ILC – key immune integrators of overall body homeostasis

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Abstract

The maintenance of the tissue barrier is essential to protect the host from external pathogens, thus ensuring the survival of the organism. This process requires the integration of various physiological signals originating from the digestive, immune, endocrine and the nervous system as indicators of overall body fitness. Innate lymphoid cells (ILC) are a group of immune cells equipped for the guarding and maintenance of the tissue barrier against invading pathogens. Extensive research has focused on the regulation of ILC by cytokines derived from immune or non-immune cells, such as the epithelium. However, recent findings suggest that ILC may play an additional role in the monitoring of the overall health status of the host. This requires the combined sensing of cytokines, metabolites, hormones and neuropeptides. ILC appear to be essential in this process functioning as hubs for the integration of different physiological signals to facilitate barrier immunity. Here we discuss the emerging literature revealing dietary, metabolic, hormonal and neuronal signals as important controllers and modulators of ILC function in health and disease.

Main text

INTRODUCTION

Innate lymphoid cells (ILC) are a diverse family of tissue-resident immune cells, which phenotypically and functionally resemble T cells. Although, the abundance of ILC in lymphoid tissues is low in comparison to T cells, barrier surfaces, such as the skin, lung, intestine but also adipose tissues harbor significant numbers of ILC [1]. This tissue residency is in concordance with a key role in maintaining and protecting the tissue barrier against invading pathogens [2]. In addition to barrier tissues ILC are also present in non-barrier tissues, such as the liver and the meninges, with an important role in maintaining tissue homeostasis [3, 4]. Several distinct populations of ILC have been identified, which as members of the lymphocyte family are characterized by an overall dependence on signaling through IL-7 receptor (CD127) or IL-15 receptor (CD122) and the common cytokine receptor γ -chain (IL-2R γ) for their maintenance and development. However, unlike adaptive lymphocytes they lack expression of somatically rearranged antigen receptors and as a consequence do not exhibit any degree of antigen specificity [5]. In addtion, ILC require the transcriptional regulators Id2 and PLZF for their development [6, 7].

ILC are divided in 3 groups, on the basis of their phenotypic and functional similarities to T helper cells [8]. Group 1 ILC (ILC1), including NK cells are characterized by the expression of the transcription factor T-box-expressed-in-T-cells (T-bet). The signature effector cytokine produced by ILC1 is interferon (IFN)- γ , which functions primarily to mount immune responses against intracellular pathogens, such as viruses or intracellular bacteria [7, 9–12]. Group 2 ILC (ILC2) express the transcription factor GATA-3 and produce the cytokines interleukin (IL)-4, IL-5, IL-9, IL-13 and amphiregulin. In contrast, ILC2 are responsible for promoting tissue repair and protection against helminth infections but may also mount pathogenic responses driving allergies and asthma [12–16]. Group 3 ILC (ILC3) include lymphoid-tissue-inducer (LTi) cells, natural-cytotoxicity-receptor-positive (NCR+) and NCR- ILC3. All ILC3 subsets share expression of the lineage defining transcription factor ROR γ t, with, NCR+ ILC3 displaying additional expresison of T-bet. The major function of ILC3 is to protect the host from bacterial infections and to prevent the location of pathogens across barrier membranes, functions mediated by the expression of the cytokines IL-22 and IL-17. However, chronic activation of this subset may contribute to chronic gastrointestinal inflammation [12, 17, 18]

The prime positioning of ILC at barrier surfaces as prevailing sites of pathogen entry, requires rapid activation by host-derived factors such as cytokines. Epithelial cells and myeloid cells act coordinately to sense infection and/or tissue damage and produce cytokines and alarmins facilitating the rapid activation of distinct ILC populations. In this regard, cytokine production of ILC1 can be stimulated by IL-12, IL-15 and IL-18 whereas IL-25, IL-33 and TSLP stimulate ILC2. In contrast, ILC3 rapidly respond to stimulation with IL-1 and IL-23 [11, 12].

While the function of cytokines in the coordination of ILC responses is well understood, the influence of additional signals is only about to be revealed. This includes the function of dietary-derived molecules, such as vitamin A, tryptophan metabolites and lipid mediators. Additionally, most recent research suggests a direct control of ILC function by neuropeptides, neurotrophic factors and steroid hormones, some of which display the capacity to stimulate ILC to an extent that clearly exceeds the stimulation by cytokines. In this review we will focus on this emerging field of non-cytokine stimulators and modulators of ILC function, many of which derived from outside the immune system and discuss their potential importance for the maintenance of ILC-mediated barrier tissues and immune homeostasis.

CONTROL OF ILC FUNCTION BY EXTRACELLULAR SIGNALING

Dietary-derived products

Beyond the imminent supply of energy to maintain body functions, there is growing evidence that dietary components can directly influence the function of immune cells and thus the well being of an individual. Indeed, dietary habits are now known to be major drivers of human diseases ranging from diabetes to inflammatory bowel disease and asthma [19, 20]. These diseases are characterized by different degrees of chronic immune activation and inflammation and have been linked to changes in life-style accompanying industrialization [21–24]. Hence the identification of pathways responsible for the sensing of dietary components on immune cells is an active area of investigation. One hypothesis in this regard is the notion that molecular pathways may have evolved to recognize the relative abundance of endogenous or exogenous metabolites as signatures of pathogenic

threats. These pathways include ligand-activated nuclear receptors or G protein-coupled receptors able to sense both dietary or microbiota-derived metabolites. Thus, the overlap between nutrient- and pathogen-sensing systems could stand at the interface of metabolic and inflammatory responses, thereby providing a possible mechanistic link between diet and disease [25].

AhR ligands

The immune system is equipped to directly respond to dietary metabolites. In this process the particular importance of ligand-activated nuclear receptors was previously demonstrated [26]. One of the most prominent receptors activated by dietary metabolites is the ligand-dependent transcription factor aryl hydrocarbon receptor (AhR), a member of the highly conserved (Pernt-Arnt-Sim) PAS family of transcription factors [27]. Activation by tryptophan metabolites, which range from environmental toxins and pollutants to dietary-derived metabolites trigger the translocation of AhR from the cytoplasm to the nucleus. Nuclear translocation facilitates the transcription of target genes, such as the microsomal cytochrome P450-dependent monooxygenases Cyp1a1 and Cyp1a2 [28]. Dietary tryptophan metabolites can be generated either endogenously or directly from cruciferous vegetables including cabbage or broccoli and play an important role for the maintenance of barrier immunity [29–32]. In this regard AhR deficient mice show an overall decrease in IL-22 producing ILC3, which leads to a dramatically increased susceptibility to die from intestinal infections with the pathogen *Citrobacter rodentium* [30, 31, 33]. Impaired immunity may be in particular caused by a specific loss of NCR+ ILC3 in the absence of AhR signaling. In addition, post-natally-imprinted cryptopatches (CP) and isolated lymphoid follicles (ILF) are impaired with AhR deficiency, further demonstrating an important link between nutrient sensing and the formation of intestinal immune structures [30, 31, 33]. In this respect, dietary derived AhR metabolites may play a central role for the maintenance of host immunity, since mice fed a AhR-ligand deficient diet failed to clear intestinal bacterial infections [30]. The central function of AhR ligands is further emphasized by the fact that constitutive expression of Cyp1a1 leads to reduced ILC3 numbers, decreased Th17 differentiation and increased susceptibility to intestinal infection [34]. Impaired immunity was the result of a constant depletion of endogenous AhR ligands and could be reversed by increasing the availability of external dietary ligands. Interestingly, the commensal microbiota may play an important role in providing endogenous AhR ligands, as colonization of germ-free mice with *Lactobacilli reuteri* provides resistance to the fungus *Candida albicans* and mucosal protection from inflammation. This was facilitated by AhR-dependent upregulation of IL-22 [35]. In fact, ligand-activated translocation of AhR into the nucleus may directly result in transcriptional upregulation of IL-22, as direct binding of AhR to the *il22* promoter was reported [31] (Figure 1). Despite substantial efforts the specific endogenous and exogenous AhR ligands in control of barrier immunity are still unknown and it will be interesting to learn whether defined ligands exist controlling ILC3-mediated immunity and barrier protection.

