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nature immunology

Innate lymphoid cells

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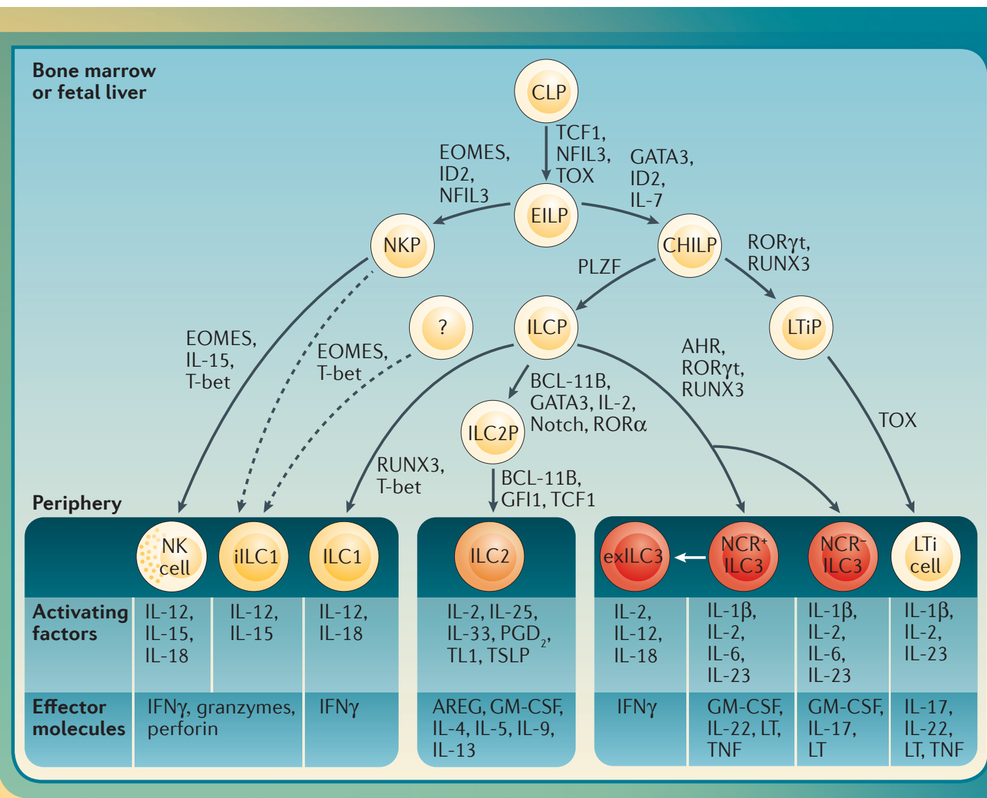
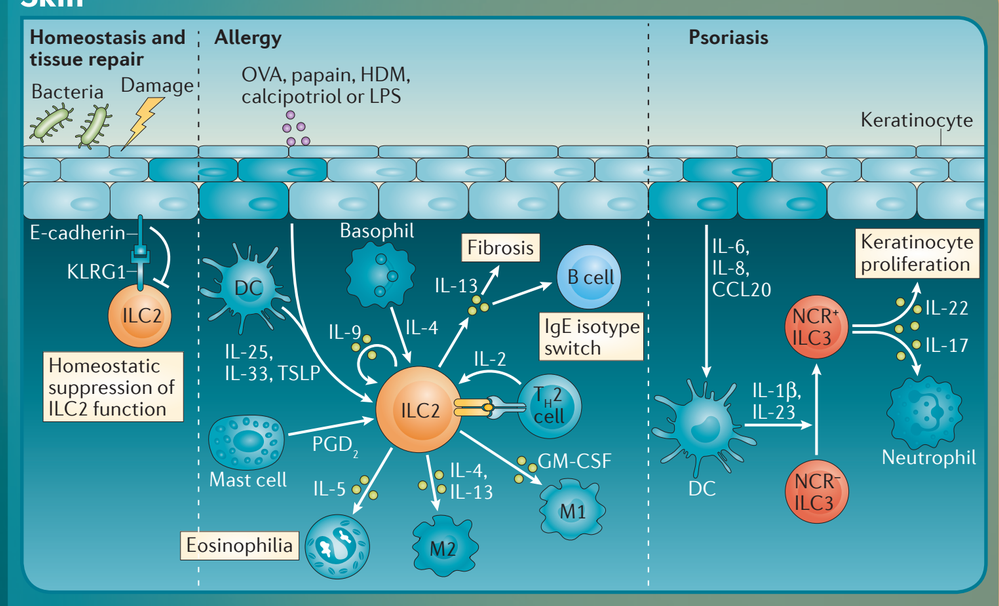
Innate lymphoid cells (ILCs) are recently described populations of lymphocytes that lack rearranged antigen-specific receptors. The ILC family has been divided into three main subsets — ILC1, ILC2 and ILC3 — and also includes natural killer (NK) cells and lymphoid tissue-inducer (LTi) cells. ILCs are increasingly appreciated to have important immune functions at mucosal surfaces, where they respond to signals they receive from other cells in the tissue microenvironment. However, they can regulate tissue homeostasis, inflammation and repair at both mucosal and non-mucosal sites, including the intestine, lungs and skin, as well as in adipose and lymphoid tissues[1]. ILC effector functions are mainly mediated through cytokine secretion and through direct cell–cell interactions with stromal cells and other immune cells. This Poster summarizes some of the key features of ILCs in homeostasis and disease.



