# SnapShot: Integrated Type 2 Immune Responses

Immunity

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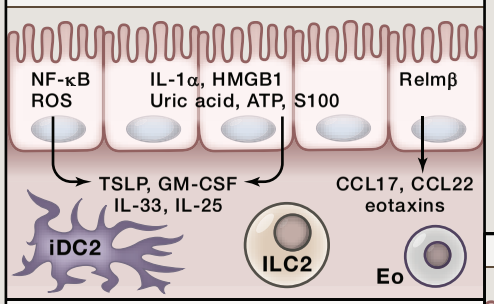
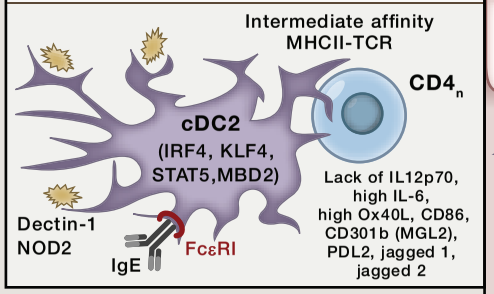
## Epithelial responses to type 2 immune stimuli

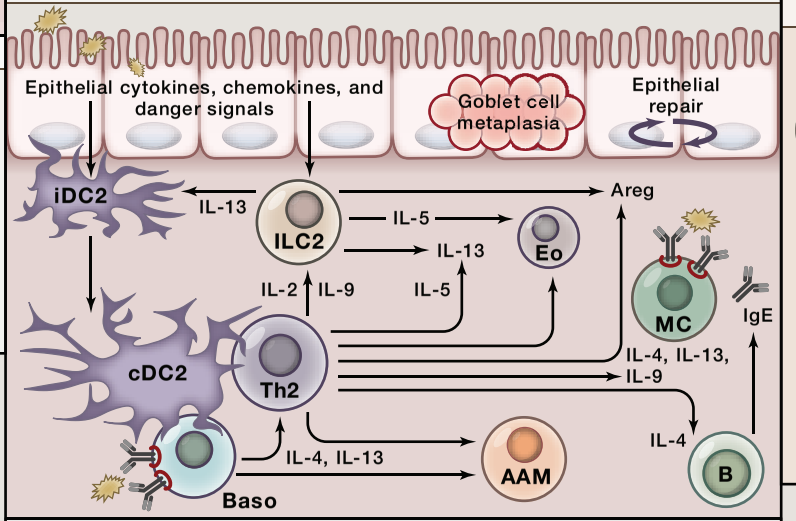



## The Th2 cell promoting DC

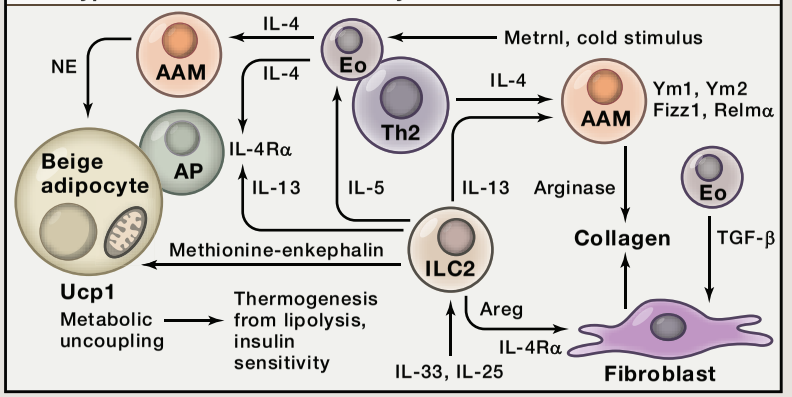



| Type 2 immune stimuli | Mechanisms |
|---|---|
| Helminths | Secreted proteases, ES62, *Schistosoma* omega-1 |
| Papain, Der p 1, Der p 9 allergens | PAR activation, ROS, tight junction, and fibrinogen cleavage |
| Der p 2, Fel d 1, nickel allergens | TLR4 agonism (direct or via MD2) |
| Alum adjuvant | Nlrp3 activation, crystal formation, extracellular DNA |
| Chitin (fungi, crustacea, insects) | Receptor?, EC activation, degraded by chitinases |
| Bee, wasp, and reptile venoms | Phospholipase A2 cleaves membrane phospholipids, others? |
| Environmental cold | Beige fat recruitment, PPARγ agonism? |