Vitamin A

Vitamin A is one of the best-characterized nutrients with diverse effects on the organism. This lipophilic micronutrient is obtained through the diet as provitamin A carotenoids from fruit or vegetables or in the form of retinyl esters found in foods of animal origins. In humans carotenoids are enzymatically cleaved, or hydrolyzed in the case of retinyl esters, to generate retinol, which is taken up from enterocytes and can be re-esterified and stored in the liver. DC and epithelial cells are able to directly convert retinol to retinal and retinoic acid (RA) by the enzymes retinol dehydrogenases (RDH) and retinaldehyde dehydrogenases (RALDH), respectively. RA as the main metabolite from vitamin A is required for the growth and development of the organism but also exerts profound effects on the immune system, controlling both innate and adaptive immune responses [25, 36–38].

Recent studies revealed the role of RA in controlling intestinal ILC3 responses. Dietary depletion of vitamin A to generate vitamin A deficient mice, resulted in substantial reduction of ILC3 numbers in comparison to animals fed vitamin A. As a consequence intestinal immunity against *Citrobacter rodentium* was profoundly impaired and infected animals showed increased mortality [39]. Reduced protection was primarily caused by a lack of IL-22 production from ILC3, as treatment with exogenous IL-22 restored immunity. Further, *in vivo* treatment with RA can boost the production of IL-22 from ILC3 and the production of Reg3 β and Reg3 γ in the colon, both well-described target genes of IL-22 signaling [36, 39, 40]. Accordingly, treatment with RA may prompt a functional amplification of ILC3 immunity and improved protection in the context of gastrointestinal bacterial infections and DSS-induced colitis [40]. Direct control of ILC3 function by RA is most likely acting on the transcriptional level mediated by the binding of heterodimeric RA receptors (RARs) and retinoid X receptor (RXRs) to RA response elements (RAREs). Indeed, ligation with RA induced the binding of RARa to the *rorc* and *il22* promoter, thus directly controlling differentiation and effector functions of ILC3 by the expression of ROR γ t, and IL-22, respectively [40, 41]. The importance of RA for ILC3 differentiation is supported by human data. *In vitro* treatment with RA augments ILC3 differentiation and IL-22 production but also drives the conversion of ILC1 to ILC3 [29]. Besides the transcriptional regulation of ILC3, RA plays an additional role in

controlling the homing of ILC3 (and ILC1 but not ILC2) into the intestinal tissue by upregulating the trafficking receptors CCR9 and the integrin α4β7 [42]. The effects of vitamin A deficiency clearly extend to the development of the immune system. In this regard, the inhibition of maternal uptake of retinoids early in ontogeny impairs the development of lymphoid tissue inducer (LTi) cells, which ultimately results in defective development of secondary lymphoid organs of the offspring [41]. In contrast to the promoting function on ILC3, RA was shown to directly suppress intestinal ILC2, an effect that was mediated by downregulation of IL-7R α upon exposure to RA [39]. Although the exact molecular basis of this mechanism remains to be revealed, increased IL-7R α expression in the absence of RA may enable ILC2 to compete more efficiently for limiting intestinal IL-7. In combination with a simultaneous loss of ILC3, increased signaling through IL-7R α may allow accumulation of ILC2 in vitamin A deficient mice [39]. Indeed, ILC2 respond with increased phosphorylation of STAT5 upon IL-7 exposure in the absence of vitamin A. The different responsiveness of ILC to RA, enables a specific expansion of IL-13 producing ILC2 and efficient expulsion of the intestinal nematode *Trichuris muris* [39]. Thus, rather than causing global immune suppression vitamin A deficiency induces an adaptation of the intestinal tissue tone, which enables the maintenance of the intestinal barrier in the context of chronic parasite infections but not bacterial infections (Figure 1). This feature is an excellent example of how ILC responses may be shaped by nutrient availability.

Lipid mediators

Lipid mediators are essential modulators of immune functions, which can be either produced from phospholipids and other lipid membrane components or from dietary fatty acids. Generally, lipid mediators can be divided into three classes. Class 1 includes prostaglandins (PGs) and leukotrienes (LTs), while class 2 lipid mediators consist of lysophospholipids or their derivatives such as sphingosine 1-phosphate (S1P), which play important role in cellular trafficking. Finally, class 3 lipids consist mainly of lipids important for the resolution of inflammation, such as the pro-resolving lipid mediators lipoxins (LXs), resolvins, maresins and protectins [43]. The majority of immunologically active lipid mediators are derived from arachidonic acid (AA). AA is synthesized from the essential polyunsaturated fatty acids (PUFAs) α-linoleic acid (18:3) and linoleic acid (18:2), critically linking the dietary supply of lipids to the ability to generate lipid signaling molecules [44].

Leukotrienes
The biochemical production of leukotrienes requires 5-lipooxygenase (5LO), a metabolic pathway downstream of AA. The first product in the 5LO pathway of AA metabolism is LTA_4, which can be further converted to the cysteinyl leukotriene (CysLT) LTC_4 but also LTB_4. The production of LTB_4 marks the final product in this pathway, whereas LTC_4 is rapidly converted into LTD_4 and further into the terminal product LTE_4. CysLTs display binding capacity for two specific receptors, CysLT1R and CysLT2R [45, 46]. CysLT1R is expressed on lung ILC2 [47] and CysLTs are the only members of the leukotriene family known to mediate a direct effect on ILC function. Culture with LTD_4 in vitro resulted in rapid activation of ILC2, which produced high levels of the cytokines IL-5 and IL-13 within six hours of stimulation. In support of a direct mode of action, intranasal administration of LTD_4 induced IL-5 production. In addition, ILC2 responses to fungal allergens (*Alternaria alternata*) are further amplified by LTD_4 [47]. This initial finding was recently confirmed by two additional studies, showing that lung ILC2 responded readily to both, *in vitro* and *in vivo* stimulation by all three members of the CysLT family (LTC_4, LTD_4 and LTE_4) in an NFAT-dependent manner [48]. In addition, CysLTs can act in concert with IL-33 to potentiate ILC2 activation in *in vitro* and *in vivo* [48, 49]. This particular mode of action appears to be conserved between mice and men, as human ILC2 express CysLT1R and are activated by CysLTs to produce the cytokines IL-4, IL-5 and IL-13. Beyond the induction of cytokines, human studies showed that LTE_4 induces migration of ILC2 and reduce the induction of apoptosis. As a result LTE_4 may be a strong driver of ILC2-mediated allergic airway inflammation, potentiating the activating function of IL-33, IL-25 and TSLP [50]. Thus, CysLTs appear to be potent modulators of pathogenic type 2 inflammation, which opens new avenues for the potential targeting of ILC2 in disease.

Prostaglandins
In contrast to the metabolism of AA by 5LO, the enzymatic breakdown by the prostaglandin G/H synthases, COX1 and COX2 results in the formation of two unstable intermediate forms, PGG_2 and PGH_2. The subsequent metabolism of these unstable intermediates by a series of specific isomerase and synthase enzymes generates prostaglandins, lipid mediators with a diverse range of functions. The most dominant bioactive prostaglandins generated in vivo include PGD_2, PGE_2 and PGI_2 and all three are potent modulators of ILC function [51].

The first member of the prostaglandin family, PGD_2 is predominantly synthesized in mast cells in the context of allergic responses. Interestingly, the PGD_2 receptor CRTH2 is selectively expressed by cells mediating type 2 immunity such as type 2 T helper cells (Th2), eosinophils and basophils [52]. CRTH2 is a Gi-coupled activating receptor and binding of PGD_2 reduces intracellular cAMP levels and triggers mobilization of Ca^{2+} [53].

Interestingly, human ILC2 were originally classified based on CRTH2 expression and CRTH2 is still the most reliable marker for the identification of human ILC2 [15]. PGD_2 has strong effects on ILC2 and induces the expression of IL-13 in human peripheral blood ILC2, even in the absence of ILC2 activating cytokines. However, the release of IL-13 can be further potentiated if ILC2 are exposed to PGD_2, IL-25 and IL-33 simultaneously [15, 54]. Subsequent studies further emphasized the importance of PGD_2 as driver of pro-inflammatory ILC2 responses, since stimulation of human peripheral blood and skin ILC2 induced both, migration and the production of IL-4, IL-5 and IL-13 [54]. PGD_2 can either act as a direct stimulator by binding to CRTH2 or by potentiating the function of IL-25 and IL-33 [54, 55]. Interestingly, combined culture of ILC2 with PGD_2, IL-25 and IL-33, appears to drive the expression of a range of pro-inflammatory cytokines such as IL-3, IL-8, IL-9, IL-21, GM-CSF and CSF-1 [54, 56]. Furthermore, PGD_2 is a conserved activator of ILC2 chemotaxis, as accumulation of lung ILC2 in the context of helminth-induced type 2 inflammation in mice was shown to depend on both, the presence of PGD_2 and the expression of CRTH2 on ILC2 [56].

