

# Disrubtion of the tight junction zo-1 by cytokine in intestinal epithelial and pr...

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Disruption of Tight Junction ZO by Cytokines in Intestinal Epithelial Cells and Probiotic Treatment Zonula occludens -1 (ZO-1) was discovered in 1986 as the first intracellular protein component of the tight junction (Bazzoni and Dejana, 2004). It belongs to a family of membrane-associated guanylate kinases (MAGUK) involved in signal transduction during cell-cell contact (Gottardi et al, 1996). It interacts with various other proteins, including ZO-2, ZO-3, occludins, claudins, and the actin cytoskeleton, in the formation of tight junctions at the surface of cells (Wittchen, Haskins and Stevenson, 1999). It is present in various types of epithelial and endothelial cells, in particular the intestinal epithelium and cerebral vasculature, where tight junctions have to be particularly efficient (Bazzoni and Dejana, 2004). The tight junction helps seal the spaces between cells to help form a confluent, continuous monolayer.

The role of ZO-1 in the tight junction in intestinal epithelial cells is to stabilize the barrier, functionally link it to the actin-myosin cytoskeleton, and limit the permeability of the cell layer to large solutes (Van Itallie et al, 2009). The permeability to solutes is measured in terms of trans-epithelial electrical resistance.

A variety of both exogenous and endogenous factors can affect the permeability of the intestinal epithelial tight junction. These include bacterial toxins, dietary glucose, cytokines and growth factors (Walsh et al., 2000).

The role of inflammation in affecting the tight junction and increasing its permeability is clear from various studies. Piche et al. (2009) demonstrated the impairment in tight junction function and decrease in expression of ZO-1 mRNA in intestinal cells of patients with active Irritable Bowel Syndrome;

however, specific cytokine mediators responsible for the effect could not be identified. Similarly, although infection with *Giardia Lamblia* has been found to disrupt ZO-1 integrity, the precise inflammatory cytokines responsible for the process have not been determined (Buret et al., 2002). Walsh et al. (2000) postulated in a review, based on evidence from several studies, that IFN-gamma alters paracellular permeability by several mechanisms, including possibly direct effects on the ZO-1 and/or via changes in the perijunctional actin cytoskeleton. This, however, has not been validated by studies that followed. Bruewer et al (2003) found that the cytokines IFN-gamma and TNF-alpha affected the epithelial barrier by causing internalization of transmembrane proteins, junction adhesion molecule 1, occludin, and claudin, however, their effects on zonula occludens 1 were minimal.

Probiotics are live microbial organisms in food supplements, or components of bacteria that have a beneficial effect on human health. The most common probiotics are *Lactobacillus* and *Bifidobacteria* (Isolauri et al., 2002). Normal intestinal flora directs the regulation of systemic and local immune responsiveness, and thus, through controlling inflammation, assists the development of normal gut barrier function. During acute inflammatory intestinal conditions, however, the balance of intestinal flora is disrupted, and an immune reaction may be generated against commensals. These findings suggest that introducing gut-friendly organisms through probiotic therapy, would serve to restore the balance of the intestinal flora which, in turn, would help reduce the inflammation (Isolauri et al., 2002). This hypothesis has also been validated through several studies. Saavedra et al.

(1994) carried out a double-blind, placebo-controlled trial on infants and found that supplementation of infant formula with known probiotics, *Bifidobacterium bifidum* and *Streptococcus thermophilus*, resulted in a decreased incidence of acute diarrhea. Similarly, Eun et al. (2011) found in an in-vitro study that pre-treatment of intestinal cells with the probiotic *Lactobacillus casei* resulted in decreased consequences of inflammation. This was evident by reversal of the disruption in ZO-1 expression, epithelial permeability and trans-epithelial resistance that had been induced by IFN-gamma and TNF-alpha.

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