Zonulin, Intestinal Permeability, and Inflammation: Bridging the Gap Between Innate Immunity and Autoimmunity

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The intestinal epithelium is the largest mucosal surface providing an interface between the external environment and the mammalian host. Its exquisite anatomical and functional arrangements and the finely-tuned coordination of digestive, absorptive, motility, neuroendocrine and immunological functions are testimonial of the complexity of the gastrointestinal system. Also pivotal is the regulation of molecular trafficking between the intestinal lumen and the submucosa via the paracellular space. Under physiological circumstances, this trafficking is safeguarded by the competency of intercellular tight junctions (TJ), structures whose physiological modulation is mediated, among others, by the TJ modulator zonulin. The structural and functional characteristics of intercellular TJ and the protean nature of the intestinal content suggest that the gut mucosa represent the "battlefield" where friends (i.e., nutrients and enteric microflora) and foes (i.e., pathogenic microorganisms and their toxins) need to be selectively recognized to reach an ideal balance between tolerance and immune response to non-self antigens. This balance is achieved by selective antigen trafficking through TJ and their sampling by the gut associated lymphoid tissue. If the tightly regulated trafficking of macromolecules is jeopardized, the excessive flow of non-self antigens in the intestinal submucosa can cause autoimmune disorders in genetically susceptible individuals.

Our data indicate that gliadin initiates intestinal permeability through a CXCR3-mediated, MyD88-dependent release of zonulin that enables paracellular translocation of gliadin and its subsequent interaction with macrophages within the intestinal submucosa. Gliadin interaction with macrophages triggers signalling through a TLR pathway, resulting in the establishment of a pro-inflammmatory (Th1-type) cytokine milieu that causes an innate immune-mediated early mucosal damage that may lead to adaptive immune response targeting either the gut (celiac disease) or other organs, pancreas in type 1 diabetes).

This new paradigm subverts traditional theories underlying the development of autoimmunity, which are based on molecular mimicry and/or the bystander effect, and suggests that the autoimmune process can be arrested if the interplay between genes and environmental triggers is prevented by re-establishing intestinal barrier competency.