Another prostaglandin member, PGI_2 is highly expressed in lung tissue and is produced by a wide array of tissue and immune cells such as smooth muscle cells, endothelial cells, fibroblasts, follicular dendritic cells and thymic nurse cells. PGI_2 is reported to mainly facilitate anti-inflammatory functions, which are mediated through binding to the prostacyclin receptor or prostaglandin I_2 receptor (IP), the cognate receptor of PGI_2. In this regard, activation of IP leads to increased intracellular cAMP levels and protein kinase A (PKA)-mediated phosphorylation of key transcription factors. This includes members of the peroxisome proliferator-activated nuclear receptor (PPAR) family, such as PPAR γ [46, 57]. PGI_2 signaling has the capacity to attenuate allergic inflammation, by suppressing IL-33-mediated expression of IL-5 and IL-13 in ILC2. In addition, ligation of IP blunts the accumulation of ILC2, presumably by downregulating the transcription factor Id2, which plays an important role in ILC2 development [58]. Moreover, endogenous PGI_2 signaling suppresses unrestricted accumulation of IL-5 and IL-13 producing ILC2 in the context of fungal allergen *Altenaria alternata*. Reduction in ILC2 ultimately resulted in decreased eosinophilic infiltration. Similar suppressive capacities are reported for human ILC2 isolated from the peripheral blood [58]. Although these findings suggest that PGI_2 could be a potential inhibitor of allergic airway inflammation, the usage of PGI_2 analogs in clinical studies failed to show any beneficial effect [46].

PGE_2 is one of the most abundantly produced PGs and modulates immune and inflammatory responses through binding to the Prostaglandin E_2 receptors 1-4 (EP1-4) [59]. Clinical data suggest an important role in systemic inflammation, as PGE_2 was downregulated in neonates experiencing sepsis but not in healthy controls [60]. Such observations triggered the further study of PGE_2 in models of LPS induced systemic inflammation in mice and led to the discovery that PGE_2 can directly affect ILC3. Treatment of mice with indomethacin (a COX1 and COX2 inhibitor) or an EP4 agonist, demonstrated that EP4 mediated signaling of PGE_2 promotes the homeostasis of ILC3 and rescues mice from LPS induced septic shock [61]. Thus, PGE_2 is able to inhibit systemic inflammation, an effect that was dependent on the production of IL-22 from ILC3. Besides these important findings PGE_2 can act as a suppressor of human ILC2. Activation of ILC2 with IL-25, IL-33, TSLP and IL-2 was blunted upon exposure to PGE_2 and resulted in reduced proliferation and cytokine release. This suppressive function of PGE_2 may be mediated by partial downregulation of GATA-3 and CD25, an effect that was directly dependent on the binding of PGE_2 to the receptors EP2 and EP4 [62].

Lipoxins

Lipoxins (LXs) are a third class of AA derived lipid mediators, which are predominately and in contrast to LTs and PGs, produced in the context of resolution of inflammation. Reported functions depend on the effected cell type and include inhibition of neutrophil activation, promotion of phagocytotic macrophages and removal of apoptotic neutrophils, important steps leading to the resolution of inflammation [63]. Lipoxin A4 (LXA_4) is generated by the conversion of AA by15-lipooxygenase (15-LO), which predominately takes place in epithelial cells, macrophages and eosinophils [46]. Both ILC2 and NK cells isolated from the peripheral blood express the LXA_4 receptor (ALX/FPR2). Ligation with LXA_4 increases NK cell-mediated depletion of eosinophils, while also reducing IL-13 expression from ILC2 activated with IL-25, IL-33 and PGD_2 [55]. Together, this suggests that LXA_4 may play an important anti-inflammatory role by restricting pathogenic ILC2 responses in the context of airway inflammation.

Lysophospholipids

Finally, Sphingosine 1-phosphate (S1P) is produced from sphingosine by sphingosine kinases, acting as second messengers or as extracellular ligands for S1P receptors (S1PR). This dual function of S1P enables important cellular processes, such as proliferation, survival and migration [64]. Recently, IL-25 was found to elicit an inflammatory phenotype in ILC2, which allows for the trafficking to distal organs. Recirculating ILC2 predominately arise from the intestinal lamina propria and selectively expressed the S1P receptors S1PR1, S1PR4 and S1PR5, which allowed migration to distal sites such as the lung upon helminth infections or treatment with IL-25. Migration of ILC2 seemed to mediate protection at the early stages of helminth infection

and contributed to worm clearance, tissue repair and host survival [65]. Thus, the rapid generation of S1P in infected tissues may be essential to prevent infection-induced pathology. Overall, this data demonstrates that intestinal ILC2 may have the potential to migrate. However, since IL25R expression appears to be restricted to the intestinal tissue at steady state, it will be interesting to see whether responsiveness to IL-25 can be turned on in other tissues and whether ILC2 resident at other body sites possess a similar migratory potential.

Taken together, lipid mediators are emerging as important regulators of ILC function in general and of ILC2 in particular (Figure 1). Thus, targeting lipid mediators to manipulate ILC function may be a promising therapeutic approach to treat ILC2-mediated inflammatory diseases, such as asthma in the future.

Neuropeptides

The sensory nervous system and the immune system were initially considered to be closed systems functioning autonomous from each other. However, this view is slowly replaced by growing evidence suggesting a coordinated function of both systems in the promotion of host defense and tissue homeostasis. Indeed, nervous-immune interactions can be facilitated through a wide array of molecular signals mediated by cell-surface G-protein- and tyrosine kinase-coupled receptors [66]. In particular, the somatosensory nervous system is positioned anatomically to be able to directly modulate immunity in secondary and primary lymphoid tissues, skin and mucosa by direct interaction with immune cells. In fact, interactions between mediators released from sensory neurons are able to directly attract and activate adaptive immune cells (T cells) and innate immune cells (mast cells, dendritic cells), but until recently it was unknown whether direct interactions between the nervous system and ILC exist and how the nervous system may influence ILC function [66–68].

This radically changed as three independent research groups put the neuropeptide Neuromedin U (NMU) in the limelight of ILC researchers. Intestinal and alveolar ILC2 were discovered to express multiple genes associated with neuropeptide signaling, including high levels of the neuropeptide receptor for NMU (Nmur1) [69–71]. Interestingly, Nmur1 expression appears to be restricted to ILC2 and no expression was detected on other lymphoid or myeloid cells [70, 71]. NMU expression is up-regulated upon exposure of mice to allergens such as house dust mite or in the context of helminth infections, suggesting a potential role in ILC2 mediated effector functions [69–71]. Indeed, stimulation of enteric ILC2 with NMU directly induced rapid cell activation, proliferation and secretion of the type 2 cytokines IL-5, IL-9, IL-13, that was dependent on cell-intrinsic expression of NMUR1 and G-protein-coupled receptor Gαq. In support of a direct control of ILC2 responses by NMU, intranasal delivery of NMU stimulated maturation, cytokine expression and proliferation of lung ILC2 and induced airway inflammation [69]. In return, ILC2-mediated airway inflammation is reduced in allergen challenged NMU KO mice [70]. Apart from activating ILC2 in airway inflammation, NMU facilitates a protective role in the context of helminth infections. Systemic administration of NMU triggered a potent ILC2 response that accelerated the expulsion of the gastrointestinal nematode *Nipostrongylus brasiliensis*. In this context, reconstitution of $Rag^{-/-}$ *Il2rg* $^{-/-}$ mice with ILC2p isolated from Nmur1 deficient mice resulted in reduced capacity to clear intestinal parasites in comparison to reconstitution with ILC2p from wild-type animals [69]. Together, this suggests an essential role in the promotion of ILC2-mediated anti-helminth immune responses. NMU appears to control ILC2 activation through extracellular signal-regulated kinase (ERK) and calcium influx dependent activation of calcineurin and nuclear factor of activated T-cells (NFAT) [71]. Interestingly, CysLTs stimulation of ILC2 induces the same signaling cascade [48]. Thus, NMU and CysLT may act similar to calcium ionophores such as ionomycin, which may explain the speed and amplitude of cytokine induction by NMU and CysLT. Collectively, these data indicate that NMU is a potent and rapid activator of both protective and pathogenic ILC2 responses.

