is needed to flesh out the molecular details and mechanisms, the finding that multiple cell types, including Treg associated with type 2 immunity, localize to metabolically active tissues like adipose and small intestines is consistent with a role for these cells in more fundamental homeostatic processes of importance to vertebrate biology, such as tolerance to food or self-antigens exposed during normal tissue turnover. Chronic intestinal parasitism induces similar activation of type 2 immune cells, but these responses are not associated with pathologic responses associated with allergy, perhaps related to the capacity to induce a more balanced immune response, which includes Treg or additional suppressive mechanisms (Fig. 2B). This balanced response contrasts with allergen-specific responses in which suppressive mechanisms are lacking, and pathologic consequences emerge (Fig. 2C). Alternatively, the age of acquisition of these highly adapted parasites may have effects on immune system development or intestinal microbiota that protect against the subsequent dysregulated type 2 immune responses to innocuous environmental antigens. We propose that parasitic helminths, rather than being attacked by the components of type 2 immunity, have evolved to elicit these localized tissue responses to facilitate their own differentiation and maintenance within the vertebrate niche. Indeed, some of the properties of type 2 immunity we have outlined, including mobilization of nutrients and preservation of tissue integrity, may be appropriated by parasites for their own purposes. Numerous examples of bacterial commensals eliciting immune reactivity from the host that facilitates their colonization have been shown (Nussbaum and Locksley 2012), and the possibility that more complex parasites do the same thing would not be unexpected.

Despite evidence for this thesis, the mechanisms underlying these processes remain woefully undefined. In this way, study of parasite

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infections may yield information regarding the precise pathways that elicit the type 2 immune response, whether through induction of canonical alarmins or other mediators (Doherty et al. 2013; Gause et al. 2013). Conversely, more information regarding the mechanisms that control the tissue localization, organization, and activation of type 2 immune cells under homeostatic conditions will reveal the terrain that establishes this network within the greater context of vertebrate development and life span. Taken together, the study of type 2 immunity has evolved greatly in recent years and will be sure to contain additional surprises in the near future.

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