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The ins and outs of innate and adaptive type 2 immunity

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Abstract

Type 2 immunity is orchestrated by a canonical group of cytokines primarily produced by innate lymphoid cells, group 2, and their adaptive counterparts, $CD4^+$ helper type 2 cells, and elaborated by myeloid cells and antibodies that accumulate in response. Here, we review the cytokine and cellular circuits that mediate type 2 immunity. Building from insights in cytokine evolution, we propose that innate type 2 immunity evolved to monitor the status of microbe-rich epithelial barriers (outside) and sterile parenchymal borders (inside) to meet the functional demands of local tissue, and when necessary, to relay information to the adaptive immune system to reinforce demarcating borders to sustain these efforts. Allergic pathology likely results from deviations in local sustaining units caused by alterations imposed by environmental effects during postnatal developmental windows and exacerbated by mutations that increase vulnerabilities. This framework positions T2 immunity as central to sustaining tissue repair and regeneration and provides a context towards understanding allergic disease.

eTOC

Type 2 immunity is orchestrated by a canonical group of cytokines and both innate and adaptive immune cells. Locksley and Molofsky review the cytokine and cellular circuits that mediate type 2 immunity and propose a conceptual framework that places T2 immunity within the mechanisms that sustain tissue repair and regeneration. Allergic disease is discussed in this context.

Introduction

Allergic pathology consists of a constellation of syndromes - predominantly at barrier tissues – linked by immune responses to otherwise innocuous environmental antigens that result in exaggerated attempts to restrict offending agents to the external space while reinforcing avoidance behaviors to limit future exposure[1]. Whereas many allergic diseases, such as atopic dermatitis (eczema), conjunctivitis, hay fever (rhinitis), asthma and food allergy are

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managed by combinations of avoidance and therapeutics, control is often incomplete, and can be refractory and progressive, leading to life-threatening conditions such as anaphylaxis, airway mucus impaction and tissue fibrosis. Although avoidance mechanisms can have evolutionary advantages (e.g., pain, itch), the rising prevalence of diverse allergic disorders, particularly in developed countries, raises questions of how this arm of immunity has become increasingly dysregulated in modern humans.

Substantial research over the past decades has identified the key role for type 2 immunity and type 2 cytokines in allergic pathology. Although clinical endotypes exist across the spectrum of allergic diseases, with typical type 2 immunity more prominent in younger patients and less apparent in some adult populations[2], the association of type 2 immunity with allergic pathology has been established by extensive animal research[3], GWAS associations[4], illuminative mutations of key transcription factors[5,6], and the therapeutic successes of biologics that target components of type 2 immunity among patients across the allergic disease spectrum[7,8]. We focus this review on type 2 cytokines as effectors of allergic pathology with an attempt to understand how these cytokines evolved in vertebrate immunity; developmental windows that accompany the ordered waves of hematopoietic ontogeny and tissue residency by immune cells that express these cytokines, which could define periods of later vulnerability; and how insights regarding the positioning and elaboration of type 2 cytokines by innate lymphocytes might illuminate deployment of these programs by adaptive lymphocytes that could account for the prevalent conscription of type 2 immunity by allergic pathology occurring later in life.

Evolution and the type 2 cytokines

The crux of type 2 immunity resides within a 600 kb region of human chromosome 5q31 and the syntenic region on mouse chromosome 11 that encompasses the type 2 cytokine locus (Figure 1A). Here, the core type 2 cytokines IL-4, IL-13 and IL-5 reside bordered (~ 2.55 Mb telomeric of IL-4) by IL-9 (in human, although located at a syntenic region of chromosome 13 in mouse) and (centromeric) by GM-CSF and IL-3, which share signaling using the common beta chain with IL-5. Each are members of the short-chain 4α-helix bundle class I cytokines, all of which are involved in immunity, and distinct from long-chain class I cytokines, such as growth hormone, erythropoietin, prolactin, leptin and the gp130 family cytokines that have diverse roles in development, hormone regulation, hematopoiesis and neuropoietic differentiation, as well as immunity, and comprise the evolutionarily older members of this cytokine family[9]. Receptors for the short- and long-chain class I cytokines, as well as the class II cytokines, comprising type I, II and III Interferons and the IL-10 family members, signal primarily via associated JAK kinases to recruit and phosphorylate STAT proteins, which form homo- and heterodimers via SH2-phosphotyrosine interactions, translocate to the nucleus and bind to specific DNA elements to induce chromatin structural changes and target transcription of hundreds to thousands of genes[10,11]. Transcriptional targets include the SOCS (suppressors of cytokine signaling) family proteins that feedback to negatively regulate the pathway, which is also controlled during homeostasis by a variety of receptor, cytoplasmic and nuclear phosphatases.

Although individual components appear earlier[12], the composite cytokine/receptor/JAK-STAT/SOCs pathway appears evolutionarily first in Bilateria (animals with bilateral symmetry as embryos), as best studied in the fruit fly. Drosophila has three chromosomally-clustered class I cytokines - Upd (Unpaired), Upd2 and Upd3 – and a single receptor (Dome), JAK (Hopscotch), STAT (Stat92E), and SOCS (Socs36E). Although cytokine components of type 2 immunity appear coincident with adaptive immunity, the fly Upd cytokines, which are more closely related to IL-6 and leptin, illustrate early roles for the pathway in tissue maintenance and homeostasis in response to perturbation, including by pathogens, at least in part by interactions with tissue stem cell compartments through effects on cell fate determination, migration, proliferation and planar polarity[13]. In the midgut (small intestine equivalent), Upd2 from intestinal stem cells (SCs) and Upd2 and Upd3 from mature enterocytes cooperate with Notch signals to upregulate Sox21a, promoting transition to enterocytes from the intermediate enteroblasts, which accumulate in the absence of STAT92E[14]. Following injury or infection, Upd3 is upregulated in damaged enterocytes, prompting proliferation of intestinal SCs, in part through induction of epidermal growth factor receptor (EGFR) ligands from adjacent muscle cells, which accelerates transition of enteroblasts to enterocytes required for healing. Activation of body cavity phagocytic plasmatocytes (macrophages) induces Upd, which further upregulates visceral muscle EGFR ligands as well as antimicrobial peptides for dissemination from the fat body. Upd induction in healthy cells adjacent to damage is also required for proper regeneration after injury to the wing disc; additional examples exist in both somatic and germ cells[15]. Upd2 and Upd3 also link neural and hematopoietic perturbations with metabolic pathways targeting insulin sensitivity and mobilization of tissue glutamate and lipid stores necessary for redirecting resources to meet local demands[16]. Although caution is warranted in generalizing from evolutionarily early innate IL-6-like cytokines, class I cytokines likely evolved as local signals that sustain tissue homeostasis and are amplified when needed by recruited immune cells to regulate target cell proliferation, metabolism, survival and fate determination to restore structural and functional integrity. As such, intimate relationships with peripheral stem cell compartments might be expected[17].

Type 2 cytokines are present in teleost fish, descendants of the earliest jawed vertebrates containing an adaptive immune system that depends on lymphocyte antigen receptors somatically diversified by RAG genes. Although IL-4 and IL-13 are separate in mammals, teleost fish have a single IL-4/IL-13 homolog that is present in multiple copies on different chromosomes, perhaps reflecting additional whole genome duplication in teleost, and that may represent the ancestral cytokine that duplicated to generate the distinct IL-4 and IL-13 loci[18]. The discovery of somatically diversified variable lymphocyte receptors (VLRs) mediated through activation-induced cytidine deaminase (AID)-driven gene conversion in jawless vertebrates (lampreys, hagfish) has furthered recognition of adaptive immunity as a hallmark of all vertebrates and facilitated identification of homologous cytokine networks that evolved to orchestrate the increasing complexity of the immune system. Despite their structural similarities, the short-chain class I cytokines lack interspecies sequence conservation, which has hindered identification of cytokine homologs in distant species. To circumvent this, an orthogonal approach was used to identify cytokine receptors instead of cognate cytokines to infer the ‘minimalist’ cytokine network needed to support

adaptive immunity (Figure 1B). Genomic and transcriptomic mining of the lamprey genome identified five receptor orthologs of short-chain class I cytokines, including IL7RA, IL4RA and the three structurally similar X-linked (in human) genes, IL13RA, IL2RG (γC), and CRLF2 (TSLPR), among 23 total class 1 receptors (as compared to 34 in human)[19]. The authors predict existence of both type I (IL4RA/IL2RG) and type II (IL4RA/IL13RA) IL-4 receptors, but whether these are targets of a single IL-4/IL-13 homolog as found in teleosts or whether lamprey has diversified IL-4 and IL-13 by duplication remains unknown. Similarly, lamprey IL7RA/IL2RG and IL7RA/TSLPR predict the presence of IL-7 and TSLP, whereas absence of IL2RA and IL2RB predicts the absence of IL-2 and IL-15. The ancestral nature of TSLPR to CSF2RA (GM-CSF receptor) and IL4RA to CSF2RB (IL-3RB) suggests a GM-CSF/IL-3/IL-5-related cytokine and consistent with the historical identification of eosinophils in lamprey[20,21]. The deep evolutionary use of receptor swapping by IL2RG, IL13RA and TSLPR in lamprey suggests the possibility of novel cytokine-receptor pairings under conditions that remain undiscovered.

