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## Toward an Etiology of Celiac Disease

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The review proposes a model of the etiology of celiac disease. It describes how an enteroviral attack by a lytic virus leads to hyper-extracellular Transglutaminase 2, (Tg2), evident at all stages of the disease by the presence of anti-tTG. The demand for Tg2 is supplied by both the cell and the lytic virus. The demand leads to excess Tg2 passing through the cell wall, excess ingress of  $\text{Ca}^{2+}$ , the destruction of the mitochondria by  $\text{Ca}^{2+}$ , and pyroptosis of the cell. The increase in extracellular Tg2 during the cell's life and following pyroptosis has two effects. First, it binds a C1r inhibitor to the vascular wall, preventing C1r-LP from converting prehaptoglobin (zonulin) into haptoglobin, causing the weakening of the tight junctions among the epithelial cells and allowing the entry of extraneous luminal materials and particularly the access of Tg2 arterial and luminal, as it is now open directly to the lumen and the mesenchyme structure. It is this Tg2 that damages the villus structure as the Tg2 binds fibronectin into the mesenchyme, causing scarring, shrinkage, and turning the villi into the rigid scarred structures characteristic of CD. The model suggests why CD is a chronic lifelong disease reactivated upon the resumption of gluten consumption. A discussion of refractory CD follows. The paper explains how extracellular transglutaminase causes prehaptoglobin (zonulin) and damages the extracellular membrane. Thus, prehaptoglobin (zonulin) is a symptom, not a cause. Notably, the paper demonstrates that the basic tenet of autoimmune diseases that the cells destroy themselves is incorrect, at least for CD. Applying this etiology to other conditions may be relevant because of the almost universal glutaminolysis in cells and the substantial amount of Gluten in modern diets.