ALLERGY

Type 2 immunity: Expanding our view

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The classical vision of type 2 immune reactions is that they are characterized by a distinct cellular and cytokine repertoire that is critical for host resistance against helminthic worm infections but, when dysregulated, may cause atopic reactions that result in conditions such as asthma, rhinitis, dermatitis, and anaphylaxis. In this traditional view, the type 2 response is categorized as an adaptive immune response with differentiated T helper cells taking center stage, driving eosinophil recruitment and immunoglobulin production via the secretion of a distinct repertoire of cytokines that include interleukin-4 (IL-4), IL-5, and IL-13. The recent discovery of a group of innate cells that has the capacity to secrete copious amounts of type 2 cytokines, potentially in the absence of adaptive immunity, has reignited interest in type 2 biology. The discovery that these innate lymphoid cells and type 2 cytokines are involved in diverse biological processes—including wound healing, control of metabolic homeostasis, and temperature—has considerably changed our view of type 2 responses and the cytokines, chemokines, and receptors that regulate these responses.

INTRODUCTION

An evolving view of type 2 immunity

Our traditional perception of the induction of a type 2 response at a mucosal surface is one that is impingent upon specialized dendritic cells (DCs) sampling antigen from the luminal compartment that is exposed to the external environment and then mobilizing to local draining lymph nodes. Here, the DCs activate naïve $CD4^+$ T cells, which, in turn, differentiate into cells that express transcription factor GATA-binding protein 3 (GATA-3) and produce combinations of classical T helper 2 (T_H2) cytokines interleukin-4 (IL-4), IL-5, IL-13, and IL-10. Specifically, the initial lymphoid organ T_H2 cells produce IL-4, with subsets of these cells then migrating to B cell zones of the lymph node, where they differentiate into T follicular helper (T_{FH}) cells and function to promote B cell responses and immunoglobulin E (IgE) class switching. Other T_H2 cells egress from the lymph node and enter the tissue, where they differentiate into mature T_H2 cells that produce IL-5 and IL-13. IgE immune complexes bind to high-affinity IgE receptors (FcεR1) on the surface of mucosal basophils and mast cells, driving their activation and the release of mediators, which, in combination with IL-5 and IL-13, mediate the classical type 2 inflammatory and structural remodeling changes observed in the tissue.

However, this view does not fully rationalize how and why a type 2 response is readily initiated and orchestrated in response to an impressive array of diverse microbial and nonmicrobial stimuli, ranging from nanometer-sized allergens to helminths that can measure many meters in length. In recent years, there have been numerous conceptual advances that have highlighted the cross-talk between resident and infiltrating immune cells, which enable sensing and subsequent response to a diverse array of extrinsic stimuli. In the context of type 2 responses, the most remarkable advance here has been the discovery of group 2 innate lymphoid cells (ILC2s) (Fig. 1). ILC2s are tissue-resident cells that represent a critical innate source of type 2 cytokines IL-5 and IL-13. This has led to a substantial refinement of the original DC-T_H2 centric view to an ILC2-DC-T_H2 cell axis driving type 2 inflammation. There is also a much greater appreciation for the fact that such a response is dictated by the microenvironment in which tissue-resident nonhematopoietic sentinels detect environmental triggers and provide cues to immune cells to initiate and shape an appropriate response. Given that expulsion of helminth parasites requires the coordinated action of immune cells, mucus production from epithelial cells, and contraction of smooth muscle cells, a type 2 response requires an effector program that engages the entire tissue. It is perhaps prudent that the tissue as a whole senses and relays information of adverse environmental fluctuations and triggers, which is fed into a central decision-making ILC2-DC-T_H2 cell algorithm that defines an appropriate tissue response. Whereas a type 2 response is protective in the context of helminth infection, it is pathological in allergic disease, and thus it is critical to define why and how inappropriate responses are initiated and sustained.

TYPE 2 RESPONSE: SENSING, INITIATION, AND ACTIVATION

Diverse stimuli trigger a type 2 response

A vast array of disparate stimuli are able to evoke a type 2 response, including helminths, allergens, specific bacterial and viral infections, and even endogenous host molecules (*1*). It seems remarkable that such seemingly distinct triggers instigate a prototypic type 2 response. Tissue-resident ILC2s are now recognized as highly responsive, early effectors in type 2 inflammation (*2*, *3*). Upon primary exposure to an appropriate trigger, ILC2s function as a prominent source of classical T_H2 cytokines IL-5, IL-9, and IL-13 long before an adaptive response is initiated. Activation of ILC2s is independent of the classical antigen-specific activation that is a hallmark of their $CD4^+$ T_H2 cell counterparts, and they generally seem poorly responsive to pattern recognition receptor (PRR) agonists—although ILC2s from the human tonsil have been demonstrated to produce IL-5 and IL-13 upon stimulation with Toll-like receptor 2 (TLR2) ligands (*4*). Rather, it is increasingly apparent that ILC2s sense and respond to cytokines and stress signals that are released from multiple cell types in the proximal environment after disruption to tissue homeostasis (Fig. 2) (*5*, *6*), which is a feature common to a diverse array of type 2 agonists.

ILC2-activating signals are the prototypical "alarmins" IL-33, IL-25, and thymic stromal lymphopoietin (TSLP), which drive ILC2 growth and cytokine production (*7*), although their relative importance may be dictated by tissue location (*8*). The epithelium is a crucial type 2