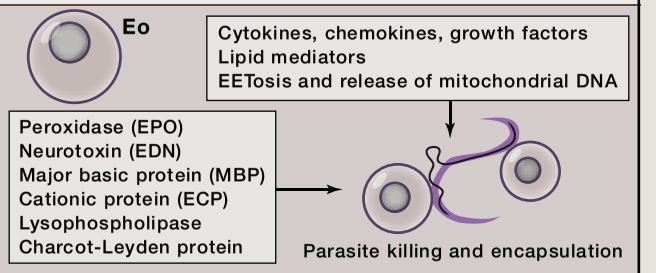
## Cellular interactions in type 2 immune responses in allergy



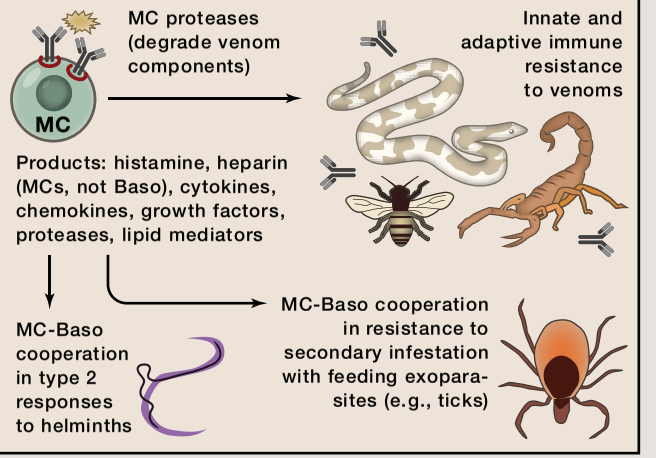

## Type 2 cell-mediated immunity in metabolism and fibrosis




## Eosinophil effector functions




## Mast cell (MC) and basophil (Baso) effector functions





| T cell receptor | Th2 cell | ILC2 |
|---|---|---|
| Transcription factors | C-Maf, GATA3, STAT5, STAT6, Eomes | GATA3, ROR-α, STAT6, Ets1 |
| Cytokines produced | IL-4, IL-5, IL-9, IL-13, Areg | IL-5, IL-13, Areg, Met-enkephalin, IL-4 (>human) |
| Cytokine receptors | IL-33R on $Th2_{mem}$, IL-25R, TSLPR, IL-21R | High IL-2R (CD25), IL-33R, IL-25R, TSLPR, IL-9R, CD127 |
| Chemokine receptors | CCR4, CCR8, CRTH2 | CCR4, CCR8, CRTH2, LTD4R |
| Other receptors | TCR | KLRG1, CD90, c-KIT |
| Innate functions | $Th2_{mem}$ can react to IL-33 in absence of TCR ligation | Many immune functions, metabolism control in beige fat |
| Adaptive functions | Promote IgE synthesis | Boost DC function, APC? |
| Diseases | Allergic asthma, rhinitis, eczema | Intrinsic asthma, nasal polyposis |

| Resistance to helminths and exoparasites | In some cases (but some MC functions may favor the parasite) | In some cases |
|---|---|---|
| Resistance to venoms | Yes, by release of proteases and perhaps heparin | ? |
| Receptors involved in stimulation (an incomplete list) | IL-4, IL-5, IL-6, IL-9, IL-33Rs, c-Kit$^{hi}$, IFN-γR, TLRs, C3aR, C5aR, etc. | IL-1R, IL-2(CD25), IL-3, IL-4, IL-5, IL-6, IL-8Rs, c-Kit$^{lo}$, TLRs, C3aR, C5aR, TSLPR, etc. |
| Allergic disorders (MCs & basophils contribute to anaphylaxis) | Positive and negative regulation of many aspects of inflammation and tissue remodeling | Promotion of inflammation; IL-4-induced development of M2 macrophages |
| Enhance IgE synthesis | Some settings | Some settings |

See online version for legend and references.

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## Cellular Interactions in Type 2 Cell-Mediated Immune Responses in Allergy

Helminths, venoms, proteases, allergens, and some bacteria and viruses (not shown) induce type 2 reactions via multiple mechanisms (see table), some of which may act in parallel or in concert. These responses are highly coordinated through collaboration of innate and adaptive immune cells via secreted cytokines and soluble mediators (not shown). Mast cells, basophils, and eosinophils can act as terminal effectors of type 2 cell-mediated immunity but also have the potential to influence the development and immunoregulation of the responses (e.g., via interleukin-4 [IL-4]/IL-13 that can enforce T helper 2 [Th2] cell polarization, cause alternatively activated macrophage [AAM] polarization, and activate DCs and innate lymphoid cells type 2 [ILC2s]). Upon recognition of type 2 cell stimuli, and instructed by epithelial cells (ECs), conventional DCs type 2 (cDC2s) polarize naive $CD4^+$ T cells ($CD4_n$) to become Th2 cells (see panel). One critical function of IL-4/IL-13 is induction of B cell immunoglobulin E (IgE) class switching, a process enhanced by CD40L. Once antigen-specific IgE is produced, IgE-dependent focused antigen presentation (via FcεRI expressed on DCs, or via CD23 on DCs or B cells, not shown) can result in generation of IgE to additional epitopes ("epitope spreading"), contributing to exacerbation of allergic disorders. IL-4/IL-13 also can induce epithelial goblet cell metaplasia, which can contribute to parasite expulsion but can cause airway obstruction with mucus in asthma. $CD4^+$ Th2 cells and ILC2s also produce amphiregulin (Areg), which promotes repair of epithelial cells via EGFR; this mechanism also might contribute to parasite expulsion.