The interaction of neurons with ILC is not limited to the function of NMU. Vasoactive intestinal peptide (VIP) is produced by neurons, endocrine cells and immune cells and most organs display substantial expression of VIP at steady state. The biological functions are ranging from the regulation of bone metabolism over embryonic development to GI tract motility [72]. In addition, recent reports suggest a direct function of VIP on ILC2. In the context of allergen exposure, activation of nociceptors results in the release of VIP [73]. Stimulation of ILC2 and Th2 cell with VIP increases the release of the effector cytokines IL-5 and IL-13. This may be in part due to increased IL-33 receptor (ST2) expression on ILC2 by VIP, amplifying the responsiveness to activation by IL-33 [73, 74]. However, even in the absence of activating signals VIP increased the release of IL-5, which initiated a chain of events ranging from chemotactic activation of eosinophils and macrophages to increased IgE secretion by B cells, mucus production by goblet cells and smooth muscle contraction. The combination of these events aggravated allergic inflammation and bronchial hyperresponsiveness [73]. This function seems to be amplified by a direct stimulatory role of IL-5 acting on nociceptors, which accelerated the release of VIP. Thus, the release of VIP and its function on ILC may act as an important feed-forward loop in chronic type 2 inflammation [73].

In contrast to the stimulating function of NMU and VIP on ILC2, a recent report suggests that the nervous system also possesses the propensity to repress ILC2 responses. β_2-adrenergic receptor (β_2AR), which signals in response to epinephrine (EPI), is expressed on murine and human ILC2 isolated from the lungs or the small intestine [75]. Strikingly, intestinal ILC2 also appear to colocalize with adrenergic neurons and β_2AR deficiency results in increased numbers of total and IL-13 expressing ILC2, exaggerated eosinophilia and reduced worm burden, after *Nipostrongylus brasiliensis* infection. Thus, this putative nervous-immune crosstalk may represent an important mechanism to prevent overactivation of ILC2 and ILC2-mediated pathology. Indeed, ablation of adrenergic signaling results in increased numbers of ILC2 and airway inflammation induced by intranasal application of IL-33 or migrating *Nipostrongylus brasiliensis* larvae. In contrast, treatment with β_2AR agonists reduces airway inflammation in wt mice in vivo by impairing ILC2-mediated effector functions and proliferation. These findings indicate that the nervous system has the ability to balance ILC responses and to either promote the activation or suppression of ILC2, which may be essential to protect the host from pathogens but also to prevent immune-mediated pathology.

Apart from direct interactions with ILC2, neuronal signals may also substantially impact on the function of ILC3. In this respect a recent report highlighted the control of ILC3 by neurotrophic factors derived from glial cells. Glial cells adjacent to enteric ILC3 exhibit stellate-shaped projections into ILC3 aggregates and regulated ILC3 responses by expression of glial-derived neurotrophic factor (GDNF) family ligands (GFL) [76]. This function was shown to be mediated by the expression of the neuroregulatory tyrosine kinase receptor RET, the putative receptor for GFL. Strikingly, ILC3-specific ablation of *Ret* led to decreased production of IL-22, impaired production of antimicrobial peptides, dysbiosis and increased susceptibility to intestinal inflammation and infection. The specific control of IL-22 production by GFL is mediated by rapid phosphorylation and activation of the p38 MAPK/ERK-AKT signaling cascade and subsequent STAT3 activation leading to efficient gut homeostasis and to vague defense [76]. Overall, the above outlined findings highlight the increasing importance of a specific crosstalk between neuronal signals and ILC-mediated barrier immunity (Figure 2). The potency of this particular interaction is best exemplified by the imminent control of cytokine secretion by NMU. This interaction may allow for the coordination of ILC responses at non-effected distal body sites and may be an essential component of barrier protection ensuring the survival of the host. It will be interesting to see, whether the manipulation of neuro-immune interactions in control of ILC function may deliver a potent tool, to either boost ILC mediated protective immunity or ablate pathogenic functions in the future.

Steroid hormones

While most cytokines in control of ILC may primarily function in the immediate tissue environment, another way of achieving immune modulation at distal body sites may be through the release of soluble mediators into the blood stream. The bi-directionally interaction of the immune and the endocrine system are well documented since the middle of the 19th century. The endocrine system predominately communicates through the release of a broad array of signaling molecules termed hormones. In particular, a distinct subset of these molecules, the steroid hormones seem to posses immunomodulatory roles [77, 78]. Steroid hormones are synthesized from cholesterol through an enzymatic process called steroidogenesis occurring in the mitochondria. Synthesized steroid hormones are secreted by the adrenal cortex, testes and ovaries and by the placenta during pregnancy. Functions underlying hormonal control include the development of sexual characteristics, coordination of host metabolism and inflammation. The two types of steroid hormones mediating all of the above mentioned effects are corticosteroids, which include glucocorticoids (GC) and mineralcorticoids, and sex steroids, such as androgens, estrogens and progestogens [78, 79].

Corticosteroids

Adrenal glucocorticoid production is induced upon activation of the hypothalamic-pituitary-adrenal (HPA) axis, acting as a neural-endocrine “hub” coordinating responses to external stimuli. This axis is triggered to increase the endogenous production of glucocorticoid upon psychological stress, physical strain and tissue trauma [78]. In addition, glucocorticoid secretion can be stimulated by cytokines such as IL-1, IL-6 and TNF acting on the hypothalamus [80]. Through interaction with ubiquitously expressed glucocorticoid receptors (GRs), glucocorticoids can facilitate pleiotropic effects on different types of cells, including immune cells [78]. Recently, GR expressed on splenic and liver ILC1 including NK cells were reported to control uncontrolled IFN-γ production in the context of septic shock induced by injection of LPS [81]. Reduced expression of IFN-γ allowed for secretion of IL-10 from a Ly6C^{high}CD11b^{low} myeloid cells and increased tolerance to endotoxin. However, the specific deletion of GR on NKp46+ ILC1 rendered mice susceptible to endotoxin-induced septic shock. Furthermore, corticosteroids are able to suppress ILC2 activation elicited by IL-33 [82]. However, the same study revealed that stimulation of ILC2 with TSLP ablates the suppressive capacity of steroids and this unresponsiveness may play an important role in steroid resistant asthma. Thus, corticosteroids appear to play a

central role in controlling ILC1 and ILC2 functions in the context of systemic infection and airway inflammation (Figure 2).

Sex steroids

Interestingly, many infections or chronic inflammatory conditions are differentially represented in women or men. In general, women develop more pronounced immune responses than men, thus being less vulnerable to viral, bacterial or parasitic infections. However, increased protection from infections in women may come to the cost of a higher risk to develop autoimmunity and allergy [83]. While the sex differences impacting on disease are well documented, little is known about the cellular and molecular mechanisms affecting the underlying immune response. Since, ILC are both, key players of barrier immunity but also critical drivers of chronic inflammation, sex differences effecting ILC biology are an area of growing importance and interest.

In this regard, male mice were recently found to display reduced numbers of both, ILC2p in the bone marrow and mature ILC2 in peripheral tissues in comparison to female mice [84]. Consequently, male mice exhibited reduced responsiveness to IL-33 or allergen-driven airway inflammation. Reduction in ILC2 accumulation was accompanied by reduced eosinophil influx and decreased production of the type 2 cytokines IL-4, IL-5 and IL-13. The underlying reason for suppressed ILC2 responses turned out to be caused by androgen. Signaling through the androgen receptor (AR) expressed on both ILC2p and ILC2, appears to limit the differentiation of ILC2p into mature ILC2 and the subsequent maintenance of this particular cell type in the tissues [84]. Interestingly, the testosterone derivate 5^{α}-dihydrotestosterone (DHT) can mediate similar suppressive effects by binding to AR and acting as an alternative ligand. In this context, ILC2-dependent airway inflammation is suppressed by DHT functioning as a direct inhibitor of ILC2 responses but also by reducing the release of IL-33 and TSLP [85].