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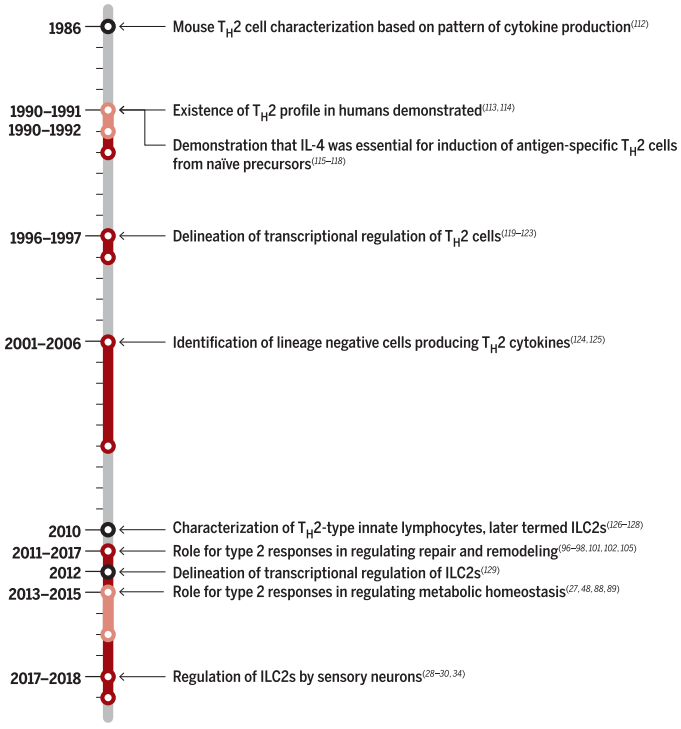

Fig. 1. A timeline of discoveries in T_H2 immune responses. Since the identification of a T_H2-specific cytokine profile by Mosmann and colleagues (*112*), a series of seminal discoveries have continued to advance the field of type 2 immunity. In more recent years, there has been fresh impetus in the field coinciding with the identification of ILC2s; an increasing awareness of how diverse exogenous stimuli can trigger type 2 responses and the importance of these responses in a broad biological processes, such as repair, remodeling, and regulation of metabolic homeostasis.

sentinel, which releases these cytokines upon exposure to appropriate exogenous stimuli. Accordingly, type 2 alveolar cells in the lung have been shown to be a robust source of IL-33 and TSLP (*9*, *10*), whereas specialized Tuft cells are seemingly the source of IL-25 (at least in the gut) (*11*). However, other tissue-resident and nonhematopoietic cells are also now recognized as potential sources of these cytokines, with alveolar macrophages (*12*), endothelial cells, and fibroblasts (*13*, *14*) shown to express IL-33 and endothelial cells (*15*) and airway smooth muscle cells producing TSLP (*16*). Furthermore, it is increasingly apparent that ILC2 activity can also be modulated by a host of other cytokines and lipid mediators produced or released in the early stages after type 2 agonist exposure. Tumor necrosis factor (TNF) family cytokine TL1A, predominantly derived from endothelial cells, is able to impart stimulatory signals to ILC2s via its receptor DR3 (*17*–*19*). In addition, we have demonstrated that epithelial-derived transforming growth factor–β (TGF-β) can function to promote ILC2 chemoactivity via TGF-βRII (*20*). Last, prostaglandins and eicosanoids are early mediators in an inflammatory response, derived from myeloid cells but also potentially nonhematopoietic cells, which have been shown to regulate ILC2 activity. Specifically, prostaglandin D_2 has been shown to promote ILC2 migration and IL-13 production (*21*–*23*), whereas cysteinyl leukotrienes stimulate ILC2 activation and production of IL-5 and IL-13 (*24*, *25*). More recent studies are starting to highlight how combinations of signals may be required for optimal ILC2 activation, with IL-33 and leukotrienes operating in tandem to promote ILC2 responses during helminth infection (*25*). It is likely that future studies will delineate how different combinations of regulators may operate to promote or regulate distinct ILC2 responses.

There has been an explosion of exciting studies that have demonstrated potential neuronal control of ILC2 function, with sensory neurons within tissues responding to a perceived threat to elicit a type 2 immune response. Sensory neurons within the lung that express the sodium ion channel Nav1.8 respond to IL-5 by releasing vasoactive intestinal peptide (VIP), which, in turn, is capable of stimulating resident ILC2s, essentially creating a self-perpetuating type 2 inflammatory loop. Accordingly, ablation or inhibition of $Nav1.8^+$ sensory neurons in mice attenuates allergen-induced airway inflammation and bronchial hyperresponsiveness (*26*). Similarly, VIP has been demonstrated to act directly on ILC2s through the vasoactive intestinal peptide receptor 2 (VPAC2) receptor to elicit IL-5 release (*27*). Parallel studies have established the importance of mucosal neuron-derived neuropeptide neuromedin U (NMU) in regulating ILC2 function via surface-expressed neuromedin U receptor 1 (Nmur1) (*28*–*30*). NMU-positive neurons were shown to lie in close proximity to ILC2s in the gut (*28*, *29*) and were capable of driving ILC2 activation, proliferation, and secretion of type 2 cytokines (*28*–*30*). In line with this, an important role for this NMU-mediated neuronal-ILC2 circuit in driving type 2 immune responses to helminths in the gut (*28*, *29*) has been proven. Furthermore, NMU was shown to function synergistically with IL-25 to promote ILC2 type 2 cytokine production in vitro and strongly amplified pulmonary allergic inflammation in mice (*30*), whereas a loss of NMU-NMUR1 signaling reduced ILC2 frequency and effector function in a house dust mite (HDM) model of allergic airway disease (*30*). In parallel, several studies have suggested that classical T_H2 cytokines and aforementioned alarmins IL-33 and TSLP may regulate neuropeptide release, highlighting the potential complex interplay between cell types and mediators in inducing a type 2 immune response (*26*, *29*, *31*–*33*). Given that sensory neurons can regulate smooth muscle contraction in response to noxious stimuli, it is plausible that a neuronal network simultaneously promotes physical reflexes and ILC2-dependent type 2 inflammation and mucus secretion to facilitate expulsion of the irritants. It is conceivable that the same network may also be integral in the clinical manifestations of allergic diseases. The most recent study in this series of neuronal-ILC2 links has detailed how ILC2 responses can be negatively regulated by a neuronal circuit, in which ligation of the β2-adrenergic receptor on ILC2s suppresses their proliferation and effector function (*34*).