The presence of lamprey class II cytokine receptors for interferons and IL-10 as well as orthologs of Stat4 and Stat6 (along with Stat1 and Stat5) suggests that polarization to Th1 and Th2 cells was supported by this minimalist network. The later diversification of IL4RA to generate IL9RA (Th9), IL21RA (T follicular helper cells; Tfh) and IL2RB (regulatory T cells, Treg) that each pair with IL2RG to tune division of labor among adaptive helper T cells in jawed vertebrates was not apparent. Presumably, diversification was driven by evolution of private ligand-binding cytokine receptors capable of engaging IL2RG through its generally ‘bland’ interface devoid of highly charged bonds, thus promoting degenerate receptor sharing[22]. In summary, the core IL-4/IL-13/IL-5 type 2 cytokines and core signaling modules represented by IL4RA, IL13RA1, IL2RG and TSLPR have a deep evolutionary relationship with the emergence of adaptive immunity in vertebrates as supported by studies in jawless vertebrates that use alternative strategies to achieve antigen receptor diversification. Although none of the type 2 core cytokines are required for hematopoiesis, key roles for IL-4/IL-13 in alternative macrophage activation, IL-13/IL-5 in eosinophil generation and accumulation, IL-3/IL-4/IL-9 in mast cell/basophil biology, GM-CSF in myeloid cell activation, and IL-3 in plasmacytoid DC activation support mechanisms by which type 2 cytokines ‘tune’ resident and recruited hematopoietic cells to reshape local tissue environments, and may have contributed to diversification of the locus[23].

Layered ontogeny and differentiation of type 2 lymphocytes

The type 2 cytokines are dominantly expressed by type 2 lymphocytes and allergic diseases are manifest predominantly at cutaneous and mucosal borders. We next consider how type 2 lymphocytes become positioned during development and the milieu in which they operate.

The concept of layered ontogeny of the immune system, proposed by the Herzenbergs in experiments revealing the derivation of B1 and B2 cells from hematopoietic stem cells purified from temporally separate periods of development[24], is now known to apply to all immune cells and reflects the different needs of tissues during embryonic differentiation, independence after birth, and additional differentiation and maintenance through adult life. Organs are thus ‘layered’ by immune cells that originate during fetal life, that expand post-

birth and that regenerate from diverse precursors across life. Different organs have different numbers of constituents from each developmental period as related to the capacity for self-renewal and turnover and dictated by functional needs of the local microenvironments that regulate niche size and access. Best characterized for macrophages, such 'layering' underpins the transition of immune cells from early developmental needs centered around growth and plasticity (e.g., synaptic pruning by brain primitive macrophages or microglia) to the increased ability to respond to injury or pathogens in post-natal life (e.g., blood-recruited monocyte-derived macrophages), in part reflecting alterations in tissue niches corresponding with developmental needs[25]. Thus, fetal-derived alveolar macrophages adeptly recycle surfactants and outcompete adult bone-marrow derived macrophages in fetal alveoli whereas adult monocyte-derived alveolar macrophages outcompete fetal macrophages in the adult niche and respond more aggressively to inflammatory airway perturbations, although both subserve core tissue homeostatic needs[26,27]. Improved fate-mapping tools in mouse have extended contributions by primitive hematopoiesis (yolk sac and embryonic hemogenic endothelial-derived precursors prior to production of definitive pluripotent hematopoietic stem cells (HSCs)) to adult tissue resident macrophage populations that are self-renewing and minimally replaced by blood monocytes not only in brain and skin, but in most tissues, particularly among macrophage populations along delimiting border tissues as opposed to interstitial cells, which derive largely from monocyte-derived precursors; similar populations are present in human fetal and adult tissues[28]. Comparable trajectories occur among mast cells, important contributors in type 2 immune pathology by virtue of IgE-mediated survival and activation pathways, with developmental heterogeneity among connective tissue and mucosal mast cells[29,30].

Like macrophages, tissue-resident lymphocytes are also comprised of sequential contributions by primitive and definitive hematopoiesis. Lineage-tracing with inducible VE-cadherin, which temporally and indelibly marks hematopoietic descendants of hemogenic endothelia, reveals that mouse dendritic epidermal T cells, or DETCs, are yolk sac-derived, self-renewing and poorly replaced by adult bone marrow precursors[31]. In human thymus, fetal but not adult HSCs are intrinsically poised to develop relatively invariant germline-encoded sequences and mature effector function, in part due to suppression of terminal deoxynucleotidyl transferase (TdT) by RNA binding protein Lin28b[32,33]. Lympho-myeloid precursors (LMPs) are present among yolk sac-derived precursors[34,35] and clonal multipotent progenitors with lymphoid potential can be derived from human induced pluripotent stem cells that resembled progenitors in mouse yolk sac and had γδ T cell potential[36]. Studies in human fetus show widespread accumulation of both myeloid and lymphoid progenitors and mature cells in tissues, including macrophages, mast cells and NK cells, that had acquired tissue-specific transcript signatures at 10–12 weeks post-conception, as well as thymic PLZF$^+$ ILCs that were absent from postnatal thymus[37]. Importantly, developmental layering also occurs among CD4 and CD8 αβ T cells, reflecting the bifurcated origins from pro-definitive, lineage-restricted HSCs and definitive pluripotent HSCs before development in the thymus. In general, naive fetal T cells express a less-diversified TCR repertoire, distribute into tissues and acquire the capacity for rapid effector responses and activation by cytokines and pattern recognition receptors that resemble nonconventional T cells and ILCs, in part through developmental expression of microRNA

switches that regulate TCR sensitivity and metabolic activity[38]. The use of promiscuous germline-like receptors, poised effector function and lower activation thresholds positions these cells for rapid responses but also lower thresholds for peripheral Treg cell conversion or anergy in response to self-antigens or non-threatening antigens encountered after birth, and consistent with original observations of perinatal tolerance by Medawar[39] and later studies in humans[40]. Fate-mapping and transfer experiments of both CD4 and CD8 neonatal cells in mice revealed retention into adulthood as major constituents of induced tissue CD4 Treg cells[41] and rapidly responding tissue CD8 T cells that generated short-term effectors but not long-lived memory cells[42]. Developmental layering of adaptive T cells populates the neonatal environment with poised effector cells highly responsive to tissue perturbations but restrained by lower thresholds for regulatory conversion, ensuring the capacity to respond quickly to danger after birth while preserving tolerance to self and innocuous newly encountered environmental antigens. Long-term memory is not necessary in the developing fetus but becomes critical in adults, where CD8 T cells can persist as functional, long-lived memory cells well beyond a single lifespan[43].

ILC2s, like neonatal CD4 T cells, are poised for rapid effector responses. Temporally controlled fate-mapping reveals three waves of ILC2 accumulation in tissues during fetal, early post-natal and adult life in the mouse[44]. Fetal-derived ILC2s labelled between E16.5–18.5 are variably replaced over time in different tissues, although retention of discrete populations of self-renewing cells is apparent. Most ILC2s appear during the post-natal wave of expansion (d3-24 in mice) that occurs concomitant with activation of the effector program marked by expression of canonical type 2 cytokines and acquisition of tissue-specific transcriptomes. ILC2s from fetal liver or adult bone marrow derive from common lymphoid precursors (CLPs) through a series of intermediate precursors that sequentially extinguish alternative ILC fates, including α4β7 lymphoid precursors (α-LPs) and common helper-like ILC progenitors (CHILPs) before restriction into ILC2 precursors (ILC2p) and mature ILC2s[45]. Genes necessary for pan-ILC development, such as Gata3, Id2, Nfil3, Tox and Tcf7, are positioned in actively transcribed areas of euchromatin in CLPs, as opposed to genes involved in T and B cell commitment like Bcl11b and Ebf1, suggesting that default genomic organization in CLPs favors ILC development[46], with ILC2p differentiation and cytokine production mediated in part by utilization of unique GATA3 enhancer elements[47]. Commitment in ILC2p cells requires interactions of the Id2 promoter via DNA loops with cis-regulatory elements, designated locus control region-1 and -2 (LCR1, LCR2), that bound GATA3 and RORα, which are required for ILC2 development[48,49]; deletion of LCR1 or GATA3 and RORα binding sites in LCR1 ablates ILC2s with development block at the ILC2p stage that is rescued by Id2 lentivirus. LCR1-deficient mice are ILC2-deficient and show attenuated responses in lung models of allergic inflammation, including house dust mite, papain and IL-33; Th2 cells are normal but diminished in numbers at the conclusion of the experiments although in vitro Th2 differentiation is normal, revealing sustained expression of Id2 through LCR1 as critical for ILC2 differentiation but not for activation of the type 2 cytokine effector program[46]. Thus, the absence of developmental positioning and activation of ILC2s had effects on the temporal accumulation of effector Th2 cells but not their function.

The perinatal period in mouse is also notable by the appearance of a population of IL7R$^+$ lymphoid-primed multipotent progenitors (LMPPs) biased to produce ILC2s and T cells as compared to IL7R$^-$ LMPPs that generated common lymphoid progenitors (CLPs)[50]. Some IL7R$^+$ LMPPs express Rag and CCR9 consistent with early T cell precursors primed for thymic entry before the postnatal period of massive T cell expansion. Although generated in Rag-deficient mice, some ILC2s, like other ILCs and NK cells[51], can be fate-mapped for Rag expression and tissue resident ILC2s can express transcripts for rearranged TCR gamma chain with frameshift and premature stop mutations suggesting potential origin as non-selected T cells[52], and consistent with the appearance of embryonic thymic ILC2s from shared T cell precursors[53]. Although further work is needed with improved time- and lineage-stamping methods to exclude contamination by small numbers of ILC progenitors, these data suggest the possibility that ILC2s that expand in mice after birth derive both from direct seeding of hemogenic endothelial-derived tissue precursors and from thymic T cell-committed precursors, some of which fail γδ TCR selection, thus creating heterogeneity that is little explored[54]. Of interest, even such thymic-derived ILC2s express type 2 cytokines whereas successfully selected γδ T cells are primed to produce type 3 (IL-17A) or type 1 (IFNγ) cytokines[55].

