

RESTORE's Protection of Tight Junctions from Gluten

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Introduction

The clinical result of tight junction or intestinal epithelial barrier dysfunction is increasingly recognized as an early step in the pathogenesis of many acute and chronic inflammatory diseases including celiac disease and inflammatory bowel disease (Crohn's Disease and ulcerative colitis) [1,2,3,4,5,6]. Celiac disease is a gluten-related autoimmune disorder of the small intestine. Over 3 million people suffer from celiac disease in the United States. It is estimated another 18 million people in the United States have gluten sensitivity.

Intercellular tight junctions allow vectorial transport of water and electrolytes across the intestinal epithelium. The anatomical and functional arrangement of the gastrointestinal tract regulates passage of micro- and macro-molecules between the environment and the host through transcellular transport (micromolecules) and paracellular diffusion (macromolecules) via modulation of the intercellular tight junctions. To prevent harm to the host and reduce inflammation, the paracellular pathway minimizes antigen presentation and toxin exposure of the gut-associated lymphoid tissue that abuts the bowel epithelium. Epithelial cells are tightly bound together to minimize the passage of large molecules between adjacent cells. These tight junctions, also called zonula occludens, form a physical barrier throughout the digestive tract that is critical to health.

Zonulin is a serine protease with structure similarities with epidermal growth factor that modulates the polymerization of actin filaments that compose the tight junction; zonulin has been established as the primary mediator of tight junction permeability. Zonulin acts as the gate-keeper of tight junctions in both the gut and the blood-brain barrier [2,3,4,5,6]. The zonulin-mediated control of nutrient and toxin gradients across the bowel wall establishes a balance between tolerance and immunity to non-self antigens. Up-regulation of zonulin leads to increasing permeability of the tight junction. In excess, this results in unregulated transmission of toxins and inorganic materials into the blood stream leading to inflammatory and autoimmune disorders [2].

A growing number of manufactured and naturally occurring elements in processed foods and monocrop farming are being implicated in tight junction damage. In the developed world, the unintentional chronic stimulation of zonulin-mediated intestinal permeability from food elements, such as gluten, compromises the tight junctions and leads to unregulated absorption of organic and inorganic material. Gluten is a protein found in foods processed from wheat and other related grains (*e.g.* kamut, barley and rye).

Our translational research of a stable, soil-derived redox supplement that safely modulates the zonulin-dependent intestinal permeability has the potential to impact many aspects of public health and a variety of translational research fields.

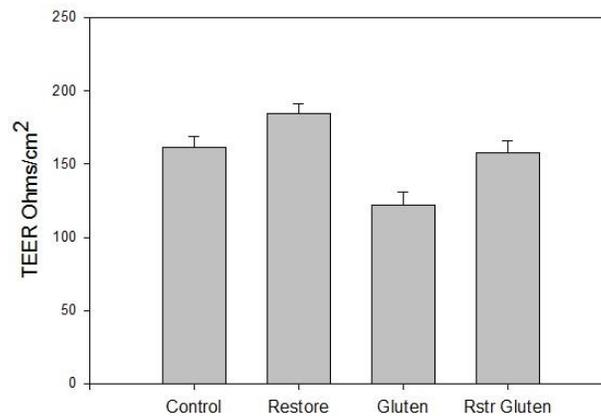
Results

RESTORE's Protection

RESTORE was found to protect the gut wall from gluten (PT-gliadin peptides) insult. A study was performed using this methodology where Transepithelial electric resistance (TEER) was measured in 24 well transwell plates using the epithelial Volt-ohmmeter fitted with a planar electrode. Caco-2 cells were seeded and incubated until a stable TEER was measured three days in a row.

RESTORE at a 20% concentration and a control (culture media without RESTORE) were placed on the cells and left overnight. These cells were then treated with and without PT-gliadin at 1 mg/ml (sigma) TEER measured at the 60 minute time point. RESTORE increased the TEER in Caco-2 (14%). PT-gliadin (gluten) dramatically decreased the TEER in both Caco-2 (24.3%) cells. RESTORE blocked this gluten dependent decrease in TEER (Figure 1) resulting in TEER that was 22% higher ($p < 0.05$, $n = 6$).

Figure 1. Average TEER in Caco-2 (large bowel) cells



Conclusion

This study illustrates RESTORE's ability to protect large bowel cells (Caco-2) from tight junction or epithelial barrier dysfunction caused by gluten. The ability to protect tight junction integrity has the potential to prevent many acute and chronic inflammatory diseases, significantly reduce healthcare costs, and dramatically improve the health of the population.

References

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