Modulating a Novel Neuroepithelial Circuit in Food Allergy to Repair Barrier Dysfunction With Larazotide Acetate and Neuregulin-1

Adur, Aryana (School: Jericho High School)

Food allergy (FA) affects 18% of the population and is driven by type-2 inflammation, epithelial barrier dysfunction, and tight junction (TJ) disruption. Recent studies identify Zonulin and Resistin-like-Molecule-beta (RELMb) as parallel disruptors of TJs through PKC-a activation. While Zonulin acts through established receptors, RELMb's receptor remains undefined; however, emerging evidence implicates ErbB3 as a potential candidate. This study aimed to (1) define RELMb-induced gut barrier disruption, (2) identify ErbB3 as RELMb's receptor, (3) determine competitive interactions between RELMb and ErbB3 canonical ligand Neuregulin-1 (NRG1), (4) evaluate therapeutic applications of Zonulin antagonist Larazotide Acetate (LA) with NRG1 in FA. Murine intestinal organoids derived from IL4raF709 and IL4raF709Retnlb-/- mice were treated with IL-13, RELMb, LA, and NRG1. RELMb increased Claudin-13/Claudin-15 ($p<0.01$) and alarmin IL-25/TSLP expression ($p<0.01$), reflecting a compensatory response to barrier leak, with RELMb-/- organoids displaying blunted alarmin transcription ($p<0.0001$). LA restored RELMb ($p<0.01$), alarmin ($p<0.001$), and TJ expression ($p<0.01$). AlphaFold-Multimer, PyMOL, and PRODIGY docking demonstrated RELMb binds with substantial affinity to ErbB3 extracellular domains 1 and 3, overlapping NRG1 binding sites. Immunofluorescence confirmed RELMb-ErbB3 colocalization, while NRG1 competitively displaced RELMb from the receptor, normalizing TJ and cytokine expression ($p<0.001$). Combined LA/NRG1 treatment produced the greatest restoration of epithelial integrity ($p<0.001$). These findings define a novel RELMb-ErbB3-NRG1 neuroepithelial circuit modulating gut permeability and highlight LA/NRG1 as a novel co-therapy to restore FA barrier and immune homeostasis.

Awards Won:
Second Award of $2,400