



Novel mechanisms of gliadin immunotoxicity?

Eduardo Arranz and Jose A Garrote

Gut 2010 59: 286-287

doi: 10.1136/gut.2009.189332

Updated information and services can be found at:

<http://gut.bmj.com/content/59/3/286.full.html>

These include:

References

This article cites 15 articles, 6 of which can be accessed free at:

<http://gut.bmj.com/content/59/3/286.full.html#ref-list-1>

Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To order reprints of this article go to:

<http://gut.bmj.com/cgi/reprintform>

To subscribe to *Gut* go to:

<http://gut.bmj.com/subscriptions>

REFERENCES

1. **Moayyedi P**, Ford AC, Talley NJ, *et al.* The efficacy of probiotics in the therapy of irritable bowel syndrome: a systematic review. *Gut* 2010;**59**:325–32.
2. **Klaenhammer TR**, Altermann E, Pfeiler E, *et al.* Functional genomics of probiotic Lactobacilli. *J Clin Gastroenterol* 2008;**42**(Suppl. 3 Pt 2):S160–2.
3. **Denou E**, Pridmore RD, Berger B, *et al.* Identification of genes associated with the long-gut-persistence phenotype of the probiotic Lactobacillus johnsonii strain NCC533 using a combination of genomics and transcriptome analysis. *J Bacteriol* 2008;**190**:3161–8.
4. **Medina M**, Izquierdo E, Ennahar S, *et al.* Differential immunomodulatory properties of Bifidobacterium logum strains: relevance to probiotic selection and clinical applications. *Clin Exp Immunol* 2007;**150**:531–8.
5. **Chang G**, Shi Y, Le G, *et al.* Effects of Lactobacillus plantarum on genes expression pattern in mice jejuna Peyer's patches. *Cell Immunol* 2009;**258**:1–8.
6. **Pineiro M**, Stanton C. Probiotic bacteria: legislative framework—requirements to evidence basis. *J Nutr* 2007;**137**(3 Suppl 2):850S–3S.
7. **Salonen A**, Palva A, de Vos WM. Microbial functionality in the human intestinal tract. *Front Biosci* 2009;**14**:3074–84.
8. **Sokol H**, Pigneur B, Watterlot L, *et al.* Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. *Proc Natl Acad Sci U S A* 2008;**105**:16731–6.
9. **Bär F**, Von Koschitzky H, Roblick U, *et al.* Cell-free supernatants of Escherichia coli Nissle 1917 modulate human colonic motility: evidence from an in vitro organ bath study. *Neurogastroenterol Motil* 2009;**21**:559–66.
10. **Agrawal A**, Houghton LA, Morris J, *et al.* Clinical trial: the effects of a fermented milk product containing Bifidobacterium lactis DN-173-010 on abdominal distension and gastrointestinal transit in irritable bowel syndrome with constipation. *Aliment Pharmacol Ther* 2009;**29**:104–14.
11. **Guyonnet D**, Schlumberger A, Mhamdi L, *et al.* Fermented milk containing Bifidobacterium lactis DN-173 010 improves gastrointestinal well-being and digestive symptoms in women reporting minor digestive symptoms: a randomised, double-blind, parallel, controlled study. *Br J Nutr* 2009;**102**:1654–62.
12. **Ait-Belgnaoui A**, Eutamene H, Houdeau E, *et al.* Lactobacillus farciminis treatment attenuates stress-induced overexpression of Fos protein in spinal and supraspinal sites after colorectal distension in rats. *Neurogastroenterol Motil* 2009;**21**:477–80.
13. **Verdú EF**, Bercik P, Verma-Gandhu M, *et al.* Specific probiotic therapy attenuates antibiotic induced visceral hypersensitivity in mice. *Gut* 2006;**55**:182–90.
14. **Rousseaux C**, Thuru X, Gelot A, *et al.* Lactobacillus acidophilus modulates intestinal pain and induces opioid and cannabinoid receptors. *Nat Med* 2007;**13**:35–7.

Novel mechanisms of gliadin immunotoxicity?

