Novel mechanisms of gliadin immunotoxicity?
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myeloid dendritic cells expressing both HLA-DQ and surface TGt.\textsuperscript{11}

In this issue of *Gut*, the papers by Luciani et al\textsuperscript{12} (see page 311) and by Zimmer et al\textsuperscript{13} (see page 300) focus on some of the unsolved questions of CoD pathogenesis. By using epithelial cell lines and human duodenal biopsies, the authors analysed the epithelial uptake and processing of gliadin peptides via intracellular compartments, which result in the activation of new signalling pathways of mucosal inflammation,\textsuperscript{12} and different routes of antigen presentation.\textsuperscript{13}

These papers describe two different pathways of endocytosis and delivery of gliadin peptides to paracrine vesicles which may be relevant in the initial steps of the development of the disease, though the mechanisms responsible for the segregation and/or accumulation of these peptides remain obscure. Rather than a primary epithelial defect in patients with CoD, this is probably due to the intrinsic properties of p31-43/49, because other peptides are removed from the vesicular system.

In the study by Luciani et al,\textsuperscript{12} all peptides can reach the late endosomes and lysosomes, but p31-43 (unlike other peptides) is retained in the latter where it is probably due to the intrinsic properties of p31-43/49; because other peptides are removed from the vesicular system.

The early effects of gliadin might be relative common,\textsuperscript{14} but signalling pathways may undergo downregulatory control in non-CoD individuals. However, in HLA-DQ2+ patients, the innate related signal may be amplified by other factors: expression of cytokine-related genes,\textsuperscript{5} TGt activation and PPAR\gamma degradation,\textsuperscript{12} or high IL15R\alpha expression,\textsuperscript{15} leading to the triggering of an adaptive immune response mediated by gluten-reactive CD4 T cells.

Zimmer et al\textsuperscript{13} confirmed that both toxic and immunogenic peptides are internalised by the enterocytes, but they follow different endocytotic pathways, as shown by p31-49 which bypasses HLA-DR+ late endosomes and escapes antigen presentation at the basolateral membrane, though we do not know the fate of these peptides: are they translocated by a protected pathway, or degraded in endosomes? The authors hypothesised that HLA-DR+ enterocytes generate a tolerogenic effect in contrast to the immunostimulatory effect mediated by HLA-DQ+ lamina propria dendritic cells. Still, these mechanisms have to be validated in vivo, and further studies should evaluate the uptake and processing of both toxic and immunogenic gliadin peptides by normal and inflamed mucosa (or in the early and late stages of the disease). Moreover, its specificity to the CoD intestine has to be confirmed, and it would be interesting to know how early inflammation is controlled by non-CoD individuals: is this related to HLA/non-HLA genes, or to other local or environmental factors? These results open the way for alternative therapies based on the use of antioxidants, TGt inhibitors (and PPAR\gamma modulators), or the re-induction of tolerance.

**Competing interests** None.

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