ILC development

Much work has been done to define the ontogeny of mouse ILCs; however, human ILC development remains largely uncharacterized. ILCs originate from a common lymphoid progenitor (CLP), which develops into either a common helper innate lymphoid progenitor (CHILP)[2] under the influence of transcription factors such as TCF1[3] and ID2, or into an NK cell progenitor (NKP)[4] under the additional influence of EOMES and NFIL3. The subsequent expression of RORγt by the CHILP leads to LTi cell differentiation via the LTi cell precursor (LTiP), whereas PLZF expression marks the development of the ILC progenitor (ILCP) which, under the influence of T-bet, GATA3 or RORγt, gives rise to the ILC1, ILC2 or ILC3 subsets, respectively[5]. NCR⁺ ILC3s are characterized by IL-22 production, whereas NCR⁻ ILC3 produce IL-17. Both subsets can differentiate into IFNγ-producing exILC3s. The development of intraepithelial ILC1s (iILC1s) remains to be elucidated.

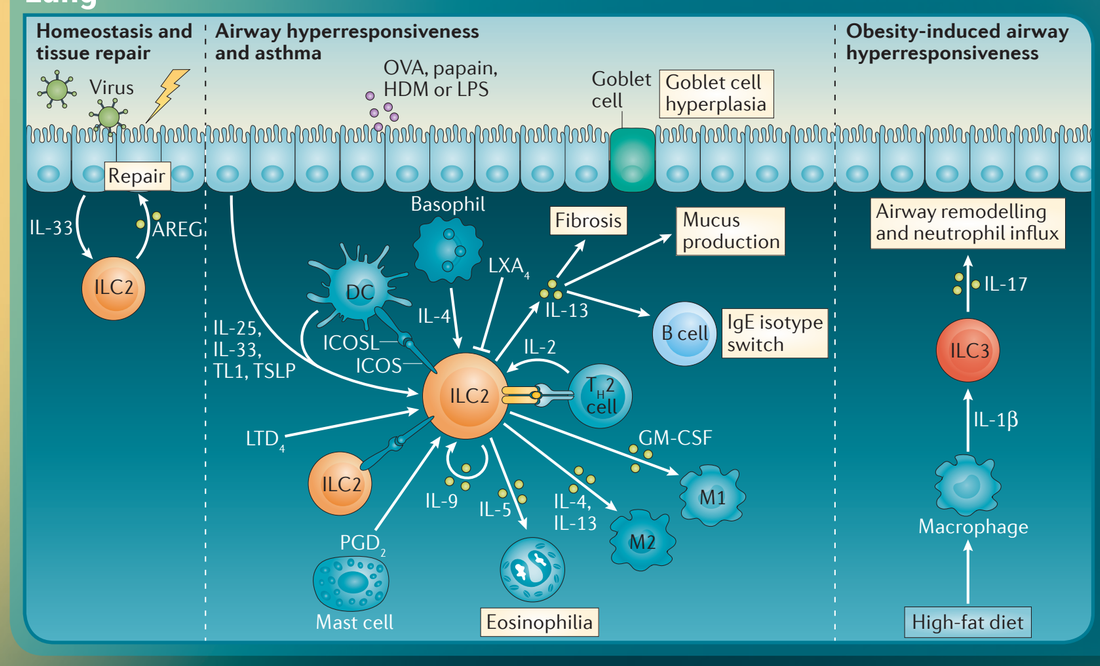


ILC2s are involved in type 2 inflammation

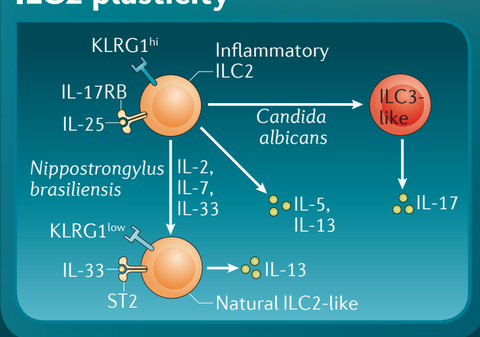
Several mouse models and clinical observations support a role for ILC2s in type 2 inflammation in the skin, lungs and intestine[6,7,8]. ILC2 activation is triggered by IL-25, IL-33, TSLP and PGD_2 produced by activated epithelial cells or immune cells in response to helminth infections or allergen exposure. The effector functions of ILC2s are largely mediated by IL-4, IL-5, IL-9 and IL-13 and promote goblet cell