While acknowledging the need for more definitive study, ILCs likely first emerge from hemogenic endothelial precursors during the transition of pro-definitive to definitive hematopoiesis and seed developing tissues essentially concurrent with colonization of fetal liver during a narrow developmental window, potentially creating bifurcating pathways for establishing distributed tissue ILC precursors while seeding fetal liver with fetal and pluripotent HSCs that support the needs of fetal and postnatal life, respectively (Figure 2). Although circulating ILC2p cells are more prevalent in human than mouse[56,57,58], the longer gestation in humans is associated with colonization of peripheral tissues by adaptive T cells that outnumber resident ILC2s at birth. Bone marrow-derived CLPs generated from definitive HSCs can adoptively replenish tissue ILC2 stores in mice, like systemic human precursors[56], by processes hastened by perturbation and resembling trajectories for monocyte-derived macrophages[59]. Despite the capacity for substantial functional tissue adaptation by adult ILC2 precursors[44,59], however, it is likely that specific properties of fetal-derived cells and/or fetal niches are temporally restricted to developmental windows and not fully recapitulated by adult precursors, as noted for macrophages[25], mast cells[60], LTic[61], nonconventional T cells[62,63], B1a cells[24] and adaptive T cells[38]. Hematopoietic reconstitution of humans genetically deficient in ILCs resulted in the slow reappearance of blood ILCs, including ILC2s[64,65], and loss of normal nasal mucosal homeostasis, thus hinting at non-redundancies of function[66]. As discussed below, the transition during birth and early postnatal life may be susceptible to misalignment between developmental and environmental demands on the immune system that can create pathways for subsequent organ pathology as predicted by consequences of ontogenic layering25,67,68.

Cellular and humoral aspects of type 2 immunity

Although not absolute, an intriguing difference in type 2 cytokine expression by ILC2s and *in vitro*-generated Th2 cells is the predominant expression of IL-13 and IL-5 by ILC2s (consistent with a role in maintaining eosinophils[69,70]) and IL-4 and IL-13 by Th2

cells[71] (where IL-5 expression increases with additional rounds of TCR stimulation[72]). Early studies used crossspecies comparisons of conserved noncoding sequences and DNase hypersensitivity sites to map key regulatory elements across the type 2 cytokine locus, leading to the epigenetic model of stepwise Th subset differentiation, including Th2 cells[73]. Incorporation of a locus control region in the 3'-end of the RAD50 gene between IL-13 and IL-5 in proximity to cytokine transcriptional domains was necessary to confer lymphocyte-specific expression[74]. Recent use of sophisticated methods for assessing gene regulation have added insights. Short-term activation of mouse lung ILC2s with IL-33 and Neuromedin U led to production of IL-13 and IL-5, whereas activation of splenic-derived, in vitro-generated Th2 cells with CD28/CD3 generated IL-4 and IL-13. Unexpectedly, stimulation resulted in ILC2 or Th2 lineage-specific three-dimensional reorganization of the locus imposing cohesion-associated insulator domains that apposed IL-13 and IL-5 in ILC2s but IL-4 and IL-13 in Th2 cells, respectively[75]. Thus, stimulation-dependent transcription factors acutely enforce geometrically divergent activation domains in the two cell types, which the authors tentatively attribute to lower SatB1 (special AT-rich sequence binding protein 1) levels in ILC2s as compared to Th2 cells. As the authors acknowledge, in vitro-generated Th2 cells are unlikely to mirror Th2 cells that mature in tissues with ILC2s and take on innate-like functions[76].

Lineage-tracing in transgenic mouse models reinforce the distinct functional and regional specialization of type 2 cytokine-producing lymphocytes. Cytokine-driven cell deletion by diphtheria toxin using IL-13-Cre or IL-5-Cre essentially phenocopy in the *N. brasiliensis* mouse model, with loss of tissue (goblet cell hyperplasia, eosinophilia) and functional (worm clearance) components of type 2 immunity, and implicating IL-13/IL-5-expressing ILC2s and Th2 cells. Of note, IL-4-mediated IgE production was unchanged or even enhanced, indicating little contribution by IL-13-producing cells to the humoral arm of type 2 immunity in this acute model[71,77]. Single-cell mRNA sequencing of cytokine-reporter^{+} Th2 cells from lung or mesenteric lymph node of *N. brasiliensis*-infected mice confirmed the segregation of IL-4^{+} Tfh lymph node cells from IL-4/IL-13+ and IL-4/IL-13/IL-5+ Th2 cells in lung tissue; tissue Th2s expressed markers typical of resident lung ILC2s, including CD25, ST2 (Il1rl1 component of the IL-33 receptor), Cysltr 1, and effectors like amphiregulin and IL-10[78].

These and other data support the compartmentalization of cellular and humoral aspects of type 2 immunity. The latter is dominantly mediated by IL-4 production (with some production of IL-13) by Tfh cells, together with B cell IgE production and FcεR1 on mast cells, basophils and populations of activated dendritic cells. In contrast, cellular type 2 immunity is dominantly promoted by IL-13 and IL-5 produced by ILC2s and Th2s (with some production of IL-4) in tissues, which mirrors widespread expression of the type II IL4RA/IL13RA1 receptor on diverse tissue cell types, including epithelia, endothelia, fibroblasts, neurons and muscle, but more limited expression on hematopoietic cells, like macrophages. Despite roles for IL-13 in human and mouse B cell IgE class-switching[79,80], the therapeutic efficacy of anti-IL4RA therapy (which blocks both cytokines) in targeting human allergic diseases may reflect the capacity to attenuate both arms of type 2 immunity, including IgE production and tissue eosinophilia that depends on IL-13-mediated stimulation of eotaxins and localizing endothelial adhesins that promote

tissue eosinophil entry[81]; indeed, anti-IL4Ra therapy is often accompanied by increases in circulating eosinophils. Selective anti-IL-13 therapeutics were less effective in asthma, perhaps due to lesser effects on IL-4-dependent IgE production (despite expression of IL-13Ra1 on human B cells) and/or interactions that affect binding to IL-13RA2, the decoy IL-13 receptor[82]; greater efficacy is seen in atopic dermatitis, where JAK inhibitors are also effective[83]. Diseases with high levels of tissue eosinophils, such as hypereosinophilic syndromes, eosinophilic vasculitis or locally infiltrative diseases like eosinophilic asthma or esophagitis, benefit from treatment directed at IL-5 or IL-5R that diminish tissue eosinophil burden directly[7,8], potentially limiting inflammation provoked by Charcot-Leyden crystals of galectin-10 oligomers[84]. Importantly, each of the biologics approved in the US for asthma (anti-IgE, anti-IL5, anti-IL5R, anti-IL-4RA, anti-TSLP), or atopic dermatitis (anti-IL4RA, anti-IL-13, JAK inhibitors), shows efficacy, that, while incomplete, corroborates the central role of the type 2 cytokines in allergic pathogenesis.

The ‘alarmins’ – thresholding type 2 immunity

The recognition of ILC2s was hastened by the earlier discoveries of IL-25 and IL-33, so-called ‘alarmins’ and members of the evolutionary ancient IL-17 and IL-1 cytokine families, respectively; each cause robust type 2 immune responses when injected into mice[85,86]. First described as a cell population during studies of IL-25[85,87], ILC2s were initially recognized as a distinct population of mesenteric adipose tissue-associated ILCs in mice and humans that released IL-5 and IL-6 spontaneously when maintained in IL-7 and markedly increased amounts of these cytokines with IL-13 when stimulated with IL-2 and either IL-33 or IL-25[88]. The cells were clustered along vessels in peritoneal mesentery surrounded by adipocytes and were activated by helminth infection to drive goblet cell hyperplasia and B1 cell expansion in association with increases in serum IL-5 and IL-13. Two publications that rapidly followed used engineered type 2 cytokine reporters to extend observations from this seminal paper. The first[89] used IL-13-eGFP reporter mice to make several sentient observations: (1) administration of IL-25 or IL-33 to SPF mice each resulted in redundant proliferation of IL-13-expressing innate lymphocytes, implicating ILC2s as the major responding cells; (2) ILC2s were activated in response to intestinal helminth infection (*N. brasiliensis*) by IL-25R- (driving early control) and IL-33R-dependent (additively affecting late clearance) mechanisms, revealing temporal nuances; (3) wild-type (WT) ILC2s but not IL-13-deficient ILC2s restored reactivity of IL-25 in IL-25R-deficient mice and restored the tissue type 2 response to *N. brasiliensis* in IL-25R-deficient and IL-25R/IL-33R-deficient mice, including goblet cell hyperplasia, eosinophilia and worm expulsion, implicating ILC2s as the necessary cell target driving early IL-13 release by alarmins; (4) the temporal delay of IL-13-producing Th2 cells in mesenteric lymph nodes in the absence of IL-25R was restored by either WT or IL-13-deficient ILC2s, indicating IL-13-independent effects of ILC2s on early CD4 T cell type 2 responses that ultimately developed even in the absence of ILC2 IL-13 production, and implicating ILC2s in optimizing the subsequent type 2 response. The third report[90] used IL-13-Cre mice to mark and delete IL-13-producing cells, identifying ILC2s as the major responding cells to systemic IL-25, IL-33 and after *N. brasiliensis* infection, while emphasizing the systemic presence of these cells in most tissues and scarcity in blood, presaging recognition of their dispersed, tissue resident phenotype[91].