A $CD4^+$ Th2 cell subset (Th9) produces IL-9 that drives ILC2 expansion and, in mice, proliferation of mast cell progenitors. ILC2s represent important early sources of IL-5 and IL-13 in responses to helminths and allergens. ILC2-derived IL-13 promotes the migration and activation of immature DCs, enforcing adaptive type 2 immunity. ILC2 functions are boosted by IL-2 (and IL-9) from $CD4^+$ Th2 cells. It is still debated whether, and to what extent, ILC2s, eosinophils, basophils, and mast cells also can act as antigen-presenting cells (APCs) in adaptive type 2 immunity in vivo.

## Differences and Similarities between Th2 Cells and ILC2

These cells share many functions, but ILC2s don't express the TCR. Emerging evidence indicates that memory Th2 cells ($Th2_{mem}$) might most resemble ILC2s in expressing high levels of IL-33R and IL-25R, secreting cytokines in the absence of TCR ligation. It is not yet clear to what extent ILC2s also contribute to IgE synthesis.

## Epithelial Responses to Type 2 Cell Stimuli

Most allergens and helminths enter the body via skin or mucosal surfaces, and innate responses of ECs at such sites (sometimes influenced by genetic or acquired impairments of epithelial barrier function) are integral components of elicited type 2 immune responses. Danger signals (like high-mobility group box 1) promote production of cytokines, thymic stromal lymphopoietin (TSLP), and/or granulocyte-macrophage colony-stimulating factor (GM-CSF) that stimulate DCs, ILCs, and other innate cells. ECs also produce chemokines (e.g., eotaxins and CCL17) that attract type 2 cells via CCR3 and CCR4 receptors.

## Eosinophil Functions

Eosinophils produce diverse products with roles in host defense (see figure), metabolism, tissue remodeling, and allergic disorders and might also contribute immunoregulatory functions. Modern asthma treatments stratify patients into eosinophil-rich or -poor subtypes.

## Mast Cell and Basophil Functions: Similarities and Differences

Mast cells (MCs) normally reside in tissues, especially in the skin and mucosal tissues, whereas basophils (Basos) are circulating granulocytes that are recruited into tissues from the blood. MCs and basophils express many high-affinity IgE receptors (FcεRIs) and can secrete distinct albeit partially overlapping spectra of products when activated by IgE and antigen or other mechanisms. Beyond roles in allergic disorders, MCs contribute to innate and adaptive (type 2) immune defenses against venoms, and MCs and basophils are thought to collaborate in orchestrating type 2 immune responses that can enhance resistance to certain internal parasites and ticks. Basophil activation tests (BATs) that measure increases in surface CD63 or CD203c (in human basophils) after crosslinking of IgE ex vivo are being evaluated to diagnose and monitor allergies.

## Type 2 Cell-Mediated Immunity in Metabolism and Fibrosis

Type 2 immune responses are also observed in adipose tissue, e.g., during cold exposure or after exercise-induced release of meteorin-like (Metrnl) hormone and, in general, are thought to promote metabolic normalcy. Cold exposure leads to accumulation of eosinophils and ILC2s that can contribute to proliferation of adipocyte progenitors (APs) and their differentiation to beige fat, where UCP1 leads to uncoupling of mitochondria and thermogenesis. IL-33 activated ILC2s and eosinophils (via IL-13 and IL-4, respectively) can contribute to this process by stimulating alternatively activated macrophage (AAM) differentiation, with ILC2-derived methionine-enkephalin and AAM-derived norepinephrine (NE) promoting lipolysis in white fat and thermogenesis in beige adipose tissue.

Eosinophils and AAMs have roles in tissue repair and in diverse fibrotic disorders. AAMs use arginine to produce hydroxyproline (a precursor of collagen) via arginase, thus moving away from pro-inflammatory NO production. Eosinophils produce TGF-β that promotes myofibroblast differentiation, together with IL-13 and Areg derived from ILC2s or Th2 cells.

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