IL-4 and IL-13 act independently and synergistically to drive type 2 inflammation
Audrey Le Floch, Jeanne Allinone, Kirsten Nagashima, George Scott, Dylan Birchard, Wei Keat Lim, Yu Bai, Seblewongel Asonat, Matthew Sleeman, Andrew Murphy, Jamie Orengo
Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA

BACKGROUND

- Dupilumab is a fully human IgG4-based anti-interleukin 4 receptor α (IL-4Ra) monoclonal antibody generated using Regeneron’s VelocImmuno® technology.
- Dupilumab inhibits both IL-4 and IL-13 signaling, key drivers of type 2 inflammation (Figure 1).
- Dupilumab has shown robust efficacy across multiple diseases with underlying type 2 signatures and is approved for treatment of moderate-to-severe asthma and atopic dermatitis.

AIM

- To tease out the distinct or overlapping functions of IL-4 and IL-13 in type 2 inflammation, by dissecting their effects on human immune and non-immune cells and identifying their respective contributions in driving asthma-related pathologies in mice.

METHODS

Mouse models of IL-4/-IL-13- and allergen-induced lung inflammation

- Allergen (HDM)-sensitized and -exposed mice were either exposed to (model 1) human IL-4 or IL-13 for 12 days, or (model 2) house dust mite (HDM) for 4 weeks and received twice-weekly injections of dupilumab (dual IL-4/-IL-13 blockade), IL-4 Ab, mouse IL-13/IL-4 fusion protein, control Ab, or no Ab. Mice were then sacrificed, and lung tissue and serum were further analyzed.
- Real-time quantitative polymerase chain reaction (qPCR)
- Flow cytometry of circulating and lung infiltrating cells
- Immunohistochemistry
- Western blotting
- Statistical analysis

RESULTS

(See detailed results in the figure captions below.)

CONCLUSIONS

Dual IL-4/-IL-13 blockade with dupilumab protects against lung function decline by impacting multiple features of the type 2 response:
- IL-4 blockade prevents goblet cell metaplasia, IgE production, FcεRI-expressing innate cell priming and pathogenic ST2+ CD4+ T cell lung infiltration
- IL-13 inhibition is required to prevent goblet cell metaplasia and has a broad impact on cytokine/chemokine gene expression in the lungs.
- Only dual IL-4/-IL-13 blockade efficiently prevents lung eosinophilia and expression of inflammatory type 2 cytokines and chemokines in the lungs.

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DISCLOSURES

Audrey Le Floch, Janae Allinone, Kirsten Nagashima, Wei Keat Lim, Yu Bai, George Scott, Dylan Birchard, Seblewongel Asonat, Matthew Sleeman, Andrew Murphy and Jamie Orengo: Regeneron Pharmaceuticals, Inc., employees and shareholders

Figure 1: Dupilumab mechanism of action

Figure 2: Both IL-4 and IL-13 promote lung eosinophilia and activate human eosinophils

Figure 3: IL-4 drives B cell activation, class switching and pathogenic ST2+ CD4+ T cell lung infiltration following lung exposure to HDM

Figure 4: IL-4 dominates IgE-dependent human mast cell responses in vivo

Figure 5: Both IL-4 and IL-13 promote lung eosinophilia and activate human eosinophils

Figure 6: Dual IL-4/-IL-13 blockade is required to broadly prevent chemokine and cytokine expression in the HDM-exposed lungs

Figure 7: IL-13 drives HDM-induced goblet cell metaplasia

Figure 8: Dual IL-4/-IL-13 blockade prevents impairment of lung function

See detailed methods and results in the text.