Beyond the modulation by male sex hormones, female sex hormones emerge as important regulators of ILC2 residing in the uterus. Uterine ILC2 were found to be nearly absent in ovariectomized mice but to increase in wild type mice treated with estrogen, a treatment that left pulmonary ILC2 unaffected [86]. This differential responsiveness to estrogen is explained by a 10^5-fold increase in estrogen receptor α (ERα) expression in uterine ILC2 in comparison to pulmonary ILC2. Further, estrogen exposure results in upregulation of the IL-1 family member *Il1f9* and decreased expression of the proapoptotic gene Bcl-2-interacting killer (*Bik)*, which suggests a key role of estrogen in the steady-state accumulation of ILC2 in the uterus [86]. Such findings are important steps towards a better understanding of ILC-mediated immune responses by sex hormones and offers the potential to shape our understanding of barrier immunology in the future (Figure 2).

CONCLUSIONS

Since the first description of ILC as essential players in barrier immunity and tissue homeostasis, extensive research has focused on understanding their function in connection to the tissue microenvironment. Cytokines produced upon tissue damage, or in the context of immune activation by pathogens were discovered to function as major controllers of ILC-mediated immunity. However, this immune centric view of ILC function is currently changing and a multitude of endogenous and exogenous factors of non-immune origin are able to substantially modulate or in some cases even directly activate ILC responses. These factors comprise dietary-derived products, neuropeptides and steroid hormones rendering ILC important hubs for the integration of signals originating from systems in direct control of organismal physiology. These organized networks include the digestive, the nervous and the endocrine system. Depending on the tissue and the trigger of the signal, such factors may exert their function on different ILC subsets, thus acting as rheostats for both the type of immune response and the magnitude. The intestinal immune system in particular is in constant contact with microbial or dietary derived products. In this regard metabolites derived from tryptophan, or vitamin A play a key role in barrier immunity through activation of AhR or RAR, respectively. Of particular interest is the direct suppression of innate type II immunity by RA, which emphasizes, that dietary metabolites not only change the amplitude of a predefined immune response, but also actively modulate the type of the immune response. This finding could be extremely important in our understanding of how changes in dietary habits may result in the development of chronic inflammatory conditions such as IBD or asthma. In this regard lipid mediators , many of which critically depend on dietary supply, crystalize as additional modulators of ILC2 immunity. Besides the local modulation of immune responses, lipids may act as potential long-range factors able to influence the immune response at distal organs. This function may be important for bolstering protection of the organism but may also contribute to immune pathology and spreading of inflammation, as evident in the atopic march. A similar long-range function on distant barrier tissues may be mediated by neuropeptides. Local immune activation may increase tissue protection at distal sites through the coordinated control of immune activation by neurons. Furthermore, the

detailed study of nervous-immune interactions may eventually reveal the underlying reasons for another unsolved riddle – the effect of mental conditions on the immune system. Although many questions remain, in particular in regard to the regulation of neuropeptides by infections, the finding that NMU is a direct inducer of ILC2-mediated cytokine release is groundbreaking [69–71]. This implicates that ILC function may be under the direct control of neurons without the previous need for licensing by cytokines. Finally, the control of ILC function by steroid hormones is another excellent example of how this fascinating group of immune cells is able to integrate signals controlling host physiology. This suggests a constant monitoring of overall body functions by ILC to maintain barrier immunology. Thus, the regulation of ILC responses at barrier tissues is a complex network of interconnecting systems, cells, and signaling molecules, which altogether act in harmony to facilitate tissue maintenance and protection against invading pathogens. However, disturbances of this finely chiseled network of tissue homeostasis may result in pathology and chronic inflammation.

FUTURE DIRECTIONS

Many chronic inflammatory conditions, currently on the rise in westernized countries manifest at tissue sites also harboring different ILC subsets. Although, ILC as primarily tissue resident immune cells are important for tissue maintenance and the reestablishment of tissue homeostasis after perturbances experienced after infection or injury, overactivation of ILC has been implicated to substantially contribute to immune pathology. In this respect ILC predominately rely on tissue-derived cytokines and locally generated signals. However, as discussed above latest developments in the field suggest the regulation of tissue resident ILC responses can be influenced by a complex network of interconnecting systems, cells, and signaling molecules such as dietary-derived products, neuropeptides and hormones. A better understanding of this complex network may provide a novel toolbox to specifically target tissue specific immune pathologies such as psoriasis, IBD or asthma.

FIGURE LEGENDS

Figure 1. Dietary products in control of ILC function.
Dietary nutrients are metabolized to form important modulators of ILC function. AhR ligands and retinoic acid (RA) derived from vitamin A maintain ILC3 and induce the production of IL-22. In return, RA exhibits direct suppression of ILC2. Essential plant-derived fatty acids polyunsaturated fatty acids (PUFA) are converted into arachidonic acid (AA) in the host and further metabolized into prostaglandins (PGs), cysteinyl leukotrienes (CysLTs), and lipoxins (LXs). Prostaglandin D_2 (PGD_2) and CysLTs activate ILC2 and support expression of the cytokines IL-5 and IL-13. In contrast prostaglandin I_2 (PGI_2) and lipoxin A_4 (LXA_4) inhibits the function of ILC2 but promote NK cell specific suppression of eosinophils. Prostaglandin E_2 (PGE_2) displays a dual role by supporting the function of ILC3 but inhibiting the activation of ILC2. Finally, the lysophospholipid S1P, derived from cellular membranes controls trafficking and migration of inflammatory ILC2.

Figure 2. Nervous and endocrine signals in control of ILC function.
Signaling mediators of the nervous system such as neuromedin U (NMU) and vasoactive intestinal peptide (VIP) induce activation of ILC2 and expression of the cytokines IL-5, IL-9 and IL-13, whereas epinephrine (EPI) represses ILC2 numbers and responses. On the other hand, glial-derived neurotrophic factor (GDNF) family ligands (GFL) is an activator of ILC3 and IL-22 secretion. The endocrine system impacts on ILC function with the release of steroid hormones (corticosteroids and sex steroids) produced by the adrenal cortex, testes and ovaries. Glucocorticosteroids (GC) are released from the adrenal glands and inhibit both secretion of ILC1-derived IFN- γ and cytokine production from ILC2. Sex hormones impact on ILC2 function and development through androgen (AR) secreted from testes, whereas estrogen (ER) produced in the uterus enhances the number of uterine ILC2.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work and approved it for publication.