hyperplasia, mucus production, eosinophilia, IgE isotype switching and fibrosis[1]. Importantly, these mechanisms are mainly protective in the setting of helminth infection, in which ILC2 responses are driven predominantly by IL-33 but can become exaggerated and cause pathology in allergy and asthma. Interestingly, ILC2s display functional plasticity, and inflammatory ILC2s may also differentiate into IL-17-producing ILC3-like cells and participate in antifungal immunity[9].

The yin and yang of ILC3s

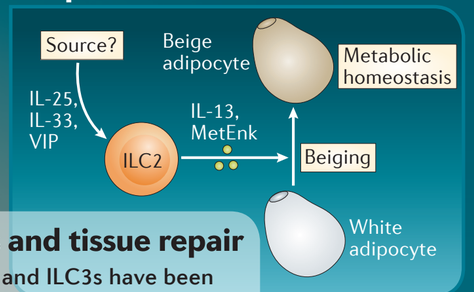
IL-22 produced by NCR⁺ ILC3s binds to the IL-22 receptor, which is exclusively expressed by non-haematopoietic cells. The tissue protective role of IL-22 in the intestine during intestinal infection has been well documented[10] and includes promotion of epithelial cell fucosylation, which supports host–microbiota symbiosis. However, the potent capacity of IL-22 to induce proliferation of stromal cells also implies that excessive IL-22 production may lead to pathology. Indeed, in a mouse model of colorectal cancer, tumour growth was enhanced by ILC3-derived IL-22[11]. Intriguingly, whereas IL-22 seems mainly protective in the intestine, IL-22-producing ILC3s accumulate in the skin of patients with psoriasis[12] and, supported by observations in a mouse model of psoriasis[13], this suggests a disease-promoting role for these cells in this tissue. Furthermore, in the lungs, ILC3s may promote obesity-induced airway hyperresponsiveness through the production of IL-17.



