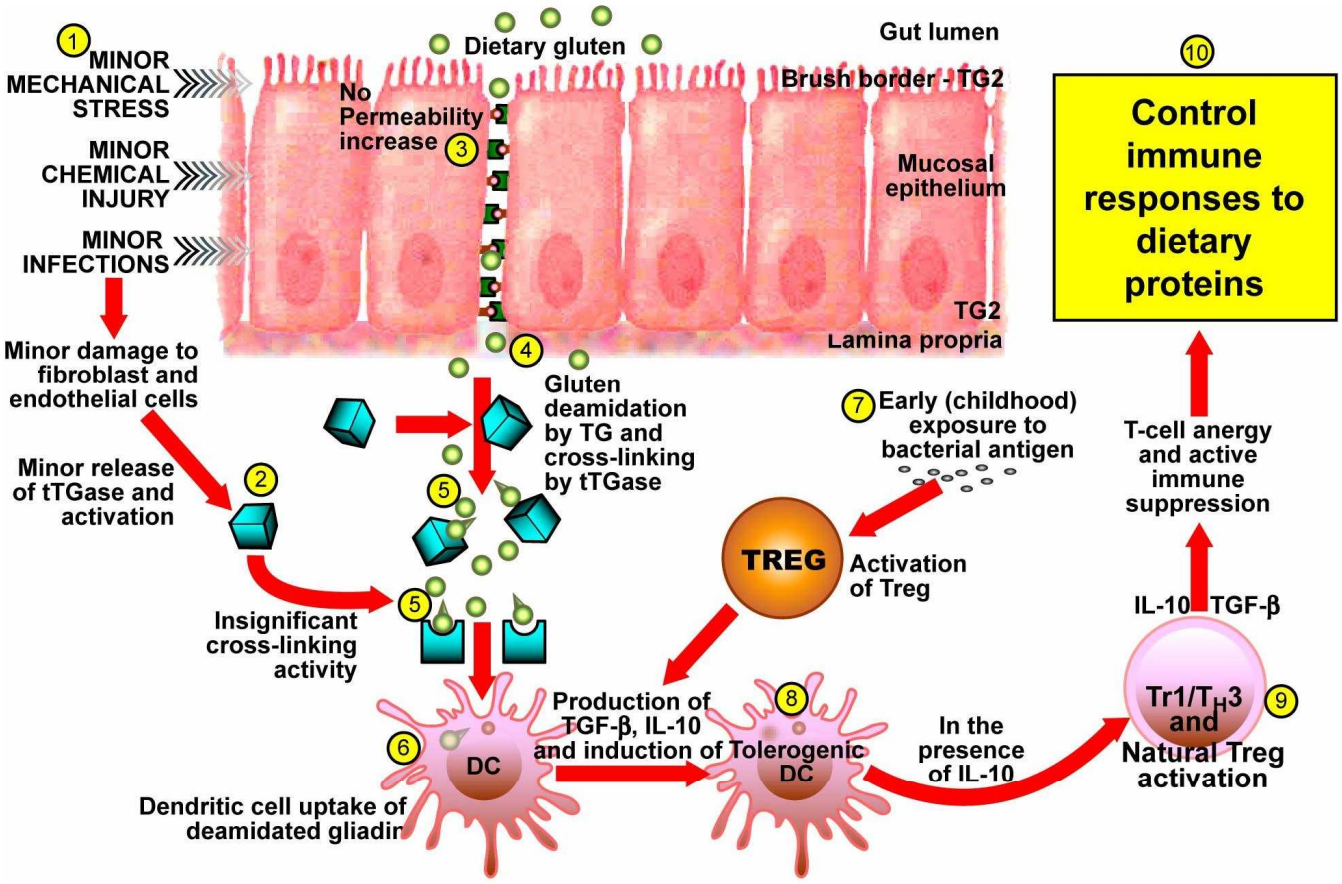

Cellular and molecular induction of immune tolerance to dietary proteins (gliadin).

Although HLA-DQ2 or HLA-DQ8 is found in roughly 30% of the western population, celiac sprue is encountered in 1 out of 50 carriers. Most carriers of these genes, like the rest of the population, harbor some form of immune protection, as shown in this figure.

In the absence of major mechanical and chemical stress or infection (1), no damage is done to fibroblasts and endothelial cells, and only small quantities of tissue transglutaminase are released into the environment (2).

Since under these conditions the tight junctions are in perfect shape (3), only a few gliadin molecules may survive digestion and be transported across the mucosal epithelium (4).

If these molecules of gliadin are deamidated by transglutaminase (5), the key regulator of the immune system called dendritic cells or antigen-presenting cells (6) prime T cells for anergy or tolerance.

Early exposure to dietary proteins and bacterial antigens such as LPs (7) can activate regulatory T cells to produce TGF-b and IL-10, inducing activation of tolerogenic DCs (8) to control immune response to dietary proteins (gliadin). Further activation of TR_1, TH_3 and natural Treg (9) by IL-10 results in induction of central or peripheral tolerance (10).

The regulatory T cells are divided into two major groups:

a - Natural Tregs, which act in a contact-dependent fashion, and express CD25 and transcription factor $FOXP^3$;

b - Adoptive Treg Type1 cells (TR_1), which function in a contact-independent manner and may or may not express CD25 and $FOXP^3$. The TR_1 and TH_3 cells preferentially synthesize immunosuppressive cytokines IL-10 and TGF-b respectively in order to maintain homeostasis of responses to foreign antigens, including gliadin.