Eduardo Arranz,¹ Jose A Garrote^{1,2}

Celiac disease (CoD) is a chronic inflammatory intestinal disorder caused by dietary gluten proteins (prolamines) from cereals in genetically predisposed individuals. The disease is manifested by a lesion which ranges from a complete transformation of the mucosa with villus atrophy and crypt cell hyperplasia to the infiltration by lymphocytes of the epithelium and lamina propria. Gluten is uniquely resistant to gastrointestinal digestion, and gluten fragments accumulate in the intestine where they trigger two distinct immune responses, mediated by the innate and adaptive immunity, and both contribute to the pathogenesis of CoD.^{1–2} Although HLA-DQ2/8 is the major predisposing factor, other non-HLA genes, some of them related to the innate response,³ and/or environmental factors might contribute to the development of the disease in a small group of DQ2+ individuals.

Immunostimulatory peptides, as assessed by using lymphocyte-based systems, have been identified in gliadin and glutenins from wheat gluten, and homologues from barley and rye. All peptides which are stimulatory when tested in vitro are also harmful in vivo. The best known is the immunogenic peptide p57-89 (33mer) from α -gliadin, which is the preferred substrate for tissue transglutaminase (TGt) and once deaminated becomes a potent activator of gluten-specific DQ2-restricted CD4+ T cells from patients with CoD, characterised by interferon γ (IFN γ) production. Other peptides, like p31-43/49 from α -gliadin, are toxic in vivo and in vitro, and have a direct effect on the epithelium, but do not stimulate gluten-specific T cells from patients with CoD.⁴ These peptides induce enterocyte expression of both interleukin 15 (IL15) and the non-classical major histocompatibility complex (MHC) class I chain-related A (MICA) molecules and HLA-E, as well as IL15 production by lamina propria mononuclear cells, which in turn promotes intraepithelial proliferation and expression of the receptors NKG2D and CD94, leading to the target killing of MICA-expressing enterocytes.^{1,2}

The molecular basis of the adaptive DQ-restricted immune response to gluten is well understood. Less clear is how

luminal gliadin peptides cross the intestinal epithelium and initiate the specific response mediated by lamina propria CD4+ T cells, and how these gluten-specific T cells control the expansion and activation of intraepithelial T lymphocytes. Moreover, little is known about the role of enterocytes in the uptake and processing of gliadin peptides, how these peptides activate innate immunity in the early stages of intestinal inflammation, and why these effects are only observed in HLA-DQ2+ patients. No specific receptor has been described for p31-43, though it has been reported that this peptide may potentiate the effect of epidermal growth factor by interference in the inactivation of its receptor,⁵ or that it may induce the early upregulation of TGt in the epithelium by a mechanism still unknown.⁶

The major route of transepithelial passage of gliadin peptides is by transcytosis, though the underlying mechanisms are not yet clear.² In active CoD, the apical-to-basal transport is increased, in an IFN γ -dependent manner, but intraepithelial processing is also altered, allowing intact and/or partially degraded toxic and immunogenic peptides to enter the mucosa.^{7–8} This depends on the intestinal inflammation of untreated CoD, which may also increase the passive paracellular diffusion of peptides through opened epithelial tight junctions via 'MyD88-dependent' release of zonulin.⁹ Other receptor-mediated mechanisms may contribute to the translocation of intact gliadin peptides to the lamina propria, by using a protected pathway driven by gluten-specific secretory IgA via transferrin receptor CD71,¹⁰ or involving

¹Mucosal Immunology Lab, Instituto de Biología y Genética Molecular (IBGM), University of Valladolid-CSIC, Valladolid, Spain; ²Research Unit, Hospital Clínico Universitario (IECSCYL), Valladolid, Spain

Correspondence to Dr Eduardo Arranz, Mucosal Immunology Lab, Dept of Paediatrics & Immunology-IBGM, University of Valladolid, Spain. C/ Ramón y Cajal, 7. 47005, Valladolid, Spain; earranz@med.uva.es

myeloid dendritic cells expressing both HLA-DQ and surface TGt.¹¹

In this issue of *Gut*, the papers by Luciani *et al*¹² (see page 311) and by Zimmer *et al*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,¹² and different routes of antigen presentation.¹³ These papers describe two different pathways of endocytosis and delivery of gliadin peptides to paranuclear 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*,¹² all peptides can reach the late endosomes and lysosomes, but p31-43 (unlike other peptides) is retained in the latter where it generates a pro-oxidative environment which induces TGt activation and degradation of peroxisome proliferator-activated receptor (PPAR) γ , a modulator of intestinal inflammation. This mechanism might explain why patients with CoD relapse after gluten reintroduction, even when signs of inflammation are absent. The early effects of gliadin might be relatively common,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,³ TGt activation and PPAR γ degradation,¹² or high

IL15R α expression,¹⁵ leading to the triggering of an adaptive immune response mediated by gluten-reactive CD4 T cells.