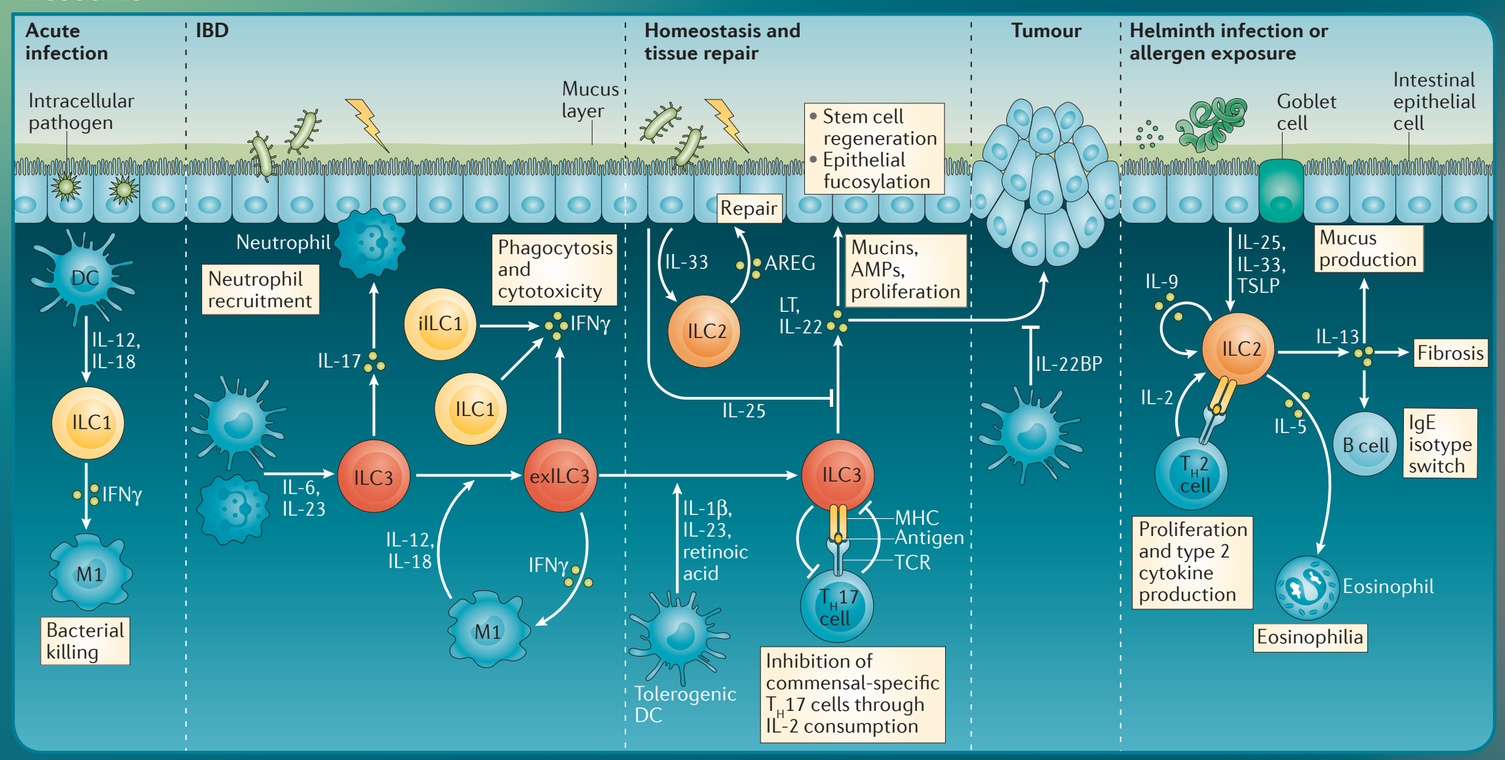
ILC2 plasticity



Adipose tissue



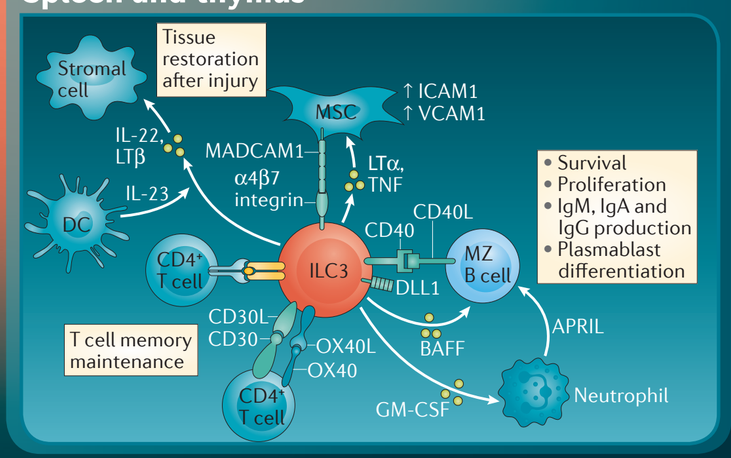
Intestine



The role for ILCs in homeostasis and tissue repair

Important tissue protective effects of ILC2s and ILC3s have been described. ILC3s produce IL-22, which is crucial for the repair of thymic tissue following viral infection[14] and for intestinal mucosal barrier protection[10]. In addition, ILC3s can suppress commensal-specific T_H17 cells through IL-2 consumption, preventing intestinal inflammation[15]. In the spleen, ILC3s interact with adaptive immune cells to maintain memory CD4⁺ T cells[16] and marginal zone (MZ) B cells[17]. Furthermore, ILC2s in adipose tissue produce met-enkephalin (MetEnk), which promotes beiging of adipose tissue[18]. Lung ILC2s contribute to tissue restoration upon viral insult through the production of AREG[19].

Spleen and thymus



ILCs contribute to intestinal inflammation and are functionally plastic

Human inflammatory bowel disease (IBD) is associated with an increased frequency of IL-17-producing ILC3s[20], which parallels findings in mice, in which *Helicobacter hepaticus*-induced colitis increases the number of IL-17- and IFNγ-producing ILC3s[21]. Noteworthy, neutralization of IL-17 in this model, or in clinical trials, does not ameliorate disease, pointing towards a crucial role for ILC3-derived IFNγ in IBD. In mice, intestinal environmental cues induce T-bet expression in RORγt⁺NCR⁺ ILC3s, which is crucial for defence against *Salmonella* infection[22]. However, this causes collateral damage that presents as enterocolitis. Paralleling these observations, human Crohn's disease is associated with an accumulation of IFNγ-producing ILC1s[23]. ILC1s can be derived from ILC3s under the influence of IL-12, whereas IL-23 and retinoic acid exposure lead to ILC3 re-differentiation[24]. Hence, a finely tuned balance of ILC1s and ILC3s ensures tissue integrity while maintaining immune defence in the intestine.