Taken together, these observations (and many since) establish ILC2s as non-redundant sources of early tissue IL-13 and IL-5 that can be triggered by alarmins IL-25 and IL-33 to elicit type 2 immunity. As noted above, tissue ILC2s in mice accumulate predominantly during postnatal expansion driven by *de novo* generation of new cells and massive proliferation over the first 3–4 weeks of life in association with type 2 cytokine expression[44]. Although initial expansion of ILC2s is essentially normal in the absence of IL-33 or IL-25, activation is variably attenuated in different tissues. This period is characterized by widespread IL-33 expression implicated in post-birth developmental processes including mechanical deformation during breathing and alveolarization of the lung[92,93], neuronal development sculpted by brain microglia[94,95], and establishment of thermogenic properties in beige and brown fat[96]. IL-33 is a marker for human arterial hemogenic endothelia[97] and can drive maturation of endothelial-derived stromal cells to support bone marrow hematopoiesis[98] and mobilization of ILC2p cells from bone marrow[99]. Tissue Treg cells are deposited during this same period to adjudicate indifference to self-antigens by tissue adapted, clonally restricted $ST2^+$ Treg cells that participate in homeostasis and repair in adipose, skeletal muscle, and other organs[100] and mediate tolerance by attenuating IL-33 sensitivity among conventional naïve T cells during the neonatal period[101]. Peripheral Treg cells are induced at mucosal and cutaneous borders to facilitate tolerance to colonizing microbes and food antigens[102,103], enabled by a neonatal wave of specialized antigen-presenting cells to control type 3 immune responses[104]. As a nuclear-localized cytokine, the mechanisms facilitating release of IL-33 after cell damage or creation of transient pore-forming pathways remain actively investigated, while enhancement of IL-33 activity following cleavage by endogenous and environmental (allergen-associated) proteases are consistent with an active role in tissue remodeling in development and repair[105,106]. Although ILC2s have not been directly implicated in these processes, their accumulation across tissues during this developmental wave suggests coordination with systemically driven signal(s). Variants in IL-33 constitute a highly replicated risk for human allergic disease, particularly asthma, across diverse populations, and were localized to a 5 kb enhancer-blocking element with surrounding cohesion and insulator CCCTC-binding factor (CTCF) sites that supported long-range looping to the IL-33 promoter, potentially through enhanced binding of the transcription factor OCT-1[107]. IL-33 signaling promotes rapid increases of cytokine mRNAs by down-regulation of the mRNA degrading protein tristetraprolin[108]. Conversely, a rare loss-of-function IL-33 allele is associated with reduced numbers of blood eosinophils and diminished asthma risk[109].

In contrast to the widespread expression of IL-33, IL-25 is produced mainly by epithelial tuft cells, rare chemosensory cells primarily in mucosa, which in small intestine develop with weaning and maturation of the hepatic bile acid cycle to become important regulators of ILC2 activation while contributing to ILC2 responses at other sites during inflammatory states[110,111]. The basal ‘inflammatory’ state of ILC2s in the small intestine lamina propria reflects residence at a highly microbial-colonized border requiring high epithelial turnover; lamina propria eosinophils also display an unusual activated, regulatory phenotype, in part driven by IL-33, that suggests an integrated type 2 response to maintain homeostasis at a site critical for nutrient acquisition and commensal control[112]. TSLP, a third alarmin that can activate ILC2s, particularly in synergy with other alarmins, is expressed among

subsets of stromal, epithelial and dendritic cells, and is induced in keratinocytes in response to inflammation caused by vitamin D-like analogs[113]. Epidermal skin residency by ILC2s is regulated by both IL-7 and TSLP and the CCR6-CCL20 axis that mediates accumulation of epidermal Treg cells in neonatal mice where ILC2 activation impacts sebaceous gland homeostasis and itch perception by sensory neurons[114,115]. Differentiated tissue ILC2s express many positive- and negative-regulating receptors for eicosanoids, neuropeptides, neurotransmitters, cytokines and hormones that titrate activation thresholds by integrating inputs from multiple cell types that act synergistically with episodic signals from alarmins[116–122]. Although ILC2 numbers and cytokine transcripts are little affected in germfree or mice deficient in IL-25, ST2 or TSLPR[123], ILC2 effector function becomes attenuated in the latter, suggesting roles for alarmins in maintaining responsiveness among tissue ILC2s; similar effects are seen in tissue Th2 cells. Studies using cohorts of ST2-, IL-25- and TSLPR-deficient mice in various combinations revealed combinatorial effects on ILC2 activation and Th2 cytokine secretion; triple-deficient (TKO; ST2/IL-25/TSLPR-deficient) mice displayed defects in elaboration of type 2 cytokines in tissue resident ILC2s and Th2 cells[77,123,124], with loss of all 3 alarmins additively blocking type 2-mediated immune pathology[125], and consistent with initial studies using alarmin blockade in humans with allergic disease[7,8]. Alarmins thus constitute checkpoints regulating activation of ILC2s and Th2 cells in tissues. Of note, humoral type 2 immunity as assessed by IgE responses, Tfh differentiation and the appearance of IL-4-expressing cells in lymph nodes was normal in alarmin TKO mice[71,77].

Type 2 immune cell niches – barriers, borders and adventitial boundaries

Accumulation of ILC2s occurs at locations providing survival factors like IL-7 in combination with alarmins that threshold activation; interfering with the former precludes postnatal expansion[44,126]. Although mechanistic details are incomplete, stromal cells likely guide initial developmental positioning of ILC2p cells, in part by providing chemokines, tethering, and terminal differentiation signals like Notch. Following post-birth expansion in mice, ILC2s accumulate in at least three areas (Figure 3). (1) Barrier ILC2s localize beneath non-sterile epithelia in the cutaneous epidermis, upper respiratory tract, lamina propria of the intestines and the reproductive and lower genitourinary tracts. (2) Border ILC2s are distributed more uniformly across natural demarcations between tissues, including the dermal and submucosal fascial planes in skin and bowel that separate these tissues from underlying structures and along the epithelial-like mesothelial linings that surround the body cavities and internal organs of the chest and abdomen, such as the pleura, pericardium and mesentery. (3) Boundary ILC2s, present in most organs, are delimited by perivascular adventitial cuffs supported by specialized fibroblasts that constitutively express IL-33 and TSLP, often accompanied by lymphatic endothelial cells that express IL-7[127].

Boundary ILC2s reside in close apposition to fibroblasts, here called adventitial stromal cells (ASCs) but with many designations that share over-lapping characteristics (e.g.; mesenchymal stromal cells, fibro-adipogenic progenitor cells, multipotent stromal cells), in the outermost layers of intermediate-to-large blood vessels within an interstitial space accommodating inter-cellular interactions in an extracellular matrix (ECM)- and neuron-rich environment where interstitial fluid can accumulate before drainage by contiguous afferent

lymphatics[128]. Perivascular adventitial cuffs are in proximity to conduits linked with the unique functionality of the tissues where they reside, such as airways in lung, ducts in liver and pancreas, and dural sinuses in the meninges[127,129]. ASCs are usually PDGFRa$^+$, GP38$^+$ (podoplanin), Sca-1$^+$, although this phenotype is not entirely specific, and express IL-33, TSLP and CCL11 (eotaxin) in resting tissues. Their presence in multiple organs suggests an organizing principle for type 2 immunity; resident IL-5 reporter$^+$ Th2 cells localize similarly in organs where this has been studied. ILC2s and Th2 cells in adventitial cuffs are generally ST2$^+$TSLPR$^+$ while expressing low levels of IL-25 and IL-18 receptors. Adventitial niches are dynamically regulated by stromal – immune cell communication, with IL-7 and TSLP sustaining and IL-33 driving activation and proliferation of type 2 immune cells; stable, prolonged expansion of IL-33$^+$ ASCs after type 2 immune activation was curtailed by deletion of IL-5/IL-13-expressing immune cells[127], emphasizing the role of reinforcing crosstalk in fibroblast-immune cell homeostasis[130]. In white adipose tissue, PDGFRa$^+$ ASCs, also designated multipotent stromal cells or adipocyte progenitor cells, were the major source of adipose tissue IL-33 and CCL11[131,132], where ILC2 activation was also mediated by cell-cell contacts between LFA1 on ILC2s and ICAM-1 on ASCs[133] as well as by sympathetic neuron-mediated release of glial-derived neurotrophic factor (GDNF)[134]. Eosinophils recruited by activated ILC2s released nerve growth factor (NGF) that promoted sympathetic axonal outgrowth, potentially reinforcing the circuit[135]. At all sites, ILC2s accumulate in proximity to sensory and autonomic neurons and are tuned positively and negatively by neuropeptides[116], which with eicosanoids amplify thresholds for alarmin signaling and control differentiation trajectories among effector subpopulations[117,118]. Thus, boundary ILC2s, and likely resident Th2s, are organized within innervated regional niches structured by ECM-promoting interactive domains and bathed by interstitial fluid and metabolites reporting tissue-specific homeostasis, and in proximity to endothelial vascular access and lymphatic egress, thereby establishing a microdomain poised for integrating perturbations from multiple cell types within small functional units. Upon localization in niches promoting their maintenance, ILC2s (and resident Th2s) proliferate, likely through intrinsic autocrine and paracrine interactions that regulate clonal expansion[75,136,137,138]. In mice, upregulation of integrin αvβ3 on activated naive T cells promoted IL-2 and CD25 expression, leading to autocrine and paracrine Stat5 signaling, and differentiation to IL-13- and IL-5-secreting Th2 cells[139]; ablation of the integrin attenuated accumulation of lung Th2 cells while IL-4 expression remained unaffected. Integrin interactions promoted T cell-T cell interactions, which could contribute to clonality seen in tissue resident cells in mice and humans[78,140]. Regulation of stromal niche size and occupancy are not well understood, although feed-forward circuits that expand alarmin-producing cells, as noted above, and the marked pliability of tissues for lymphocyte residency suggest the potential for dynamic changes[141]. Tertiary lymphoid organs (TLO) in lung (induced bronchus-associated lymphoid tissue, iBALT), adipose (fat-associated lymphoid clusters, FALC) and other tissues can form in continuity with adventitial niches and expand the pool of alarmin$^+$ stromal cells resulting in protective or pathologic contributions to allergic disease in different contexts[142,143]. Roles for IL-13 and IL-22 in sequentially driving activation and proliferation of stromal precursors that nucleate TLO formation have been shown in both mice and humans[144].

Aside from adventitial cuffs, ILC2s are distributed at tissue-demarcating borders surrounding organs and along fascial-adipocyte planes beneath the dermis and lamina propria of externally exposed barrier tissues. These border ILC2s are typically ST2$^+$ and also in proximity to ASCs that can express IL-33[127]. In mesenteric adipose tissue, serosal IL-33$^+$ mesothelial cells respond to injury by activating resident border ILC2s, revealing a responsive interface to announce disruption[131]. Finally, barrier ILC2s, prevalent in upper respiratory tract, intestinal lamina propria and epidermis, are characterized by high-turnover and basal responses to non-IL-33-mediated activation, as discussed in the next section. In small intestinal lamina propria, barrier ILC2s constitutively express the IL-25 receptor and TSLPR whereas skin epidermal ILC2s express TSLPR and the IL-18 receptor, suggesting barrier-specific regulatory activity[123]. On an organismal scale (Figure 3), ILC2s are arranged with an ‘outside-in’ and ‘inside-out’ perspective with a shared cored program; outer barrier ILC2s integrate external perturbations with tissue signals to regulate activation, whereas inner boundary ILC2s are positioned to integrate organ-specific perturbations with tissue signals to regulate activation, and each is reinforced by internal border ILC2s responsive to loss of homeostasis by the overlying domains.

