



Zonulin & Intestinal Permeability

Clinical overview

Zonulin is a key regulator of intestinal permeability. Its release signals the opening of tight junctions (TJs) between gut epithelial cells, allowing larger molecules (including antigens) to pass into the immune-rich lamina propria. This mechanism underpins what is commonly known as 'leaky gut'.

What are tight junctions?

Tight junctions are protein complexes (e.g. occludin, claudin) that form a seal between adjacent intestinal cells, helping to control what passes from the gut lumen into systemic circulation. Under normal conditions, this prevents exposure to potentially immunogenic food particles or microbes.

What triggers zonulin release?

- Gliadin (from gluten)
- Pathogen overgrowth (bacteria, viruses, fungi)
- Proinflammatory cytokines (e.g. TNF- α , IL-6)
- EGF and Epidermal Growth Factor Receptor (EGFr) activation
- Autoimmune and inflammatory conditions
- Chronic stress and dysbiosis

The gluten-zonulin pathway (simplified)

- Gluten is broken down into gliadin peptides in the gut.
- Gliadin binds to the CXCR3 receptor on intestinal cells, triggering MyD88-dependent signalling.
- This leads to zonulin release from enterocytes.
- Zonulin binds to PAR2 and EGFr, causing actin filament retraction and tight junction opening.
- Allows gliadin peptides (and antigens) to permeate the gut lining to immune cells in the lamina propria.

Why this matters in practice

- Zonulin elevation is an early marker of impaired gut barrier function.
- Disrupted tight junctions allow food antigens, toxins, and microbes to cross the gut barrier, triggering immune activation and systemic inflammation.
- Zonulin is measurable via the KBMO Gut Barrier Panel, revealing gut permeability and immune reactivity.
- Persistent TJ disruption contributes to the pathogenesis of many chronic conditions, including autoimmune disease, skin disorders, and mood-related issues.

Therapeutic considerations

- Remove triggers: gluten, gut infections, pro-inflammatory foods.
- Support barrier repair: e.g. glutamine, zinc carnosine, polyphenols, SCFAs.
- Consider microbiome rebalancing and stress reduction strategies.
- Use FIT test results (zonulin, occludin, Candida, food antigens) for a phased intervention plan.