Abbreviations

AHR, aryl hydrocarbon receptor; AMPs, antimicrobial peptides; APRIL, a proliferation-inducing ligand; AREG, amphiregulin; BAFF, B cell activating factor; BCL-11B, B cell lymphoma 11B; CCL20, CC-chemokine ligand 20; CD30L, CD30 ligand; CD40L, CD40 ligand; DC, dendritic cell; DLL1, delta-like protein 1; EILP, early ILC progenitor; EOMES, eomesodermin; GFI1, growth factor independent protein 1; GM-CSF, granulocyte–macrophage colony-stimulating factor; HDM, house dust mite; ICAM1, intercellular adhesion molecule 1; ICOS, inducible T cell costimulator; ICOSL, ICOS ligand; ID2, inhibitor of DNA binding 2; IFNγ, interferon-γ; IL, interleukin; IL-17RB, IL-17 receptor B; IL-22BP, IL-22 binding protein; KLRG1, killer-cell lectin like receptor G1; LTD_4, leukotriene D_4; LPS, lipopolysaccharide; LT, lymphotoxin; LTβR, lymphotoxin-β receptor; LXA_4, lipoxin A_4; M1, type 1 macrophage; M2, type 2 macrophage; MADCAM1, mucosal addressin cell adhesion molecule 1; NCR, natural cytotoxicity receptor; NFIL3, nuclear factor IL-3 induced; OVA, ovalbumin; OX40L, OX40 ligand; PGD_2, prostaglandin D_2; PLZF, promyelocytic leukaemia zinc finger protein; ROR, retinoic acid receptor-related orphan receptor; RUNX3, runt-related transcription factor 3; ST2, IL-33 receptor; TCF1, T cell factor 1; TCR, T cell receptor; T_H, T helper; TL1, TNF-like ligand 1; TNF, tumor necrosis factor; TSLP, thymic stromal lymphopoietin; VCAM1, vascular cell adhesion molecule 1; VIP, vasoactive intestinal peptide.

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The author apologizes to colleagues whose work has not been cited owing to space limitations.

References and a table of the surface markers expressed by human and mouse ILCs are available online.

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