Following disruptive perturbations that exceed the homeostatic capacity of the local cellular network, ILC2s integrate alarmins with signals from multiple cell types, proliferate and mature along trajectories that promote interactions with circulating hematopoietic cells recruited to the tissue[59,145]; proliferating, activated ILC2s can upregulate S-1-P receptors and undergo retrograde trafficking via lymphatics to enter blood, although whether emigrants represent a subset of the total population is unknown[146]. Border ILC2s, where studied, are typically resident and self-renewing, with no clear evidence for egress, and may even have precursor relationships with barrier or adventitial boundary ILC2s, although further study is needed. Proliferation leading to tissue eviction can be driven by IL-33 or IL-25, and perhaps other activating signals, dependent on geographic differences in expression of the relevant alarmin and alarmin receptors by resident ILC2s[147]. Egress of mature ILC2s from tissue is accompanied by differentiation of locally embedded ILC2 precursors and entry of blood-borne precursors from bone marrow or other tissues, perhaps by creating space or freeing survival ligands, although the precise contributions of ILC2 precursors versus proliferating, mature effectors remains unclear. Activated migratory ILC2s can enter distal tissues and affect target tissues for many months; whether epigenetically modified ‘memory’ tissue ILC2s represent local, recruited, or combinations of cells from both bone marrow and perturbed tissues requires more granularity[59]. Although cohesive in principle, much regarding the mechanistic underpinnings of these processes requires further study.

Type 2 immunity and tissue homeostasis

Contributions of ILCs, including ILC2s, to tissue homeostasis and repair after injury have been described in numerous organs, including the intestines, lung, adipose tissues, skin, muscle, heart, brain and bone marrow[116,148]. Most studies involve genetically homogeneous mice under SPF conditions, which rely on resident ILC2s rather than tissue resident Th2 cells likely present in ‘wildling’ mice and humans[149]. However, the overlapping phenotypes of these cells support comparable functions, with caveats regarding unsuspected

developmental roles as noted above. Involvement of ILC2s and type 2 cytokines in regulation of epithelial barriers, repair and regeneration suggest proximity to peripheral tissue stem cell niches, specialized regenerative microdomains protected from external injury where intrinsic stem cell and extrinsic signals from cells and ECM interact to regulate stem cell fate in close approximation to lymphatic endothelia actively involved in these processes[150,151]; maintenance of tissue stem cell niches is critical for sustaining homeostasis and dysfunction is associated with senescence and aging[152]. Activated ILC2s can support aged or regenerating tissues[153,154,155] and effects of ILC2s in altering trajectories of stem cell compartments to affect barrier physiology reveal shared aspects that hint at principles that might guide this process.

The capacity for barrier ILC2s to alter physiology in response to external stimuli is well illustrated in the small intestine. Epithelial tuft cells in mucosal epithelia express multiple GPCRs, including GPR91, which binds succinate, a metabolite secreted by the protist *Tritrichomonas muris*, an intestinal commensal of wild mice[156]. Following detection of luminal succinate, tuft cells release IL-25, which activates lamina propria ILC2s, which constitutively express the IL-25 heterodimeric receptor, IL-17RA/IL-17RB, and release type 2 cytokines and amphiregulin[157,158]. In turn, IL-13 acts directly on crypt transit-amplifying cells to slow transit time, thus altering the tempo at which cells move into the gradient of BMPs that increases as cells ascend the villi[159]. Secretory cell fates arise after fewer divisions than absorptive enterocytes such that prolonging ‘dwell-time’ at critical thresholds for differentiation favors entrance into the secretory cell lineage and increased numbers of goblet and tuft cells. The secretory cell bias, together with increased gut motility, underpins the ‘weep-and-sweep’ response to luminal parasite infestation[160,161]. Helminths like *N. brasiliensis* produce succinate but engage additional tuft cell receptors responsible for IL-25 release[158], while *Heligmosomoides*, which enters the intestinal lumen after maturation from subepithelial granulomas, targets the BMP gradient to attenuate the host epithelial response[162]. Epithelial tuft cells express many tissue-specific GPCRs; type 2 taste receptor cells (sweet, bitter, umami) share features with tuft cells, including developmental dependence on Pou2f3, expression of IL-25, and overlapping signal transduction cascades, underscoring the adaptable capacity of this sentinel chemosensory system[163]. The small intestinal ILC2 circuit is restrained intrinsically by negative feedback on IL-25 receptor signaling, primarily by A20 (TNFAIP3) but also CISH and SOCS1[157,164,165], and is affected in BALB/c mice, which lack a key co-factor required with Pou2f3 for optimal tuft cell differentiation and are thus less responsive to *Tritrichomonas*[166].

Two additional aspects of the small intestinal ILC2 response are noteworthy. First, despite intrinsic down-regulation, epithelial alterations induced by commensals like *Tritrichomonas* and *H. polygyrus* in C57BL/6 mice are themselves long-lived, persisting after resolution of infection and manifest as ‘memory’ responses to secondary homologous or even heterologous luminal infestation; more dramatic effects can be elicited by deletion of A20 in ILC2s, revealing the dedicated role for intrinsic IL-25 expression in small intestinal physiology[157] (of note, lampreys express IL-25 but not IL-33[167]). Whether memory is mediated at the level of crypt long-lived epithelial stem cells, niche stromal cells and/or ILC2s through epigenetic alterations remains incompletely studied. In human chronic allergic rhinosinusitis with nasal polyps, basal epithelial progenitor cells expressed an IL-13-

mediated transcriptional signature and showed altered differentiation trajectories[168]. Success in treating polyposis non-surgically by antibodies blocking type 2 cytokines, however, suggests a need for extrinsic immune signals to sustain the pathology. ILC2 activation in response to helminth infection drives proliferation and migration of IL25R$^+$ ILC2s into circulation, where these cells access distal tissues, including lung and conjunctivae, and establish protective responses in uninvolved mucosa[146,169]. The ability of migratory ILC2s to alter mucosal responses in distal tissues suggests that extrinsic signals can drive epithelial changes in heterologous tissues. Further study is required to assess whether lasting epigenetic changes are induced in target epithelial stem cell or stromal populations, as noted in inflammatory states[170], or rather are sustained by 'memory' ILC2s[171,172] or resident Th2 cells at these sites.

ILC2 involvement in the hair follicle response to cutaneous injury induced by the commensal mite, *Demodex*, also suggests a relationship with regenerative compartments. Common inhabitants of mammalian hair follicles, *Demodex* are contained at small numbers and spread by host-to-host transmission. In the absence of IL-4/IL-13 or IL-13Ra1, control of *Demodex* infestation is lost, resulting in mite overgrowth and inflammatory dermopathy with hair follicle damage; transfer of cytokine-competent ILC2s was sufficient to re-establish control of mites in IL-4/IL-13-deficient mice[173]. Of note, blepharitis, inflammation of eyelid hair follicles, can be associated with outgrowth of *Demodex* mites in patients treated for atopic dermatitis with antibodies that block cytokine binding to IL-4Ra[174]. Like systemically arrayed ILC2s, epidermal ILC2s were IL-5$^+$IL-13$^+$ at birth, but subsequently produced IL-13 synchronously with onset of anagen, the hair follicle growth phase. In the absence of IL-13 or its receptor, hair follicle stem cell proliferation increased, consistent with a role for IL-13 in attenuating processive differentiation of transiting stem cells. Perturbations of the skin by *Demodex* colonization or tape stripping in the absence of IL-4/IL-13 signaling were associated with loss of dermal integrity and cytokine- or receptor-deficient mice with *Demodex* developed premature skin senescence with hair loss, dermal collagen deposition and skin stiffening. Although ILC2s expanded in response to inflammation, Th2 cells and Tregs also accumulated[173]. Studies investigating transient depletion of Tregs in mice during the period of postnatal expansion in skin noted IL-13-mediated accumulation of IL33$^+$ subdermal fibroblasts, leading to development of an enlarged subdermal collagenous, fascia associated with recruited Th2 cells and eosinophils. These perinatal alterations, otherwise uneventful and morphologically resolving over time, created an altered border milieu with impact on skin responses in adult animals: full-thickness cutaneous wounds healed quicker and antigen-driven cutaneous challenges generated biased type 2 immune responses[175]. Taken together, activated epidermal skin ILC2s impact stem cell compartments to mediate hair follicle homeostasis. When perturbations overwhelm local control, IL-33$^+$ 'border' fascial fibroblasts, potentially in response to IL-13, activate a structural transition to expand the niche for type 2 innate and adaptive immune cells and reinforce the deeper barrier to protect internal tissues. As revealed in this study, perturbation of immune regulation during the neonatal window drove establishment of a memory state that manifested as a heightened type 2 immune response to subsequently encountered antigens in adult mice.