Zimmer *et al*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 γ modulators), or the re-induction of tolerance.

Competing interests None.

Provenance and peer review Commissioned; externally peer reviewed.

Gut 2010;**59**:286–287. doi:10.1136/gut.2009.189332

REFERENCES

1. **Jabri B**, Sollid LM. Mechanisms of disease: immunopathogenesis of celiac disease. *Nat Clin Pract Gastroenterol Hepatol* 2006;**3**:516–25.
2. **Meresse B**, Ripoche J, Heyman M, *et al*. Celiac disease: from oral tolerance to intestinal

inflammation, autoimmunity and lymphomatogenesis. *Mucosal Immunol* 2009;**2**:8–23.

3. **Hunt KA**, Zernakova A, Turner G, *et al*. Newly identified genetic risk variants for celiac disease related to the immune response. *Nat Genet* 2008;**40**:395–402.
4. **Maiuri L**, Ciacci C, Ricciardelli I, *et al*. Association between innate response to gliadin and activation of pathogenic T cells in coeliac disease. *Lancet* 2003;**362**:30–7.
5. **Barone MV**, Gimigliano A, Castoria G, *et al*. Growth factor-like activity of gliadin, an alimentary protein: implications for celiac disease. *Gut* 2007;**56**:480–8.
6. **Maiuri L**, Ciacci C, Ricciardelli I, *et al*. Unexpected role of surface transglutaminase type II in celiac disease. *Gastroenterology* 2005;**129**:1400–13.
7. **Matysiak-Budnik T**, Candah C, Dugave C, *et al*. Alterations of the intestinal transport and processing of gliadin peptides in celiac disease. *Gastroenterology* 2003;**125**:696–707.
8. **Lammers KM**, Lu R, Brownley J, *et al*. Gliadin induces an increase in intestinal permeability and zonulin release by binding to the chemokine receptor CXCR3. *Gastroenterology* 2008;**135**:194–204.
9. **Schumann M**, Richter JF, Wedell I, *et al*. Mechanisms of epithelial translocation of the α -gliadin 33-mer in Celiac sprue. *Gut* 2008;**57**:747–54.
10. **Matysiak-Budnik T**, Cruz-Moura I, Arcos-Fajardo M, *et al*. Secretory IgA mediates retrotranscytosis of intact gliadin peptides via the transferrin receptor in celiac disease. *J Exp Med* 2008;**205**:143–54.
11. **Ráki M**, Tollefsen S, Molberg Ø, *et al*. A unique dendritic cell subset accumulates in the celiac lesion and efficiently activates gluten-reactive T cells. *Gastroenterology* 2006;**131**:428–38.
12. **Luciani A**, Vilella VR, Vasaturo A, *et al*. Lysosomal accumulation of gliadin p31-43 peptide induces oxidative stress and Tissue Transglutaminase mediated PPAR downregulation in intestinal epithelial cells and coeliac mucosa. *Gut* 2010;**59**:311–9.
13. **Zimmer K-P**, Fischer I, Mothes T, *et al*. Endocytotic segregation of gliadin peptide 31-49 in enterocytes. *Gut* 2010;**59**:300–10.
14. **Bernardo D**, Garrote JA, Fernandez-Salazar L, *et al*. Is gliadin really safe for non-coeliac individuals? Production of interleukin-15 in biopsy culture from non-coeliac individuals challenged with gliadin peptides. *Gut* 2007;**56**:889–90.
15. **Bernardo D**, Garrote JA, Allegretti Y, *et al*. Higher constitutive IL-15R α expression and lower IL-15 response threshold in coeliac disease patients. *Clin Exp Immunol* 2008;**154**:64–73.