Although many of the microenvironment-derived mediators that shape ILC2 function are becoming apparent, far less is known about the mechanisms by which the broad array of type 2 stimulating agents trigger the expression and/or release of these fundamentally important mediators. PRR agonists, allergen-derived proteases, and tissue damage have been implicated in driving the release of these mediators. The potent ILC2 activator IL-33 is a prototypical damage-associated molecular pattern—constitutively expressed as a procytokine in the nucleus of cells and released in response to any stimuli that drives necrotic cell death, cell stretching, or cellular stress (*35*–*37*)—but is then subject to extracellular processing and modifications that can modulate its activity (*38*–*40*). HDM was shown to elicit the release of IL-33 as well as IL-25 and TSLP in mice in a process that was mediated by TLR4 on airway structural cells (*41*)—potentially attributable to low levels of endotoxin in HDM preparations, which have been associated with induction of type 2 immune responses (*42*). IL-33 can also be released from epithelial cells seemingly independently of cell death in a process that is dependent on allergen-intrinsic proteases

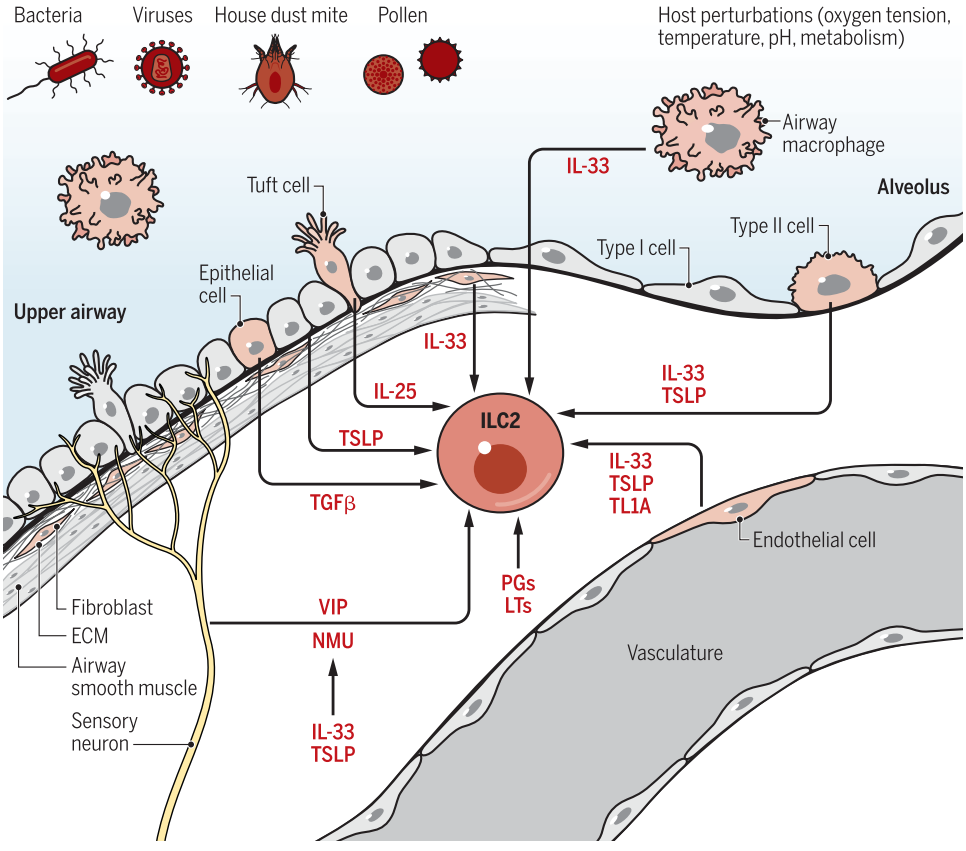

Fig. 2. ILC2s sense microenvironmental cues to elicit a type 2 response. Lung-resident cells function as specialized tissue sentinels to detect a broad array of stimuli, including allergens, specific viruses, bacteria, or general host perturbations away from a homeostatic basal state. Subsequently, these sensors release a disparate set of mediators, including IL-25, TSLP, IL-33, TL1A, leukotrienes (LTs), prostaglandins (PGs), and neuropeptides VIP and NMU. These mediators converge to activate ILC2s, which produce IL-5, IL-13, and IL-9 and so function as a fundamental decision-maker in bridging tissue perturbation and induction of a T_H2 response. ECM, extracellular matrix.

and mediated by protease-activated receptor–2 (PAR-2) activation (*40*, *43*). TSLP expression can be induced in cells via an array of stimuli (*44*), with subsequent release from airway epithelial cells demonstrated to be driven by allergen (*45*) and host-derived proteases (*46*). Whereas protease-mediated TSLP release is seemingly in part mediated by activation of PAR-2 activation (*45*), cysteine protease papain–mediated TSLP release is dependent on induction of reactive oxygen species and signaling through TLR4 (*47*). Although our understanding here is still in its infancy, there is a growing appreciation that perturbations in tissue metabolism, oxygen tension, temperature, and pH may also operate upstream to elicit the release of ILC2-modifying mediators (*1*, *5*, *48*, *49*). The host response to deficiency in micronutrients has also been shown to trigger type 2 immune responses. Notably, a lack of vitamin A was found to elicit a switch from the usual intestinal ILC3 to IL-13–producing ILC2, leading to enhanced antihelminth immunity (*50*). The diversity and nonspecific nature of signals that drive the release of these early type 2–promoting factors potentially rationalize how ILC2s can respond to seemingly very distinct environmental stimuli; they often sense fluctuations away from the basal homeostatic norm of the tissue rather than features specific to each stimuli. Tissue perturbations in the absence of an exogenous trigger have been shown to be sufficient to promote a type 2 inflammatory response (*51*, *52*).

Priming a type 2 adaptive response

The classical paradigm in which populations of DCs sample antigen before migrating to localized lymph nodes to elicit a T_H2 $CD4^+$ T cell response must now be contextualized within a network of multicellular cooperation and tissue microenvironmental cues. It is now acknowledged that ILC2s engage in a complex bidirectional cross-talk with DCs and T_H2 cells in a localized tissue setting, functioning to modulate the amplitude of the type 2 response to appropriately respond to the perceived environmental threat.