Adipose represents a tissue rich in ILC2s, as noted in the initial description of ILC2s[88], and ILC2 production of IL-13, IL-5 and Met-enkephalin has been implicated in sustaining thermogenic responses of adipocyte beiging and resident myeloid populations like eosinophils and alternatively activated macrophages[176,177,178]; the loss of type 2 immunity was associated with diminished insulin sensitivity and infiltration by inflammatory cells, promoting obesity. After intestinal *H. polygyrus* infection, Th2 cells infiltrated mesenteric adipose adjacent to granulomas where larval forms matured and produced amphiregulin and TGFβ in response to stromal multipotent progenitor cells expressing TSLP and IL-33, resulting in expansion of the stromal cell population and consistent with the crosstalk noted above[179]. Th2-stromal cell alterations persisted many months after drug cure of infection, suggesting a self-sustaining state associated with declining numbers of mature adipocytes and improved systemic metabolic homeostasis, as previously noted after helminth infection[180] and consistent with effects of IL-13 on muscle fatty acid oxidation and mitochondrial biogenesis[181]. Single-cell mRNA analysis of resident Th2 cells revealed expression of genes typical of resident ILC2s, including PPARγ, Neuromedin 1 receptor, CALCA, KLRG1 and Arg-1, revealing reiterative adaption imposed by the tissue on type 2 immune lymphocytes of both innate and adaptive lineages[77,179]. Mechanistically, amphiregulin from activated Th2 cells inhibited maturation of multipotent progenitors to mature adipocytes, suggesting consistent effects of type 2 immunity in altering proliferation and differentiation of tissue stem cells. Functionally, increased collagen deposition at sites of granuloma-induced injury resulted in barrier reinforcement, revealing a highly localized response to helminth-mediated perturbation accompanied by re-direction of body metabolic resources to support the structural alterations.

These examples suggest some organizational principles underlying the deployment of type 2 immunity (Figure 3). Barrier ILC2s relay signals from epithelial sensory cells, such as keratinocytes in skin or tuft cells and enteroendocrine cells in gut, and respond to tissue-specific activation cues, such as TSLP/IL-18 or IL-25, respectively, to produce canonical outputs, including IL-13, IL-5 and amphiregulin, that act on the stem cell compartment to alter the composition and physical properties of the barrier while sustaining macrophage and eosinophil populations and stromal alarmin$^+$ support cells, thus constraining type 2 lymphocytes to relevant niches and avoiding pathology. We envision that upstream physical signals that trigger activation cues are linked to tissue function, such as vitamin D metabolites or inflammasome assembly and IL-18 production in skin in response to sun exposure and injury, GPCR engagement and acetylcholine release in upper respiratory tract, or IL-25 and eicosanoid release in small intestine in response to luminal constituents. When perturbations exceed the ability to maintain homeostasis, ILC2s proliferate, differentiate and spread systemically while cDC2s are also activated to migrate and initiate an adaptive type 2 immune response, leading to production of Th2 cells and IgE. Type 2 cytokines produced during ILC2 expansion and Th2 recruitment feed-forward to expand the bordering stromal network of IL-33+ cells, thereby priming the perturbed tissue by enlarging barrier and border niches and the carrying capacity for type 2 lymphocytes while reinforcing subepithelial and serosal borders by inducing collagen deposition in deeper tissues. Migratory ILC2s in blood can enter distal sites and alter stroma, stem cells and mucosa, reinforcing barriers in the presence of environmental perturbants.

In parenchymal tissues like lung and liver, adventitial boundary ILC2s are positioned in proximity to cells that can monitor interstitial fluids in proximity to conduits related to tissue-specific functions, such as bile or pancreatic duct content or oxygen exchange. Although the nature of such sensors remains unknown, we speculate that such biologic outputs are translated through dynamic signals, like eicosanoids and neuropeptides, that contribute to the basal activity of tissue ILC2s[69,70]. With disturbances that trigger alarmin release, ILC2s relay cytokines to vessels and lymph nodes to alter the cellular milieu and flag areas (via cytokine-mediated induction of adhesins and chemokines) for deployment of myeloid and adaptive Th2 cells to reinforce functional integrity by cytokine and growth factor regulation through cellular and tissue containment mediated by myeloid cells, including AAMs and eosinophils (Figure 3). Homeostasis is restored in microdomains using all aspects of recently proposed mechanistic pathways underlying immunological ‘scars’ - cellular reprogramming, reconfiguration of cellular content and structural remodeling[68] – while systemically altering metabolic homeostasis to provide energetic support to sustain tissue functionality. Clearly, further understanding is needed, particularly at reproductive and genitourinary tract borders where inflammatory effects and oncogenic transformation have profound negative effects on functional integrity of the tissues that are likely countered by homeostatic regulation by type 2 immunity.

Developmental windows and temporal vulnerabilities drive allergic pathology

Type 2 immune responses are associated with intestinal and migratory helminth infections and provide host protection against mucosal injury through epithelial reorganization and barrier reinforcement, as noted above, and their downstream effects, including metabolic adaptation and colonization resistance[183]. Given the reliance of helminths on host survival for reproduction and transmission, evolution has sculpted interactions by which parasites induce type 2 responses to enhance their own survival and minimize damage, particularly at nutrient interfaces in small intestine. Although results are mixed, therapeutic infections with non-replicating or self-limited helminths have been used in attempts to attenuate inflammatory bowel disease[183]. Morbidity of intestinal soil-transmitted and vector-transmitted organisms remains high, but much of the debilitation occurs after accumulation of repetitive injury over many years and often at post-reproductive ages. Efforts to understand the protective effects of tissue type 2 responses may lead to mechanistic understanding that minimizes cumulative damage to organs and tissues. Despite association of IL-13 with pathologic fibrosis, attenuating type 2 immunity can increase tissue damage in some models of fibrosis[184] and anti-IL-13 therapeutics have not shown efficacy in human pulmonary interstitial fibrosis[185]. Further work is warranted.

We envision at least two mechanisms predisposing to development of allergies in early life (Figure 4). First, perturbations that affect *developmental windows* during which deposition and expansion of ILC2s (and Th2s during adaptive responses) occur in tissues could alter niche size, composition or quality and affect type 2 cytokine outputs involved in homeostasis. Second, *temporal vulnerability windows* when environmental perturbations create stress on resident immune cells that drive unbalanced immune and regenerative

responses resulting in allergic pathology. Allergic mechanisms through both pathways reflect gene-environment interactions orchestrated by type 2 immunity and consistent with genetic studies implicating enhancers of immune genes in allergic pathogenesis with roles that include epithelial responses to infectious agents[186], and likely contributing to the risk of allergy early in life when stabilization of the barrier microbiota remains fluid[187].

Developmental windows reflect periods when the relevant cell types, including ILC2s, stromal fibroblasts, macrophages and mast cells, are deposited and mature in tissues, thus creating microdomains where type 2 cytokines bridge vascular access and macrophage-mediated interactions with fibroblasts and parenchymal tissues. Genetic and maternal effects on cell types that affect ILC2 niche size or composition could cause changes in outputs during the perinatal expansion with the potential to enlarge or misposition the type 2 niche due to positive feedback on alarmin^{+} stromal cells[188]. Such alterations would be consistent with effects of gain-of-function or loss-of-function genes[5,6,109] involved with expression of alarmins or type 2 cytokines and potentially those that impact mast cell function[189], but also effects of maternal nutrition, infections and transfer and quality of antibodies like IgE.

Temporal vulnerability windows reflect periods when environmental exposures to infectious agents or inflammatory moieties occur during post-birth transitional states, particularly during periods of increased energetic needs that drive decisions between tolerance and resistance[190]. Human energetic needs follow stereotyped inflection points over lifespan[191]. After rapid increase to a peak at the first year of life, energy expenditures decline to adult levels after puberty, follow a stable plateau from ages 20–60, and then progressively decline, revealing a large footprint for resource needs in the initial perinatal period. Resource allocations may be less tolerant of deviations during this period and explain the epidemiologic associations of asthma and early life exposures to respiratory viruses[3], inflammatory stimuli envisioned by the ‘hygiene hypothesis’ or exposure to antibiotics, potentially damaging food additives or novel chemicals[192], and the proclivity towards tissue Th2 development in response to airway perturbation[193]. Epigenetic alterations in mucosal niches may lead to fixed areas of exuberant type 2 responses, as in chronic allergic rhinosinusitis with nasal polyps or recurrent, fixed mucus airway plugging in asthma[168,194]. Mutations in genes affecting epithelial integrity (e.g., filaggrin) or leading to lymphopenia, dysregulated T cell signaling or Treg function[195] would similarly increase pressure on epithelial stem cell compartments during periods when tissue-intrinsic developmental windows become stressed by fluctuations in microbial control during colonization post-birth or loss of tolerance to innocuous environmental antigens[196]. Mutations in B cell receptor signaling affecting IgE receptor-mediated apoptosis in IgE plasma cells could impede normal tolerance mechanisms[197]. Inhibition and niche confinement of ILC2s by interferons is important in facilitating optimal parenchymal responses to inflammatory organisms[198,199], but whether this mechanism is operative during the period of post-natal ILC2 (mice) or Th2 expansion (humans) is unknown. Interferons induced in SPF mice co-housed with pet store mice waned after ~2 months when the microbiota stabilized and inhibition of innate type 2 immune responses in lung was largely, but not completely, recovered, although long-term commensals like helminths and protists were not explored[200]. Type 2 niches typically exclude inflammatory type 1 cells by unknown mechanisms, but in lung, severe viral-induced inflammation drove niche invasion by inflammatory lymphocytes,

in part through increased IL-7 induction in ASCs, resulting in damage to alveolar stem cells and structural compromise[201]. As with susceptibility to infectious diseases, where the impact of underlying genetic mutations in shaping vulnerability increasingly supports early epidemiologic observations[202,203], allergic diseases are likely to be defined increasingly by the impact of mutations on environmental windows of vulnerability at the nexus of immune-mediated regeneration and repair[195].