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REFERENCES

1. Sonnenberg GF, Artis D (2015) Innate lymphoid cells in the initiation, regulation and resolution of inflammation. Nat Med 21:698–708 . doi: 10.1038/nm.3892
2. Eberl G, Colonna M, Di Santo JP, McKenzie ANJ (2015) Innate lymphoid cells: A new paradigm in immunology. Science (80-) 348:aaa6566-aaa6566 . doi: 10.1126/science.aaa6566
3. Liu M, Zhang C (2017) The role of innate lymphoid cells in immune-mediated liver diseases. Front. Immunol. 8
4. Xiong T, Turner J (2018) Innate lymphoid cells in autoimmunity and chronic inflammatory diseases. Semin Immunopathol. doi: 10.1007/s00281-018-0670-4
5. Spits H, Artis D, Colonna M, et al (2013) Innate lymphoid cells-a proposal for uniform nomenclature. Nat Rev Immunol 13:145–149 . doi: 10.1038/nri3365
6. Constantinides MG, McDonald BD, Verhoef PA, Bendelac A (2014) A committed precursor to innate lymphoid cells. Nature 508:397–401 . doi: 10.1038/nature13047
7. Klose CSN, Flach M, Möhle L, et al (2014) Differentiation of type 1 ILCs from a common progenitor to all helper-like innate lymphoid cell lineages. Cell 157:340–356 . doi: 10.1016/j.cell.2014.03.030
8. Serafini N, Vosshenrich CAJ, Di Santo JP (2015) Transcriptional regulation of innate lymphoid cell fate. Nat Rev Immunol 15:415–428 . doi: 10.1038/nri3855
9. Fuchs A, Vermi W, Lee JS, et al (2013) Intraepithelial type 1 innate lymphoid cells are a unique subset of il-12- and il-15-responsive ifn-??-producing cells. Immunity 38:769–781 . doi: 10.1016/j.immuni.2013.02.010
10. Bernink JH, Peters CP, Munneke M, et al (2013) Human type 1 innate lymphoid cells accumulate in inflamed mucosal tissues. Nat Immunol 14:221–229 . doi: 10.1038/ni2534
11. Zook EC, Kee BL (2016) Development of innate lymphoid cells. Nat Immunol 17:775–782 . doi: 10.1038/ni.3481
12. Artis D, Spits H (2015) The biology of innate lymphoid cells. Nature 517:293–301
13. Moro K, Yamada T, Tanabe M, et al (2010) Innate production of TH2 cytokines by adipose tissue-associated c-Kit+Sca-1+ lymphoid cells. Nature 463:540–544 . doi: 10.1038/nature08636
14. Price AE, Liang H-E, Sullivan BM, et al (2010) Systemically dispersed innate IL-13-expressing cells in type 2 immunity. Proc Natl Acad Sci 107:11489–11494 . doi: 10.1073/pnas.1003988107
15. Mjösberg JM, Trifari S, Crellin NK, et al (2011) Human IL-25- and IL-33-responsive type 2 innate lymphoid cells are defined by expression of CRTH2 and CD161. Nat Immunol 12:1055–1062 . doi: 10.1038/ni.2104
16. Monticelli LA, Sonnenberg GF, Abt MC, et al (2011) Innate lymphoid cells promote lung-tissue homeostasis after infection with influenza virus. Nat Immunol 12:1045–1054 . doi: 10.1038/ni.2131
17. Cella M, Fuchs A, Vermi W, et al (2009) A human natural killer cell subset provides an innate source of IL-22 for mucosal immunity. Nature 457:722–725 . doi: 10.1038/nature07537
18. Buonocore S, Ahern PP, Uhlig HH, et al (2010) Innate lymphoid cells drive interleukin-23-dependent innate intestinal pathology. Nature 464:1371–1375 . doi: 10.1038/nature08949
19. Eder W, Ege MJ, von Mutius E (2006) The Asthma Epidemic. N Engl J Med 355:2226–2235 . doi: 10.1056/NEJMra054308
20. Maslowski KM, MacKay CR (2011) Diet, gut microbiota and immune responses. Nat. Immunol. 12:5–9
21. Strachan DP (1989) Hay fever, hygiene, and household size. BMJ 299:1259–1260 . doi: 10.1136/bmj.299.6710.1259
22. Strachan DP (2000) Family size, infection and atopy: the first decade of the “hygiene hypothesis”. Thorax 55 Suppl 1:S2–S10 . doi: 10.1136/thorax.55.suppl_1.S2
23. Wills-Karp M, Santeliz J, Karp CL (2001) The germless theory of allergic disease: revisiting the hygiene hypothesis. Nat Rev Immunol 1:69–75 . doi: 10.1038/35095579
24. Yazdanbakhsh M, Kremsner PG, Van Ree R (2002) Immunology: Allergy, parasites, and the hygiene hypothesis. Science (80-.). 296:490–494
25. Veldhoen M, Brucklacher-Waldert V (2012) Dietary influences on intestinal immunity. Nat. Rev. Immunol. 12:696–708
26. Wheeler MA, Rothhammer V, Quintana FJ (2017) Control of immune-mediated pathology via the aryl hydrocarbon receptor. J. Biol. Chem. 292:12383–12389
27. Gu Y-Z, Hogenesch JB, Bradfield CA (2000) The PAS Superfamily: Sensors of Environmental and Developmental Signals. Annu Rev Pharmacol Toxicol 40:519–561 . doi: 10.1146/annurev.pharmtox.40.1.519
28. Cella M, Colonna M (2015) Aryl hydrocarbon receptor: Linking environment to immunity. Semin. Immunol. 27:310–314
29. Bernink JH, Krabbendam L, Germar K, et al (2015) Interleukin-12 and -23 Control Plasticity Of Cd127+ Group 1 And Group 3 Innate Lymphoid Cells In The Intestinal Lamina Propria. Immunity 43:146–160 . doi: 10.1016/j.immuni.2015.06.019

30. Kiss EA, Vonarbourg C, Kopfmann S, et al (2011) Natural aryl hydrocarbon receptor ligands control organogenesis of intestinal lymphoid follicles. Science (80-) 334:1561–1565 . doi: 10.1126/science.1214914
31. Qiu J, Heller JJ, Guo X, et al (2012) The Aryl Hydrocarbon Receptor Regulates Gut Immunity through Modulation of Innate Lymphoid Cells. Immunity 36:92–104 . doi: 10.1016/j.immuni.2011.11.011
32. Li Y, Innocentin S, Withers DR, et al (2011) Exogenous stimuli maintain intraepithelial lymphocytes via aryl hydrocarbon receptor activation. Cell 147:629–640 . doi: 10.1016/j.cell.2011.09.025
33. Lee JS, Cella M, McDonald KG, et al (2012) AHR drives the development of gut ILC22 cells and postnatal lymphoid tissues via pathways dependent on and independent of Notch. Nat Immunol 13:144–152 . doi: 10.1038/ni.2187
34. Schiering C, Wincent E, Metidji A, et al (2017) Feedback control of AHR signalling regulates intestinal immunity. Nature 542:242–245 . doi: 10.1038/nature21080
35. Zelante T, Iannitti RG, Cunha C, et al (2013) Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22. Immunity 39:372–385 . doi: 10.1016/j.immuni.2013.08.003
36. Hall JA, Grainger JR, Spencer SP, Belkaid Y (2011) The role of retinoic acid in tolerance and immunity. Immunity 35:13–22
37. Duester G (2008) Retinoic Acid Synthesis and Signaling during Early Organogenesis. Cell 134:921–931
38. Liu Z-M, Wang K-P, Ma J, Guo Zheng S (2015) The role of all-trans retinoic acid in the biology of Foxp3+ regulatory T cells. Cell Mol Immunol 12:553–7 . doi: 10.1038/cmi.2014.133
39. Spencer SP, Wilhelm C, Yang Q, et al (2014) Adaptation of innate lymphoid cells to a micronutrient deficiency promotes type 2 barrier immunity. Science (80-) 343:432–437 . doi: 10.1126/science.1247606
40. Mielke LA, Jones SA, Raverdeau M, et al (2013) Retinoic acid expression associates with enhanced IL-22 production by γδ T cells and innate lymphoid cells and attenuation of intestinal inflammation. J Exp Med 210:1117–1124 . doi: 10.1084/jem.20121588
41. Van De Pavert SA, Ferreira M, Domingues RG, et al (2014) Maternal retinoids control type 3 innate lymphoid cells and set the offspring immunity. Nature 508:123–127 . doi: 10.1038/nature13158
42. Kim MH, Taparowsky EJ, Kim Correspondence CH, Kim CH (2015) Retinoic Acid Differentially Regulates the Migration of Innate Lymphoid Cell Subsets to the Gut. Immunity 43:107–119 . doi: 10.1016/j.immuni.2015.06.009
43. Murakami M (2011) Lipid Mediators in Life Science. Exp Anim 60:7–20 . doi: 10.1538/expanim.60.7
44. de Jong AJ, Kloppenburg M, Toes REM, Ioan-Facsinay A (2014) Fatty acids, lipid mediators, and T-cell function. Front. Immunol. 5
45. Theron AJ, Steel HC, Tintinger GR, et al (2014) Cysteinyl leukotriene receptor-1 antagonists as modulators of innate immune cell function. J. Immunol. Res. 2014
46. Cavagnero K, Doherty TA (2017) Cytokine and Lipid Mediator Regulation of Group 2 Innate Lymphoid Cells (ILC2s) in Human Allergic Airway Disease. J cytokine Biol 2:
47. Doherty TA, Khorram N, Lund S, et al (2013) Lung type 2 innate lymphoid cells express cysteinyl leukotriene receptor 1, which regulates TH2 cytokine production. J Allergy Clin Immunol 132:205–13 . doi: 10.1016/j.jaci.2013.03.048
48. von Moltke J, O'Leary CE, Barrett NA, et al (2017) Leukotrienes provide an NFAT-dependent signal that synergizes with IL-33 to activate ILC2s. J Exp Med 214:27–37 . doi: 10.1084/jem.20161274
49. Lund SJ, Portillo A, Cavagnero K, et al (2017) Leukotriene C4 Potentiates IL-33-Induced Group 2 Innate Lymphoid Cell Activation and Lung Inflammation. J Immunol 199:1096–1104 . doi: 10.4049/jimmunol.1601569
50. Salimi M, Stöger L, Liu W, et al (2017) Cysteinyl leukotriene E4 activates human group 2 innate lymphoid cells and enhances the effect of prostaglandin D2 and epithelial cytokines. J Allergy Clin Immunol 12:556–562 . doi: 10.1016/j.jaci.2016.12.958
51. Ricciotti E, Fitzgerald GA (2011) Prostaglandins and inflammation. Arterioscler Thromb Vasc Biol 31:986–1000 . doi: 10.1161/ATVBAHA.110.207449
52. Boyce JA (2007) Mast cells and eicosanoid mediators: A system of reciprocal paracrine and autocrine regulation. Immunol. Rev. 217:168–185
53. Konya V, Mjösberg J (2016) Lipid mediators as regulators of human ILC2 function in allergic diseases. Immunol Lett 179:36–42 . doi: 10.1016/j.imlet.2016.07.006
54. Xue L, Salimi M, Panse I, et al (2014) Prostaglandin D2 activates group 2 innate lymphoid cells through chemoattractant receptor-homologous molecule expressed on TH2 cells. J Allergy Clin Immunol 133: . doi: 10.1016/j.jaci.2013.10.056
55. Barnig C, Cernadas M, Dutile S, et al (2013) Lipoxin A4 regulates natural killer cell and type 2 innate lymphoid cell activation in asthma. Sci Transl Med 5: . doi: 10.1126/scitranslmed.3004812
56. Tait Wojno ED, Monticelli LA, Tran S V., et al (2015) The prostaglandin D2 receptor CRTH2 regulates accumulation of group 2 innate lymphoid cells in the inflamed lung. Mucosal Immunol 8:1313–1323 .

