Determining the Cellular Origin of Elevated IgE: Implications for Allergic Disease Prevention

CASE WESTERN RESERVE UNIVERSITY School of Medicine

Master of Public Health Program

RYAN SZCZEPANIK [1], HIROYUKI NAGASHIMA [1], JOHN O'SHEA [1]

[1] Lymphocyte Cell Biology Section, Molecular Immunology and Inflammation Branch, National Institute of Arthritis, and Musculoskeletal and Skin Disease (NIAMS), National Institutes of Health (NIH), Bethesda

National Institute of Arthritis and Musculoskeletal and Skin Diseases

BACKGROUND

- STAT6 is a cellular protein that promotes inflammation when activated
- Rare mutations of STAT6 create an activating mutation (AM), associated with severe allergic disease and elevated serum IgE
- Specific cell types produce more IgE than others, but it is unclear which types
- Determining a cellular origin of this disease provides valuable clinical insight into the drivers of allergic disease

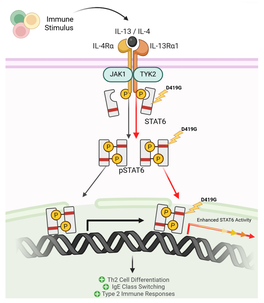


Fig 1: STAT6 activation following IL-4 or IL-13 stimulation
Immune stimulus leads to cytokine secretion and binding of IL-4 / IL-13 to associated receptor. Binding of IL-4 or IL-13 activates receptor-associated JAKs, leading to STAT6 phosphorylation, dimerization, and nuclear translocation.

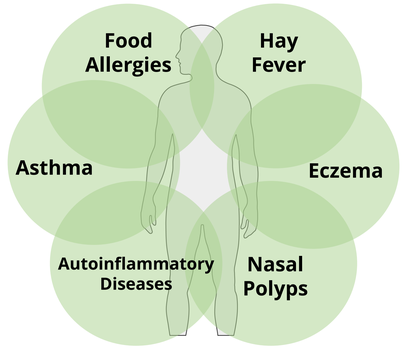


Fig 2. Clinical conditions driven by IgE expression
Clinical conditions that are considered a Type 2 immune response, typically associated with inflammatory conditions / diseases. Expression of the IgE antibody. Figure adapted from (https://allergyasthmanetwork.org/health-a-z/type-2-inflammation-resources/)

METHODS

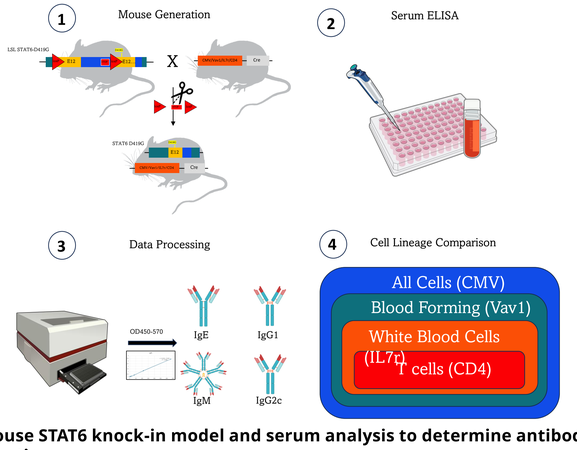


Fig 3. Mouse STAT6 knock-in model and serum analysis to determine antibody concentration.
1. Floxed conditional knock-in (cKI) of STAT6-D419G mice and CMV/Vav1/IL7R/CD4 Cre mice generate tissue-specific mutations.
2. Serum collected from mice analyzed via high-sensitivity sandwich ELISA 3. Plate reader analyzes optical density used to calculate original immunoglobulin concentration. 4. Nested box diagram of Cre models and associated cell compartments.

- Mouse models were created to produce the STAT6 AM disease in only specific cell compartments
- Antibody concentration was determined using an enzyme-linked immunosorbent assay (ELISA), and quantified from standard curves

RESULTS

- The concentration of IgE antibodies in CD4-Cre T cells were comparable to the control.
- The concentration of IgE antibodies were elevated in CMV-Cre, Vav1-Cre, and IL7R-Cre STAT6-D419G mice compared to control.