Several populations of DCs have an intrinsic capacity to preferentially induce a T_H2 response (*53*, *54*), including $CD11c^+$ $CD8a^-$ DCs in the spleen (*55*), FcεR1-expressing DCs in the lung (*56*), plasmacytoid DCs in the blood (*57*), and Langerhans cells in the skin (*58*). Recognition of specific exogenous stimuli by DCs through TLRs, NOD-like receptors, and C-type lectin receptors have all been associated with DC activation and ensuing induction of a T_H2 response, with signal duration and amplitude seemingly key in defining a type 2 preference (*1*, *42*, *59*). Specifically, sustained extracellular signal–regulated kinase signaling in DCs has been shown to inhibit IL-12p70 production through phosphorylation and stabilization of c-Fos, enhance IL-10 production, and support T_H2-biased responses (*59*). The central role for DCs in eliciting T_H2 inflammation has been highlighted by the diminished responses to helminths (*60*) and allergen (*56*, *61*) after global or subset-specific depletion of DCs. DCs alone, however, are not sufficient to elicit an optimal T_H2 response. IL-33, IL-25, and TSLP released from nonhematopoietic tissue–resident cells, in addition to facilitating ILC2 responses, have also been shown to instruct DCs to promote a T_H2 response (*41*, *53*, *62*, *63*). ILC2-derived IL-13 has been shown to license the migration of activated lung tissue DCs to draining lymph nodes and ensuing priming of T_H2 $CD4^+$ T cells (*64*).

T_H2 effector cell differentiation and cytokine production are initiated in lymphoid organs but take place after tissue entry, and again, IL-33, IL-25, and TSLP have been implicated in the terminal differentiation of T_H2 $CD4^+$ T cells in the tissues (*65*, *66*). Moreover, ILC2s are now appreciated to directly regulate T_H2 $CD4^+$ T cells. ILC2 have been shown to express major histocompatibility complex II (MHC II), CD80, CD86, and OX40L and can directly present antigen to T cells, although less efficiently than DCs, inducing T cell IL-2 and IL-4 production (*67*–*69*). Consequently, these T_H2 $CD4^+$ T cell–derived cytokines feedback to promote ILC2 proliferation and cytokine production (*67*, *68*). Moreover, IL-2 is required for IL-9 production by ILC2s, which subsequently acts in an autocrine fashion to promote ILC2 survival by up-regulating BCL-3 (*70*, *71*). The importance of this ILC2-T_H2 $CD4^+$ T cell cross-talk has been highlighted by the demonstration that MHC II–deficient ILC2s are unable to cause the efficient expulsion

of parasitic helminths (*67*). Conversely, however, another study has reported a comparable T_H2 response to helminth infection in mice with MHC II–deficient ILC2s (*65*), emphasizing that further studies are required to fully support the assertion that ILC2s are critical for an effective T_H2 response. It seems intuitive that adaptive interactions are important for maintaining ILC2s at the site of tissue inflammation as a type 2 response progresses, and ILC2 cytokine dependency shifts from those derived from resident nonhematopoietic cells such as the epithelium to those provided by the adaptive response (*7*). Although this network of interactions provides positive reinforcement of the type 2 signature, it also provides a means to negatively regulate ILC2 function and resolve inflammation after clearance of antigen and ensuing loss of T_H2 cell support to the ILC2.

Furthermore, it must be considered how this ILC2-DC-T_H2 axis is modulated by signals imparted by proximal cells activated or recruited to the tissue as part of an ongoing type 2 response. Prostaglandins and leukotrienes are increasingly recognized as potent modulators of ILC2 function as discussed above, and their levels are elevated as a consequence of myeloid cell recruitment and mast cell activation (*7*). Although seemingly context-dependent, depletion of basophils has been shown to result in an impaired T_H2 response (*72*). Accordingly, basophil-derived IL-4 is important for skewing of DCs toward a type 2 response and has been demonstrated to directly promote ILC2 activation in some models (*73*, *74*). T_H9 cell–derived IL-9 functions to promote ILC2 survival (*71*), although the dependence of both ILC2 and T_H2 cells on IL-2 means that both can be negatively regulated by regulatory T (T_{reg}) cells through the removal of IL-2 from the environment (*75*). Furthermore, studies in mice (*76*) and humans (*77*) have shown that immunosuppressive cytokines IL-10 and TGF-β prevent production of T_H2 cytokines by ILC2s, whereas type I and II interferons (IFNs) and IL-27 suppress ILC2 function and limit allergic airway inflammation in mice (*78*). The discovery of ILC2s has led to a much greater appreciation of the role of tissue microenvironment and cues derived from nonimmune cells in driving type 2 immune responses.

Besides the role of ILC2s in priming T_H2 cells after the initial exposure to antigen, it is now also apparent that ILC2s are fundamentally important to the establishment of an effector memory T_H2 cell responses upon antigenic rechallenge. It was recently demonstrated that ILC2-DC cross-talk is necessary for the recruitment of effector memory T_H2 $CD4^+$ T cells into the lungs or skin of sensitized mice after allergen rechallenge, in which ILC2-derived IL-13 promoted the production of T_H2 cell–attracting chemokine CCL17 through $IRF4^+CD11b^+CD103$ DCs (*79*). Thus, ILC2 programming of sentinel DCs is critical to the establishment of an effector memory T_H2 cell response to allergens at barrier sites. Tissue-resident memory T cells can also function to alert and recruit other immune components upon rechallenge, although the presence of tissue-resident T_H2 memory cells in the airways had not previously been proven. However, a recent study highlighted the IL-2–dependent accumulation and persistence of tissue-resident T_H2 memory cells in the lung after exposure to HDM allergen and demonstrated that this population was sufficient to drive asthma-associated pathology (*80*).

Heterogeneity and plasticity in a T_H2 cell response

T_H2 cells are conventionally defined as a lineage that produces IL-4, IL-5, IL-13, and IL-10 while expressing transcription factor GATA-3. This is an oversimplification because there is considerable heterogeneity in T_H2 cytokine profiles and functionality. T_{FH} cells are a $BCL\text{-}6^+$ $CXCR5^+$ lineage that constitutes the primary producers of IL-4 in lymphoid tissue, where they operate within germinal centers to provide B cell help to support antibody class switching (*81*). Conversely, TGF-β can reprogram T_H2 cells in combination with other cytokines to drive their differentiation to IL-9–producing T_H9 cells (*82*). Single-cell analysis of in vitro polarized $CD4^+$ T cells has demonstrated intercellular heterogeneity in which multiple and variable type 1 and 2 cytokines can be expressed simultaneously in an individual T cell (*83*). TSLP-activated DCs have been shown to prime naïve human peripheral blood $CD4^+$ T cells to an "inflammatory" T_H2 population that produces IL-4, IL-5, and IL-13 but no IL-10 and high amounts of TNF-α in a process that was dependent on TSLP-induced OX40L expression (*84*). Furthermore, an inflammatory subtype of antigen-specific T_H2 cells that express CD161 have been demonstrated to be driving pathology in allergic disease and deleted during allergen-specific immunotherapy (*85*). Subsets of T_H2 memory cells that coexpress GATA-3 and RAR-related orphan receptor–γt and produce T_H2 and T_H17 cytokines have also been shown to accumulate in the blood of atopic asthmatics and the allergic lungs of mice (*86*). These IL-17–producing T_H2 cells have been postulated to represent the key pathogenic population promoting exacerbations of allergic asthma. It is conceivable that the plasticity within T_H2 cells could yield "pathological" and "protective" responses, raising the question as to what drives this differential and whether is it possible to alter this balance.