doi: 10.1038/mi.2015.21
57. Dorris SL, Peebles RS (2012) PGI2 as a regulator of inflammatory diseases. Mediators Inflamm 2012:926968 . doi: 10.1155/2012/926968
58. Zhou W, Toki S, Zhang J, et al (2016) Prostaglandin I2 signaling and inhibition of group 2 innate lymphoid cell responses. Am J Respir Crit Care Med 193:31–42 . doi: 10.1164/rccm.201410-1793OC
59. Harizi H (2013) The immunobiology of prostanoid receptor signaling in connecting innate and adaptive immunity. Biomed Res. Int. 2013
60. Smith CL, Dickinson P, Forster T, et al (2014) Identification of a human neonatal immune-metabolic network associated with bacterial infection. Nat Commun 5: . doi: 10.1038/ncomms5649
61. Duffin R, OConnor RA, Crittenden S, et al (2016) Prostaglandin E2 constrains systemic inflammation through an innate lymphoid cell-IL-22 axis. Science (80-) 351:1333–1338 . doi: 10.1126/science.aad9903
62. Maric J, Ravindran A, Mazzurana L, et al (2017) PGE 2 suppresses human group 2 innate lymphoid cell function. J Allergy Clin Immunol. doi: 10.1016/j.jaci.2017.09.050
63. Serhan CN (2007) Resolution Phase of Inflammation: Novel Endogenous Anti-Inflammatory and Proresolving Lipid Mediators and Pathways. Annu Rev Immunol 25:101–137 . doi: 10.1146/annurev.immunol.25.022106.141647
64. Takabe K, Paugh SW, Milstien S, Spiegel S (2008) "Inside-Out" Signaling of Sphingosine-1-Phosphate: Therapeutic Targets. Pharmacol Rev 60:181–195 . doi: 10.1124/pr.107.07113
65. Huang Y, Mao K, Chen X, et al (2018) S1P-dependent interorgan trafficking of group 2 innate lymphoid cells supports host defense. Science 359:114–119 . doi: 10.1126/science.aam5809
66. Talbot S, Foster SL, Woolf CJ (2016) Neuroimmunity: Physiology and Pathology. Annu Rev Immunol 34:421–447 . doi: 10.1146/annurev-immunol-041015-055340
67. Chiu IM, Von Hehn CA, Woolf CJ (2012) Neurogenic inflammation and the peripheral nervous system in host defense and immunopathology. Nat. Neurosci. 15:1063–1067
68. Foster SL, Seehus CR, Woolf CJ, Talbot S (2017) Sense and immunity: Context-dependent neuro-immune interplay. Front. Immunol. 8
69. Klose CSN, Mahlakõiv T, Moeller JB, et al (2017) The neuropeptide neuromedin U stimulates innate lymphoid cells and type 2 inflammation. Nature 549:282–286 . doi: 10.1038/nature23676
70. Wallrapp A, Riesenfeld SJ, Burkett PR, et al (2017) The neuropeptide NMU amplifies ILC2-driven allergic lung inflammation. Nature 549:351–356 . doi: 10.1038/nature24029
71. Cardoso V, Chesné J, Ribeiro H, et al (2017) Neuronal regulation of type 2 innate lymphoid cells via neuromedin U. Nature 549:277–281 . doi: 10.1038/nature23469
72. Ganea D, Hooper KM, Kong W (2015) The neuropeptide vasoactive intestinal peptide: direct effects on immune cells and involvement in inflammatory and autoimmune diseases. Acta Physiol (Oxf) 213:442–52 . doi: 10.1111/apha.12427
73. Talbot S, Abdulnour REE, Burkett PR, et al (2015) Silencing Nociceptor Neurons Reduces Allergic Airway Inflammation. Neuron 87:341–355 . doi: 10.1016/j.neuron.2015.06.007
74. Nussbaum JC, Van Dyken SJ, Von Moltke J, et al (2013) Type 2 innate lymphoid cells control eosinophil homeostasis. Nature 502:245–248 . doi: 10.1038/nature12526
75. Moriyama S, Brestoff JR, Flamar A-L, et al (2018) B ₂ -Adrenergic Receptor–Mediated Negative Regulation of Group 2 Innate Lymphoid Cell Responses. Science (80-) 359:1056–1061 . doi: 10.1126/science.aan4829
76. Ibiza S, García-Cassani B, Ribeiro H, et al (2016) Glial-cell-derived neuroregulators control type 3 innate lymphoid cells and gut defence. Nature 535:440–443 . doi: 10.1038/nature18644
77. Ashwell JD, Lu FW, Vacchio MS (2000) Glucocorticoids in T cell development and function. Annu Rev Immunol 18:309–45 . doi: 10.1146/annurev.immunol.18.1.309
78. Cain DW, Cidlowski JA (2017) Immune regulation by glucocorticoids. Nat. Rev. Immunol. 17:233–247
79. Miller WL, Auchus RJ (2011) The molecular biology, biochemistry, and physiology of human steroidogenesis and its disorders. Endocr Rev 32:81–151 . doi: 10.1210/er.2010-0013
80. Dunn AJ (2000) Cytokine Activation of the HPA Axis. Ann N Y Acad Sci 917:608–617 . doi: 10.1111/j.1749-6632.2000.tb05426.x
81. Quatrini L, Wieduwild E, Guia S, et al (2017) Host resistance to endotoxic shock requires the neuroendocrine regulation of group 1 innate lymphoid cells. J Exp Med jem.20171048 . doi: 10.1084/jem.20171048
82. Kabata H, Moro K, Fukunaga K, et al (2013) Thymic stromal lymphopoietin induces corticosteroid resistance in natural helper cells during airway inflammation. Nat Commun 4: . doi: 10.1038/ncomms3675
83. Laffont S, Blanquart E, Guéry J-C (2017) Sex Differences in Asthma: A Key Role of Androgen-Signaling in Group 2 Innate Lymphoid Cells. Front Immunol 8: . doi: 10.3389/fimmu.2017.01069
84. Laffont S, Blanquart E, Savignac M, et al (2017) Androgen signaling negatively controls group 2 innate lymphoid cells. J Exp Med 214:1581–1592 . doi: 10.1084/jem.20161807

85. Cephus JY, Stier MT, Fuseini H, et al (2017) Testosterone Attenuates Group 2 Innate Lymphoid Cell-Mediated Airway Inflammation. Cell Rep 21:2487–2499 . doi: 10.1016/j.celrep.2017.10.110
86. Bartemes K, Chen C-C, Iijima K, et al (2017) IL-33–Responsive Group 2 Innate Lymphoid Cells Are Regulated by Female Sex Hormones in the Uterus. J Immunol ji1602085 . doi: 10.4049/jimmunol.1602085

