ROLE OF IL-33 IN MODULATING HUMAN ALLERGEN SPECIFIC PATHOGENIC CD4+ T CELL RESPONSES

Nahir Garabatos, PhD
Postdoctoral Research Associate
Dr. Erik Wambre’s Lab
Benaroya Research Institute, Seattle WA
IL-33 plays an important role in allergy and inflammation

- IL-33, also called alarmin, is a pro-inflammatory cytokine induced by inflammatory stimulation leading to Type 2 immune responses in tissue epithelial cells.

- IL-33 mediates its biological effects via IL-1 receptor-like 1 (ST2).

- IL-33 acts on several cell types as a central mediator of atopic diseases including: food allergies, asthma and atopic dermatitis.

- Because IL-33 acts upstream in the type-2 immune cascade, it represent an attractive therapeutic target for the treatment of atopic diseases over competing agents that block only a subset of the cytokines responsible for atopic diseases.
A distinct TH2 cell subset is associated with type I allergic diseases

- CD27 expression distinguishes a **protective (CD27+)** from a **pathogenic (CD27-)** allergen specific T cell response developed in different allergy disorders.

- TH2A cell subset (CRTH2+, CD161+, CD27-, CD45RB- and CD49d+) represents a phenotypically distinct TH2 subpopulation confined to atopic individuals, which encompass the vast majority of pathogenic (CD27-negative) allergen-specific TH2 cells involved in type I allergic diseases.

✓ TH2A cells constitute potential biomarker and therapeutic target.
Allergic disease related differences emerged in the TH2 cell responses

- TH2A cell subset produced more transcript of IL-5 and IL-9 compared to conventional TH2 cells.
- They also selectively expressed IL-33R (IL1RL1 or ST2) and may differentially contribute to atopic diseases (TH2 driven pathology).
Role of IL-33 in promoting the activity of peanut-specific TH2A cells: Methods

• **Peanut Allergy** was used as an experimental model (10 peanut allergic patients).

• CD154 upregulation following short stimulation of PBMCs with Peanut extract was used to track peanut reactive T cells and evaluate **influence of recombinant IL-33 on functional properties of peanut-reactive CD4+ T cell subsets.**
Peanut specific TH2A cells express high RNA levels of IL-33 Receptor

- Peanut reactive T cells (CD154+) from patients fall into 2 subsets according to CD27 expression.
- Peanut specific TH2 cells are include within TH2A subset.
- Peanut-reactive TH2A cells (CD27 negative) express high mRNA levels of IL33 Receptor.
- Upon TCR stimulation, allergen-specific TH2 cells up-regulated expression of IL-33 Receptor.
Cytokine profiles between CD27- and CD27+ allergen-specific T cell subsets are highly divergent:

- **CD27 negative Peanut specific T cell subset** secrete higher level of the cardinal Type 2 effector cytokines than their CD27 positive counterpart.
IL-33 enhance pro-inflammatory function of allergen specific TH2A cell responses

Upon TCR stimulation, IL-33 regulate the pathogenicity of allergen-specific CD4+ TH2A cells.
Allergen specific TH2A cells are critical target of IL-33 in allergic inflammation

- IL-33 selectively amplify peanut specific TH2A cell responses
- As expected in adaptive immunity, IL-33-induced upregulation of IL-4 and IL-5 require previous TCR triggering
Allergen specific TH2A cells are critical target of IL-33 in allergic inflammation

- Upon TCR stimulation, IL-33 selectively enhances TH2 cytokine expression and production by allergen-specific TH2A cells
Expression of effector cytokines by allergen-specific TH2 cells depends on IL-33 cytokine at sites of tissue damage, revealing a tissue checkpoint that regulates allergic immunity.
Conclusions

- TH2A cell subset represents a phenotypically and functionally distinct TH2 subpopulation in atopic individuals that includes all allergen-specific TH2 cells and specifically express IL-33 receptor (ST2).

- Production of effector cytokines by activated allergen-specific T\(_h\)2A cells is modulated by IL-33.

- As an enhancer of allergic immune response, IL-33 represent an attractive therapeutic target in the treatment of atopic diseases over competing agents that block only a subset of the cytokines responsible for atopic diseases.
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