TYPE 2 RESPONSES: HOMEOSTATIC VERSUS PATHOLOGICAL

Type 2–mediated pathology was thought to be an inappropriate triggering of an immune pathway that evolved to provide protection against helminth infection. However, a more contemporary view is that type 2 responses have a more general role in defense against noxious environmental stimuli as well as being key to host immunosurveillance at barrier sites (Fig. 3).

Is a type 2 response a regulator of normality?

The eosinophilic pathology characteristic of a type 2 immune reaction occurs as a consequence of an inappropriate immune response to an allergen or irritant, or as an organized response to initiate a program of tissue repair to mitigate the collateral damage associated with a helminth infection. However, an alternative view suggests that type 2 immunity may be of benefit to the host even apart from immune defense against helminth infections (*6*). The vast majority of allergic reactions occur at the interface of the body with the external environment—at the skin and mucosal surfaces. Thus, type 2 immune reactions have been described as a method of protection against noxious substances. Local immune cells resident at barrier sites are strategically placed to monitor the local environment. They have the capacity to recognize antigens displayed within tissues after a variety of stressors and respond quickly and efficiently without the need for clonal expansion. The effects of a type 2 response at our surface tissue sites play important roles in eliminating, restricting, and neutralizing noxious environmental substances or triggers as well as repairing the damage caused and minimizing inflammation (*87*). Thus, the overall function of type 2 inflammation can be thought of as regulation of tissue homeostasis and of the ensuing response if the epithelial barriers have been breached. It has been proposed that allergic immune reactions actually evolved to gauge the nature and quality of the local environment, activate a deterrent response, and enforce a change of environment whenever allergies are encountered (*6*).

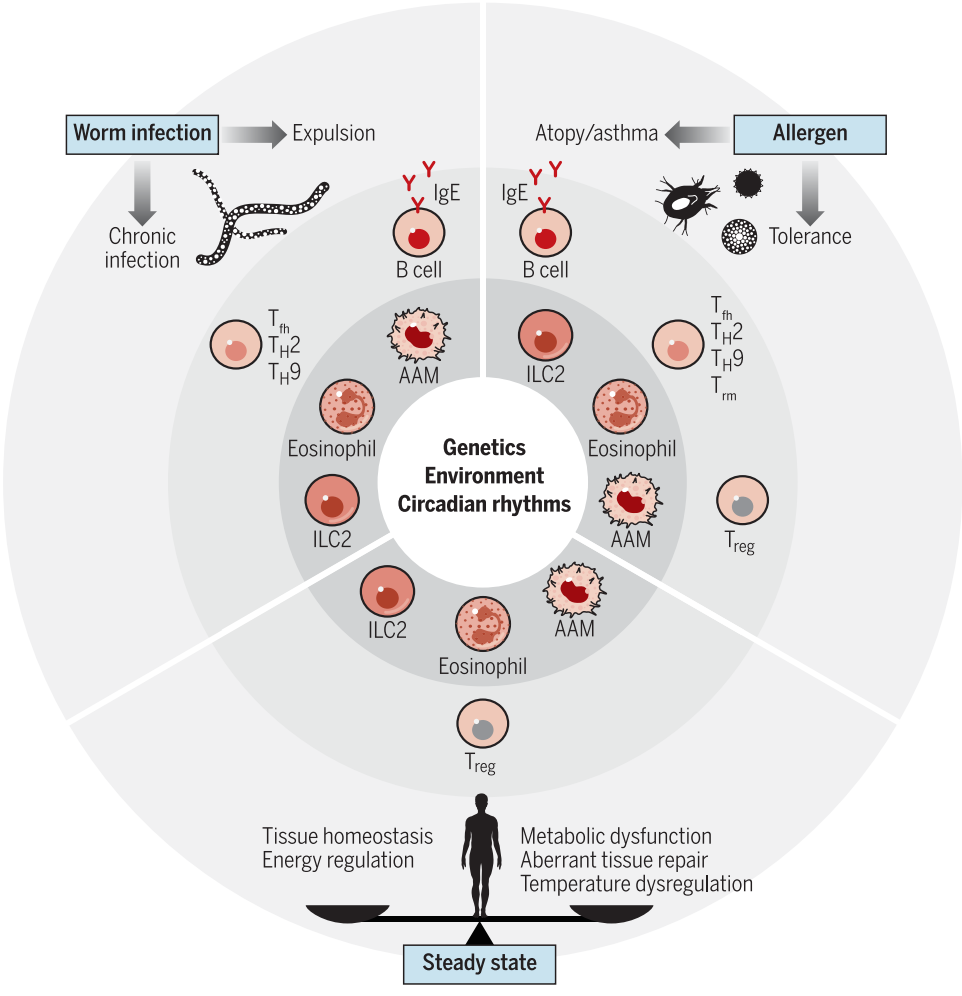

Fig. 3. Type 2 immunity contributes to both homeostatic and pathologic processes. Cells associated with type 2 immunity—eosinophils, ILC2, and alternatively activated macrophages (AAMs)—are important for basic metabolic processes required to maintain thermostatic and metabolic homeostasis and to drive pathology during allergic disease and facilitate clearance of parasitic worms. These individual processes seem to be distinguished by virtue of the adaptive cells involved. T_{reg} cells influence maintenance of homeostasis, whereas different effector T cell subsets direct the nuances of pathological immune reactions.