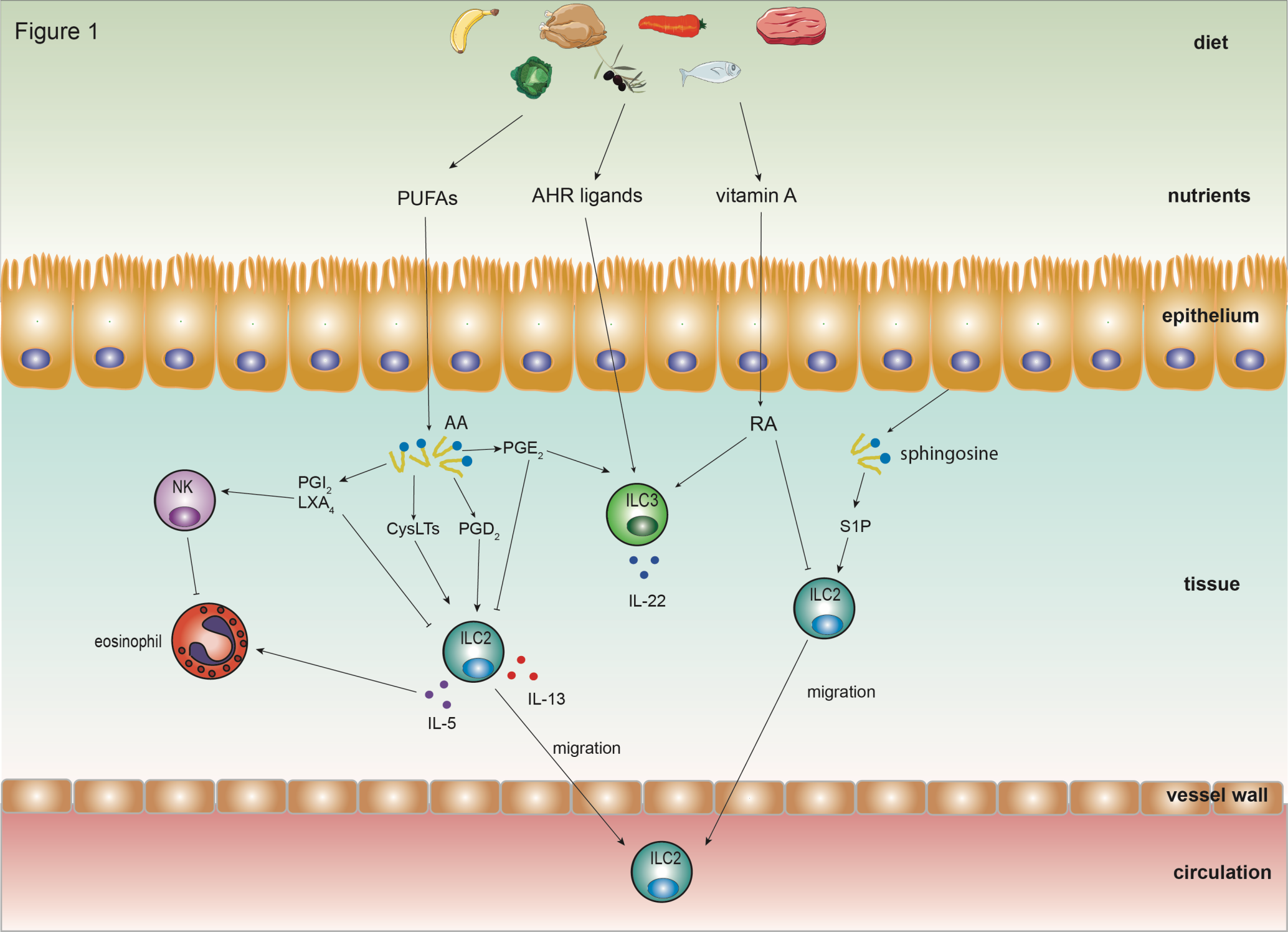
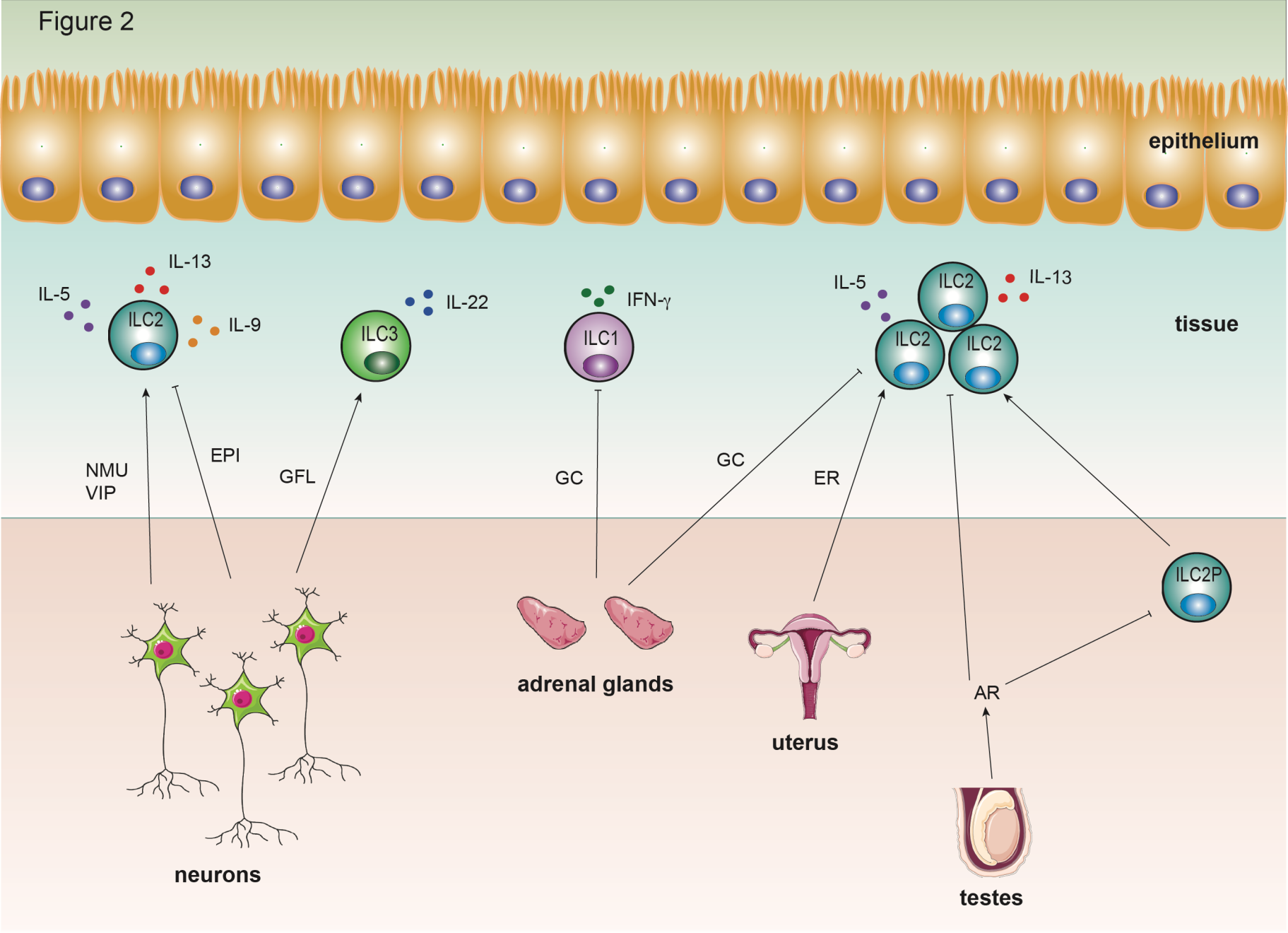


Figure 1
diet
PUFAs
AHR ligands
vitamin A
nutrients
epithelium
AA
RA
sphingosine
PGE2
PGI2
LXA4
NK
CysLTs
PGD2
ILC3
S1P
IL-22
tissue
ILC2
eosinophil
ILC2
IL-13
IL-5
migration
migration
vessel wall
ILC2
circulation

Figure 2


epithelium
IL-13
IL-5
ILC2
IL-9
ILC3
IL-22
IFN-γ
ILC1
IL-5
ILC2
IL-13
ILC2
ILC2
tissue
NMU
VIP
EPI
GFL
GC
GC
ER
ILC2P
adrenal glands
uterus
AR
neurons
testes