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Gliadin Peptide P31-43 as Trigger of the Proliferative and Stress/Innate Immune Response of the Celiac Small Intestinal Mucosa

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Ingested food can cause tissue inflammation through different mechanisms. In the intestine, and particularly in the enterocyte, nutrients are modulators of various cellular functions and may be involved in tissue immune response and inflammation. An example of an intestinal inflammatory and remodeling response of the intestine to food is the small intestinal celiac lesion induced by gluten,an alimentary protein present in wheat and other cereals. Celiac disease (CD) is characterized by inflammatory and structural changes resulting in remodeling of the small intestinal mucosa. Gliadin, the major protein component of wheat and other cereals, is a peculiar protein very rich in glutamine and proline. Several gliadin peptides are recognized by T-cells (TC) of the celiac intestine, and can induce the adaptive immune response, but most of them are digested by gastric, pancreatic and intestinal proteases. Only two main peptides remain undigested: the 33-mer (P55–87) and the 25-mer (P31–55). Consequently, these two peptides are the main peptides that are active in vivo in the celiac intestine after gluten ingestion (1).

The inflammation of the intestinal mucosa is due not only to the adaptive but also to the innate immune responses to wheat gliadin. The A-gliadin 33-mer that is deamidated by tissue transglutaminase (tTG), binds to human leukocyte antigen (HLA) DQ2 and/or DQ8 and induces an adaptive Th1 pro-inflammatory response. The P31–43 peptide, which is contained in the 25-mer, is not recognized by TC (2) in the celiac intestine and is able to damage the celiac intestinal mucosa in vitro and in vivo. Moreover, the P31–43 gliadin peptide is able to initiate both a stress and an innate immune response with interleukin-15 (IL-15) as a major mediator (3).

Although the structural changes of the celiac mucosa are considered a consequence of sustained mucosal inflammation due to the Th1-TC response, recent data have shown that gliadin peptides, in particular P31–43, induce proliferation and other effects in celiac enterocytes. This processes have profound effects in inducing the crypt hyperplasia, which is characteristic of the remodeling of the celiac mucosa. Moreover, gliadin peptide P31-43 induce alterations of structure (cell shape, actin modifications, increased permeability and vesicular trafficking alterations), signaling and proliferation and stress/innate immunity activation in several cell lines.

Taken together, these data suggest that gliadin peptides (i.e., P31–43) can have several different non-T cell mediated effects, both in cell lines and cells and in biopsies from CD patients, that can be grouped into three sets: cell structural changes, including signaling/proliferative effects and stress/ innate immunity activation. How these mechanisms of disease are related to the genetics of CD is still unclear

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