A distinct example of a noxious stimulus might be change in temperature. Thermoregulation has been proposed to involve an innate type 2 immune circuit that incorporates ILC2, eosinophils, and type 2 cytokines as vital controllers of adipocyte precursor number and fate, as well as overall adipose tissue homeostasis (*88*). Acclimatization to environmental cold is orchestrated by this type 2 immune cellular circuit coordinating with cytokines (IL-33, IL-4, and IL-13), which sequentially regulate the expansion, commitment, and differentiation of adipocyte precursors into beige adipocytes. This "beiging" process leads to increased energy expenditure and decreased adiposity (*89*). This innate type 2 immune metabolic circuit also exerts a critical role in the regulation of energy metabolism. Eosinophils and alternatively activated macrophages reside in visceral adipose tissue (VAT), where they promote insulin sensitivity and lean physiology (*48*). These innate immune effects are maintained in the VAT by ILC2, and any dysregulation in these relationships results in obesity, insulin resistance, and a decrease in oxidative metabolism, thus affecting energy expenditure. Proof that IL-33 is vital to maintain metabolic health comes from mice in which IL-33 was knocked out, who developed metabolic abnormalities even if kept on a normal diet (*89*). Local IL-33 production promotes ILC2 function and T_{reg} cell maintenance in the VAT, whereas exogenous IL-2 expands the T_{reg} cell and ILC2 pool (*90*). Moreover, ILC2s are also present in human white fat, and their activation is decreased in obese individuals. This ILC2/IL-33–mediated pathway that maintains metabolic homeostasis is counter-regulated by IFNγ, which inhibits IL-33–induced activation of ILC2 and accumulation of T_{reg} cells in infected tissue and adipose tissue. This IFNγ-driven repression intensified with age and also with obesity but would likely be beneficial during infection to divert metabolic effort into maximizing the efficiency of host defense pathways against rapidly proliferating microbes (*90*).

Eosinophils are resident within the gastrointestinal tract and are maintained within this location via secretion of IL-5 from local ILC2s (*27*). Eating increases levels of VIP, and because ILC2 express the VIP receptor VAPC2, they are activated to release IL-5. Thus, secretion of IL-5 follows strong circadian patterns and is regulated by food intake. Although these tissue-resident ILC2s clearly play a role in basal eosinophil production and accumulation in the healthy gastrointestinal tract, it is not known precisely what influence local eosinophils and ILC2s have on nutrient uptake. In addition, local microbiota likely influence the phenotype and function of immune cells within this circuit, affecting their ability to both maintain metabolic homeostasis and cope with perturbations generated during inflammatory reactions.

Type 2 pathology is driven by both innate and adaptive immunity

The characteristic hallmark feature of type 2 inflammation is the balance of granulocytes recruited to the inflammatory site. A type 2 response is characterized by eosinophil recruitment rather than neutrophils, which are more generally associated with viral or bacterial infections. These eosinophils are thought to be recruited via eotaxin driven by IL-13 expression and maintained within tissues by IL-5. As discussed above, the discovery of ILC2s challenged this view because they are able to release large amounts of these cytokines and facilitate many pathophysiological features of a type 2 immune response—potentially even in the absence of an adaptive immune system (*91*). Furthermore, it has been suggested that ILC2 cells are instrumental in facilitating T_H2 differentiation to generate an optimal T cell response (*64*, *67*, *68*), although contention exists in aspects of this work (*65*), highlighting the necessity of further studies. Considering this body of work as a whole, it is important to note that many of

these studies were executed by using the enzyme papain rather than an actual allergen. Although some features were also exhibited with acute delivery of dust mite or fungal allergens, most of the experiments were performed with papain, and intact enzyme activity was found to be critical (*64*). This enzymatic activity promotes release of IL-33, and although this may also occur during worm-induced tissue damage, it would be interesting to determine whether similar pathways operate with physiologically relevant allergens. This is an important point because ILC2 activation was found to be dependent on T_H2 cells after chronic exposure to HDM (*92*). Moreover, accumulation of ILC2s in the airways was independent of IL-33. In this HDM-driven model, ILC2s were not found to be an early source of type 2 cytokines but rather follow the lead from T_H2 cells. Full-length IL-33 was recently described as an environmental sensor, detecting proteolytic activity associated with a spectrum of allergens encompassing bacteria, fungi, mites, and pollens (*40*). Allergen-derived proteases rapidly cleaved full-length IL-33–facilitating ILC2 activation, whereas prevention of this cleavage prevented development of allergic-mediated pathology. Therefore, although within tissues T_H2 cells and ILC2s differentiate independently, they also drive overlapping effector pathways contingent on the availability of the local tissue-derived alarmin signals. In circumstances in which both T_H2 cells and ILC2s are present, the relative contribution of each to the ensuing pathology is dependent on the balance in numbers of each cell type, as well as the amount of GATA3 and ST2 that they express. Importantly, T_H2 cells are capable of innate functions according to the stimulus encountered and contribute to both allergic pathology and helminth infection (*93*). In addition, loss of ILC2s does not affect T_{FH} function, T_H2 cell priming in the lymph nodes, or acquisition of T_H2 effector function in tissues (*65*). Collectively, these data change our view of innate and adaptive immunity being distinct entities and present a concept that interaction between various arms of the system facilitates the most effective immune response, but the nuances of each reaction are contextual, set by individual environmental circumstances.

Do type 2 responses regulate the balance between repair and remodeling?

A type 2 response has been considered as a counterbalance for tissue-damaging inflammation initiated by type 1 immune responses. For example, type 2 inflammation is triggered as a consequence of helminth infection to instigate a program of tissue repair to mitigate the damaging effects of the worm migrating through vital organs such as lungs and the liver (*94*). Thus, the normal inflammatory response to harmful stimuli is followed by a phase of repair and regulation to restore tissue homeostasis. This wound-repair response relies on generation and deposition of extracellular matrix proteins such as collagens and fibronectin around the damaged area. These connective tissue proteins may be secreted by immune cells or by myofibroblasts, which migrate into the area or expand as a result of proliferation. Although this process ordinarily allows for efficient healing, chronic inflammation can lead to exaggerated repair mechanisms, which involves uncontrolled myofibroblast differentiation and activation coupled with excessive collagen deposition, ultimately leading to fibrosis and impaired organ function (*95*). The signals that down-regulate the repair cycle and prevent this tissue-damaging fibrosis and scar formation are not well understood.