While many illustrative mutations exist, here we briefly review loss-of-function mutations in type 17 immunity due to dominant-negative Stat3 mutations, biallelic mutations in ZNF341, which regulates Stat3 transcription, and mutations in IL6ST (gp130) implicated in IL-6 and IL-11 signaling that lead to canonical hyper-IgE syndrome[204]. Complicated by cutaneous and mucosal Staphylococcal and fungal infections, patients develop eosinophilia but little food allergy or anaphylaxis in part due to diminished mast cell degranulation due to attenuated Stat3 activation. While not entirely clear, loss of negative regulation of IgE class switching by IL-21 on B cells may contribute to the hyper-IgE response[205]. Loss of control during colonization by cutaneous commensals normally constrained by IL-17 and type 3 responses may lead to activation of ILC2s and Th2 cells in response to injury-induced stem cell proliferation and reinforcement of alarmin$^+$ stromal cells, accounting for the high IgE, eosinophilia and atopic dermatitis that occur. Over-lapping phenotypes with mutations in the TGFβR signaling pathway revealed cross-regulation between Stat3 and induction of a negative regulator of SMAD2/3 nuclear localization resulting in increased TGFβ signaling with enhanced IL-4Ra and GATA3 expression in T cells associated with eosinophilia, hyper-IgE and atopic syndromes that respond to therapies targeting type 2 cytokines[206]. Periods of immune dissonance when two pathogens require antagonistic Th subset responses also expose temporal windows of vulnerability. In SPF mice (immunologically akin to newborn humans), viral challenges at the peak of early type 2 immune responses to parasitic helminths can lead to loss of virologic control and poor outcomes whereas prior helminth infections given time to establish mucosal homeostasis protect against subsequent challenges[207,208,209].

Closing remarks

We focused here on innate type 2 immunity as elaborated by core type 2 cytokines by lymphoid cells in attempting to construct an evolutionary-based model for this pathway in vertebrate health that might be subject to deviation early in life and the increased risk for atopy. Clearly, many other cells and pathways are involved in both homeostasis and allergic pathology, including Treg, non-conventional T cells, B cells and other antigen-presenting cells, and but briefly discussed here. We focused on the core type 2 cytokines due to the successful therapeutic targeting of this pathway in human allergic diseases, while acknowledging key roles for mast cells and IgE (and IgG) antibodies in food allergy, anaphylaxis, urticaria and itch syndromes that can be driven by alternative pathways[189,210], and addressed elsewhere in this Issue. The tissue adaptability of ILC2s and Th2 cells and the evolutionarily honed diversification by domain swapping among the core type 2 cytokines and their receptors create strategies for synthetic receptor engineering[211] and cell-based therapies[212] to exploit regenerative pathways while reducing inflammatory costs to tissue[213]. Further study may yield unexpected opportunities to improve health by targeted deployment

of components of type 2 immunity during critical windows of need while enlightening the ins and outs of allergic diseases.

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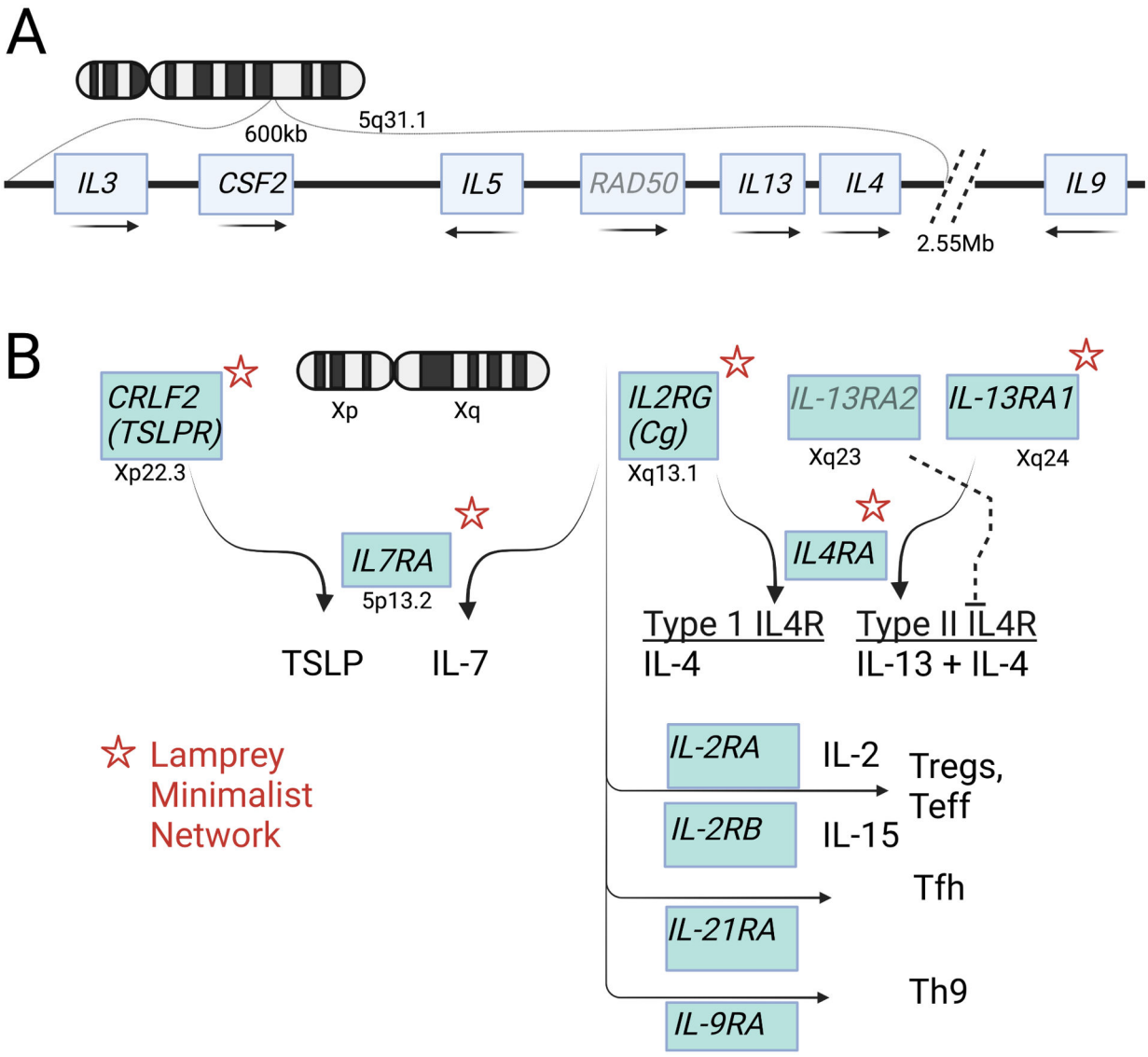

Figure 1. The cytokines and core components of type 2 immunity.

A. Genomic organization of the core type 2 cytokines on human chromosome 5q31.1. Transcription orientation indicated by arrows. **B.** Human cytokine signaling receptors on the X chromosome. Asterisks indicate homologs found in the lamprey cytokine receptor network. Further diversification of subsets of CD4 lymphocytes in jawed vertebrates is accompanied by appearance of additional partners for the common γ chain.

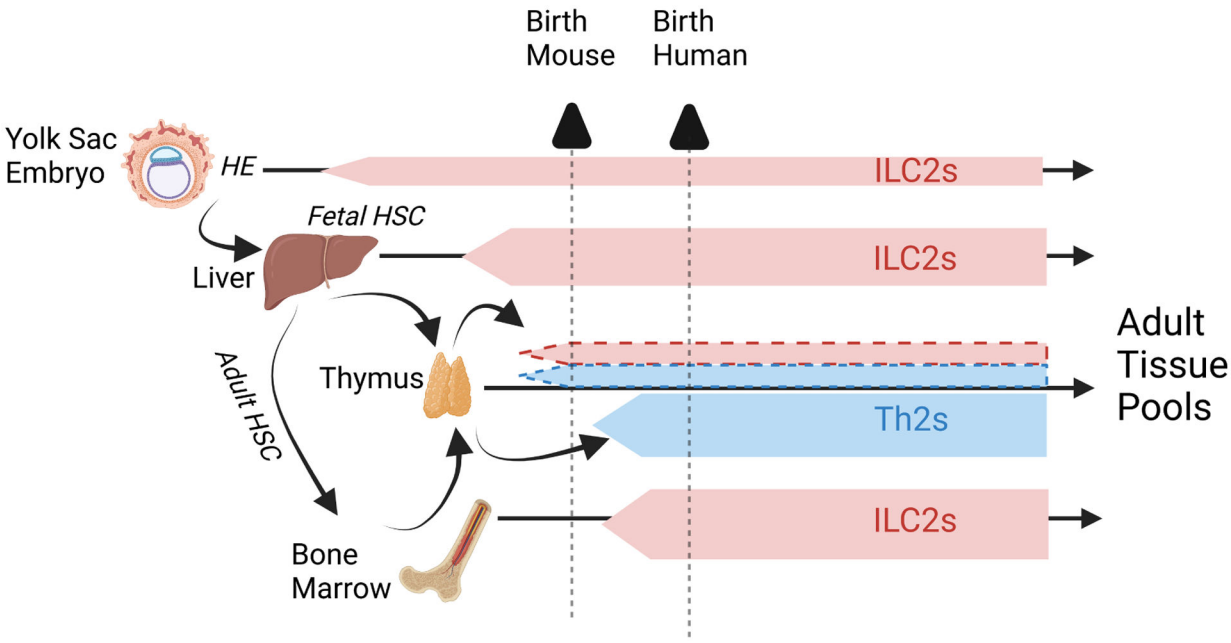

Figure 2. Layered ontogeny underlies the distributed network of type 2 immune lymphocytes.

Although tissue resident ILC2s and Th2s derive from upstream precursors, we figuratively represent their origins from populations designated ILC2s or Th2s for illustrative purposes. Tissue ILC2s are comprised of populations originating from primitive hematopoiesis originating in yolk sac and liver, and bone marrow definitive HSCs. Additional heterogeneity may reflect derivation of some ILC2s from thymic pre-T cell precursors (dotted red borders). Adaptive Th2s arise from definitive adult bone marrow HSCs after thymic education and export as naive T cell precursors. Neonatal adaptive T cells can also arise from fetal HSCs, comprising a small population of tissue cells with rapid effector function (dotted blue borders). The triangles at top denote the different layering of peripheral tissues at the time of birth in mouse and human.

