Abstract (less than 250 words)

Background: Psychological stress can exacerbate the development of allergies; however, the underlying mechanisms remain poorly understood. IgE-mediated cutaneous allergic inflammation (IgE-CAI) is a basophil-dependent skin allergy with eosinophil infiltration at inflammatory sites. Its resolution involves anti-inflammatory programmed death ligand 2 (PD-L2)$^{+}$ macrophages.

Objective: This study sought to elucidate the cellular and molecular mechanisms by which psychological stress exacerbates IgE-CAI.

Methods: Neural tissue involved in stress-induced IgE-CAI exacerbation was identified by performing denervation and brain destruction experiments in mice. Immune cell transplantation, RNA sequencing, flow cytometry, and ELISA were used to identify and characterize immune cells with stress-altered functioning, followed by identification of key factors involved in IgE-CAI exacerbation.

Results: Stress-induced exacerbation of IgE-CAI was found to be sympathetic and β2-adrenergic receptor (Adrb2)-dependent. Adoptive transfer experiments revealed that stress diminished the anti-inflammatory functions of PD-L2^{+} macrophages through Adrb2, exacerbating the inflammation. RNA sequencing analysis indicated that PD-L2^{+} macrophages in stressed mice exhibit reduced expression of efferocytosis-related genes, including *Gas6* and *MerTK*. Consequently, the efferocytic capacity of these macrophages decreased, resulting in increased numbers of dead cells in the lesions. The exacerbation and upregulation of Ccl24 expression in IgE-CAI skin lesions were countered by a caspase-1 inhibitor.

Conclusions: Psychological stress diminishes the efferocytotic capacity of PD-L2^{+} macrophages, causing an accumulation of dead cells. This, in turn, heightens eosinophil infiltration through caspase-1-dependent production of Ccl24, exacerbating IgE-CAI.