The initial trigger for genesis of repair pathways are not well understood, but increasing evidence confirms that, at mucosal surfaces, the barrier epithelial cells and underlying stromal cells are active immunologically and cooperate with immune effector cells to stimulate inflammation and repair in parallel or, in some diseases, promote exaggerated inflammation and abnormal remodeling. Located at the barrier between tissue and the external environment, mucosal epithelial cells are ideally placed to act as sensors: sampling and reacting to environmental change. Their ability to secrete a triad of alarmin cytokines—IL-25, IL-33, and TSLP—places them in a central role for directing both inflammation and repair processes. Although each of these cytokines has well-described roles in the development of type 2 inflammation, each has also been described as contributing to tissue repair and harmful remodeling in a variety of different organs and diseases (*95*). Expression of IL-33, IL-25, and TSLP has been described in tissue from a variety of different fibrotic diseases and may influence development of remodeling via accumulation of ILC2 within the tissue or by directly facilitating extracellular matrix production (*96*–*98*). The relationship between inflammation and tissue remodeling was examined by targeting these epithelial-derived alarmins by neutralizing antibodies or knockout mice in a variety of different models of tissue fibrosis. Collective disruption of IL-33, IL-25, and TSLP was necessary to suppress tissue fibrosis driven by either helminths or allergens (*99*). Using combinations of antibodies with specific knockout mice has been used to show that this triad of cytokines exert overlapping effects (*99*). This highlights the degree of redundancy in the progression of type 2 pathology. By contrast, blockade during the initial establishment of inflammation was protective and suggests that early intervention would be necessary to prevent fibrosis developing. However, the role of each individual cytokine varied according to the type of disease and the particular tissue environment.

Many of the cells involved in the development of type 2 immune reactions also have roles in wound repair. T_H2 cells and ILC2s secrete IL-4 and IL-13, which are vital for the generation of alternatively activated macrophages that not only contribute to the repair process but also, in some instances, can directly affect matrix regulation via generation of specific proteases—for example, the matrix metalloproteinase family. Although tissue-resident macrophages exhibit an alternatively activated phenotype, recruited monocyte-derived macrophages also readily adopt this phenotype given the cytokine milieu that is characteristic of type 2 inflammation. These macrophages are then exquisitely sensitive to IL-4 and IL-13 because of their expression of IL-4Rα (*100*). The presence of apoptotic cells gives an additional signal to the macrophages to initiate a program of tissue repair (*101*). IL-4Rα$^+$ macrophages [Mφ(IL-4)s] express a distinct set of molecules that are also involved in wound repair and metabolism: α1 type 1 collagen, together with the chitinase-like molecules YM1, Relmα, and arginase. Collagens are vital to remodel the tissue and, in conjunction with Relmα, form a lattice-like matrix for tissue regeneration and repair. Tissue-specific soluble collagens act via the surface receptor unconventional myosin 18A to drive repair. Surfactant protein A in the lung and C1q in the peritoneum and liver enhance IL-4–dependent macrophage activation and proliferation (*102*). The expression of chitinase-like proteins (CLPs) by Mφ(IL-4) is thought to provide a link between type 2 inflammation and a neutrophil/IL-17 pathway to promote tissue repair. Tissue damage leads to secretion of CLPs, which elicit IL-1 release, leading to enhanced IL-17 secretion and downstream neutrophil recruitment (*100*). In addition, CLPs can enhance type 2 cytokine secretion from T_H2 cells and suppress IFNγ production. Although it is accepted that neutrophils and Mφ(IL-4) collaborate to facilitate the killing of worms, the role of neutrophils during pulmonary allergic type 2 immunes responses is less clear.

Depletion of macrophages in the airways leads to enhanced allergic immunity (*103*) and diminished worm expulsion (*104*).

Tissue-resident ILC2s are also ideally placed to promote wound repair, as exhibited by their role in wound healing after respiratory viral infection via the secretion of the epidermal growth factor (EGF) cytokine family member amphiregulin (*105*). Amphiregulin/EGF receptor (EGFR) is emerging as a key pathway regulating type 2 inflammation and repair. Expressed by a range of innate and adaptive cells including eosinophils, mast cells, basophils, and some CD4 cells, amphiregulin can promote cell proliferation as well as differentiation and facilitates cross-talk with EGFR-expressing epithelial cells to modulate repair programs (*106*). An elegant series of studies showed that treatment with IL-33 or transfer of ILC2 ameliorated intestinal inflammation via an amphiregulin-dependent pathway, leading the authors to hypothesize that cytokine cues from damaged gut epithelial cells activated local innate cells to secrete growth factors essential for innate lymphoid cell–dependent restoration of epithelial barrier function (*107*). In the lung, however, the picture is less clear. ILC2s have been shown to disturb pulmonary barrier integrity, disrupting tight junctions via secretion of IL-13 (*108*). Exposure to the fungal allergen *Alternaria alternata* induces the secretion of amphiregulin in the lung, and its cognate receptor, EGFR, is expressed in lungs from adult asthmatics, but it is unclear how the amphiregulin/ILC2 pathway contributes to the remodeling process during allergic inflammation.

Resolution of inflammation and tissue repair is necessary for restoration of tissue architecture, but if unchecked, tissue remodeling can lead to scarring and impaired organ function. The relationship between repair and inflammation and the signals required to reduce repair and thus prevent fibrosis are not well understood. Recent discoveries showing that metabolic phenotype regulates cell phenotype and function may hold a clue as to the mechanisms underlying this switch. In particular, Mφ(IL-4)s are thought to be critical in the decision process. Generally, tissue-resident macrophages display an anti-inflammatory phenotype and are thus well placed to initiate repair. In the gut, macrophages express IL-10, which limits inflammation, and suppress the metabolic program that is usually associated with proinflammatory pathways. Defective IL-10 signaling in macrophages facilitates the switch from oxidative phosphorylation to glycolytic metabolism and enhanced inflammation (*109*, *110*). Enhanced utilization of glucose is characteristic of the metabolic signature of Mφ(IL-4), and this switch from fatty acid oxidation to oxidative phosphorylation is critical for Mφ(IL-4) activation and thus the ensuing contribution to repair (*111*). However, the exact consequences of this bioenergetics change on particular growth factors or cellular pathways are not yet clear. Still, clarity regarding these processes is critical to be able to control successful resolution of inflammation and tissue repair while preventing harmful fibrosis and organ compromise.