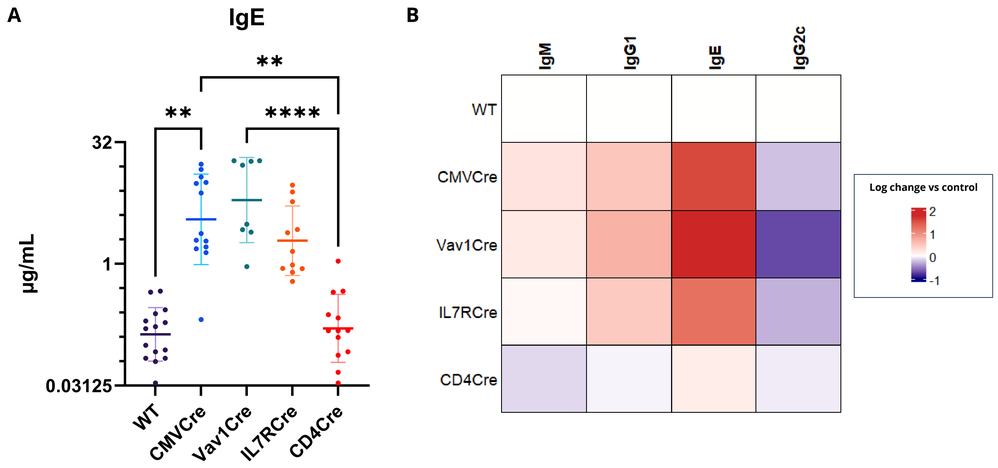


Fig 4: Serum antibody concentrations in control and lineage-specific STAT6 activating mutation mice.
A. Each point represents the IgE concentration of one mouse from the WT (n=15), CMVCre (n=13), Vav1Cre (n=8), IL7RCre (n=11), or CD4Cre (n=13) groups. Concentrations were calculated from ELISA standard curves. Bars indicate mean ± one standard deviation. Y-axis is on the $\log_2$ scale. B. Heatmap of antibody expression by cell lineage murine model compared to control. Mean values were normalized over the WT condition mean. Red indicates greater antibody expression compared to control, while blue indicates lower expression.

DISCUSSION AND FUTURE DIRECTION

- The STAT6 AM in CD4+ cells alone (T cells) does not produce the characteristic elevated IgE response
- The difference in IL7RCre and CD4Cre indicate one or more Common Lymphoid Precursor drives response, likely B-cells
- Targeted therapies for severe allergic diseases can be generated from cell compartment determination

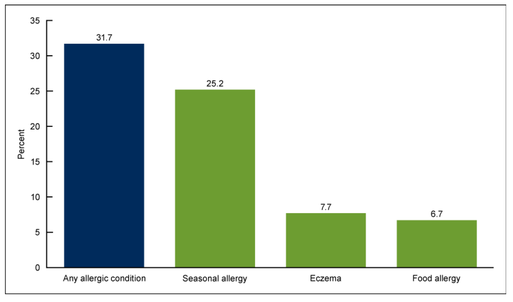


Figure 6: Percentage of adults with a diagnosed seasonal allergy, eczema, food allergy, or any of these allergic conditions: United States, 2024
Adults were considered to have any allergic condition if they were diagnosed with one or more of three selected conditions: seasonal allergy, eczema, or food allergy. Categories for each allergic condition were not mutually exclusive. Estimates are based on household interviews of a sample of the U.S. civilian noninstitutionalized population. Sources: National Center for Health Statistics, National Health Interview Survey, 2024. Bottoms-McClain L, Giri A, Ng AE. Diagnosed allergic conditions in adults: United States, 2024. NCHS Data Brief. 2026 Jan;(545):1–11. DOI: https://dx.doi.org/10.15620/cdc/174634

Conclusion

STAT6-AM produces cell lineage-dependent changes in antibody expression. Ubiquitous through lymphocytic expression increased IgE, whereas CD4-Cre-targeted expression did not. These findings indicate that one or more non-T hematopoietic compartments contribute to the hyper-IgE phenotype.

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