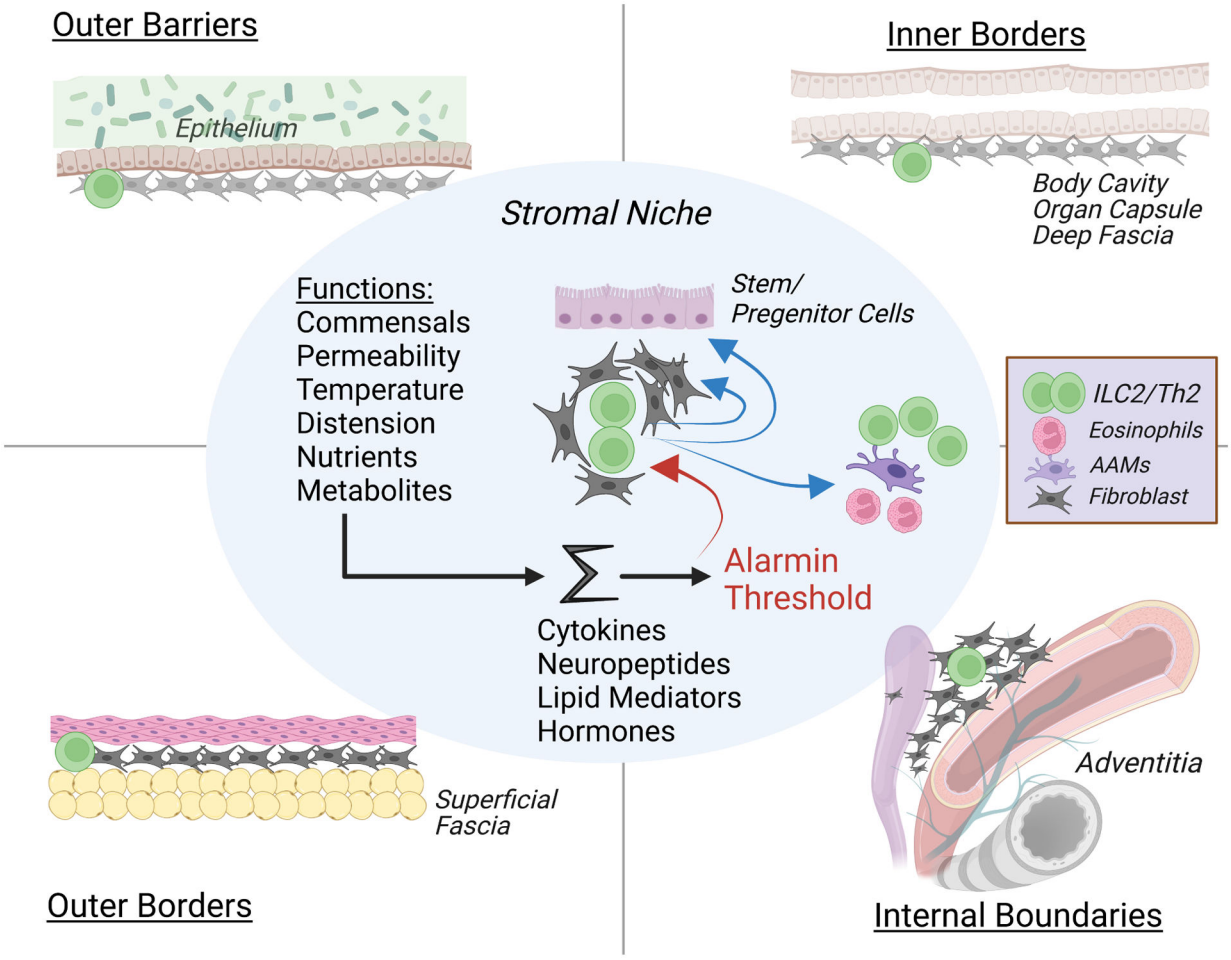

Figure 3. The ins- and-outs of tissue surveillance by type 2 immune lymphocytes – an organizational model.

The Center grouping depicts core shared components of ILC2s in a stromal niche that likely applies to resident Th2s in the adapted state. Tissue function is translated by many cell types into signaling pathways that are integrated and thresholded by resident alarmin signals, transmitted in part by stromal niche fibroblasts to ILC2s which release type 2 cytokines that feedback on niche stromal cells and regulate myeloid cell activation and recruitment. With sufficient perturbation, ILC2s proliferate, increase cytokine outputs and migrate from the niche to interact with resident cells and tissues. Outer Barriers (upper left) are externally-oriented epidermis in skin and mucosa, where ILC2s can be activated by barrier-specific alarmins, like IL-25 in small intestine or TSLP/IL-18 in skin. Outer Barrier tissues are supported by Outer Borders (lower left) consisting of subepithelial fascial planes that support resident ILC2s that when activated can facilitate niche enlargement to house recruited Th2 cells and myeloid cells that increase local collagen deposition and reinforce the physical border internal to the external barrier. Inner Borders (upper right) represent serosal mesothelial linings surrounding internal organs, which also support ILC2/stromal niches and use type 2 cytokines to enlarge the niche and enhance structural support. Internal Boundaries (lower right) depict organization of ILC2s in proximity to vascular and ductal structures that allow monitoring of regional homeostasis in tissues.

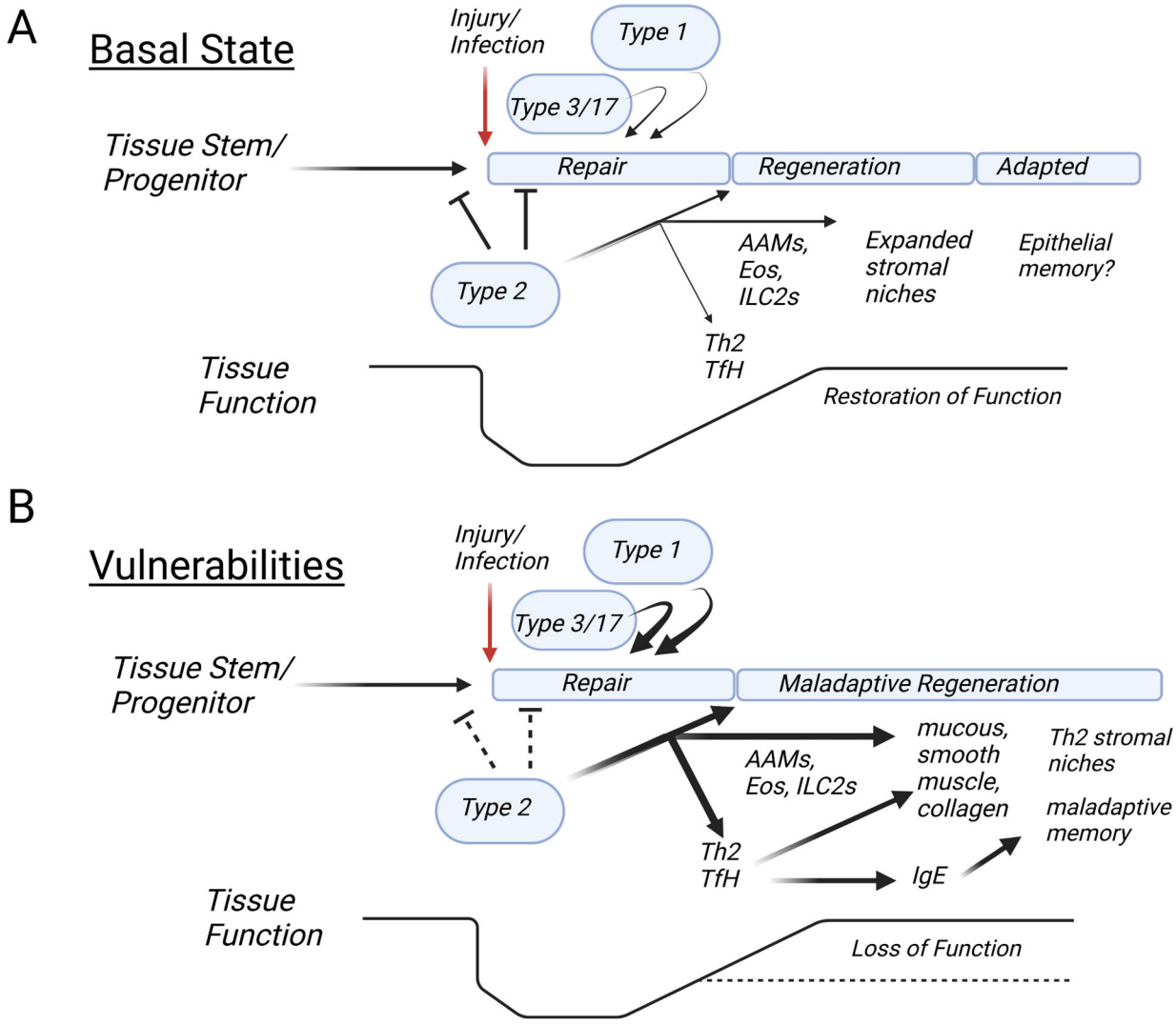

Figure 4. Vulnerabilities to type 2 pathology.

A. In the basal state, injury induces alarmin-mediated ILC2/Th2 outputs that inhibit normal stem cell transitions while the epithelium regenerates by engaging immediate type 3 responses and later type 1 immunity to enforce training. With repair, type 2 cytokines activate myeloid cells (AAMs, eosinophils) to mediate regulatory control and expand the type 2 immune cell niche using structural reinforcement as necessary. Systemic spread of type 2 lymphocytes contributes to metabolic homeostasis needed to support the altered tissue state and local function is sustained or even improved, depending on the context of the inciting event. **B.** Vulnerabilities occur when mutations interact with environmental exposures during critical developmental windows that affect local tissue functions or output of type 2 cytokines. The tempo of repair becomes altered, resulting in an excess of tissue AAMs, eosinophils and alarmin^{+} stroma that support an enlarged niche with potential for development of tertiary lymphoid structures promoting local Tfh and Th2 differentiation. The misalignment of repair and regeneration with immune signals, particularly as affected

by underlying mutations, can lead to aberrant epithelial and tissue responses manifest as allergic pathology and loss of function.