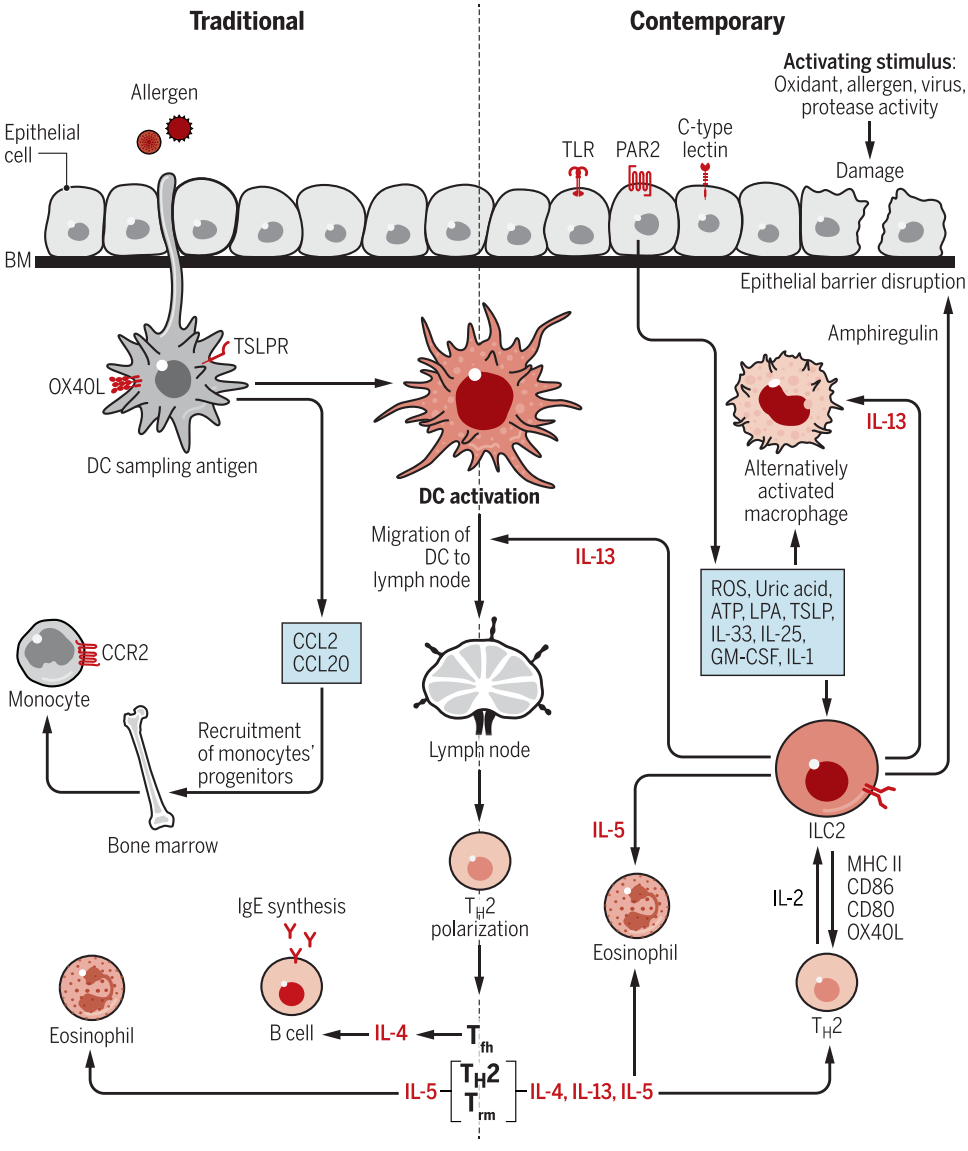

Fig. 4. Broadening our view of type 2 immune reactions. The discovery of ILC2s has radically changed our view of type 2 responses as a process that regulates immunity to allergens and helminths into one of a vital rheostat for maintenance and restoration of homeostasis after environmental stimuli. The ability of ILC2 to sense the local environment and interact with a panoply of immune and stromal cells enables them to take center stage in the fight to maintain health and prevent disease. ATP, adenosine 5′-triphosphate; GM-CSF, granulocyte-macrophage colony-stimulating factor; LPA, lysophosphatidic acid; ROS, reactive oxygen species.

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CONCLUSION

Our contemporary view of what directs and defines type 2 inflammation better appreciates the complex microenvironmental cross-talk between resident and inflammatory cells, which enables the sensing of diverse extrinsic stimuli and the ensuing elicitation of a tightly regulated, potentially heterogeneous, tissue-specific response. The seminal discovery of ILC2s

has firmly positioned them as a hub juxtaposed with DCs and T_H2 cells in a decision-making algorithm that responds to microenvironmental needs to elicit an appropriate effector program. This ILC2-DC-T_H2 axis is informed and guided by diverse cues received by disparate populations of tissue-resident sentinels with prominent roles ascribed to the epithelium and, more recently, sensory neurons. Subsequently, a complex cross-talk between ILC2s, DCs, and T_H2 cells, as well as resident and infiltrating cells, functions to direct and fine-tune the initiated type 2 response through regulatory circuits that reinforce and restrict its magnitude and focus (Fig. 4). In addition, it is clear that type 2 immune reactions are contextual and dependent on a wide variety of factors, including age of individual, health, and nutritional status, and as such, we see a graded spectrum of responses with substantial heterogeneity. Although type 2 immunity was initially linked to host defense against helminths or occurs because of a loss of tolerance to environmental proteins, our contemporary view is that type 2 responses may have broad applicability in immunosurveillance at tissue barrier sites to noxious environmental stimuli and the instigation of tissue-specific effector and repair responses, with the ultimate goal of restoring tissue homeostasis.

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