A MOUSE MODEL FOR CELIAC DISEASE

Mauro Rossi

Principal investigator
Mauro Rossi

Other components of the research group
Paolo Bergamo
Diomira Luongo
Francesco Maurano
Giuseppe Mazzarella
Vera Rotondi Aufiero
Lucia Treppiccione

Background

The development of adequate in vivo models could make feasible a chronological assessment of the pathogenic mechanisms occurring in Celiac disease (CD). Furthermore, these models could be of help in providing information about the residual toxicity of new cereals before to introduce them into CD patient's diet. Indeed, an association of gluten sensitivity with the expression of the DQ8 heterodimer is indicated by the greater immune response to gluten induced in transgenic mice expressing the HLA-DQ8 compared with HLA-DQ6-transgenic mice, (Black et al, J Immunol 2002; 169:5595). Intriguingly, gliadin alone decreases intestinal antioxidant and detoxifying defenses in these mice, but it is unable to induce an enteropathy (Bergamo et al, Mol. Nutr. Food Res. 2011, 55, S248). Following intra-gastric immunization of DQ8 mice, we identified two immunodominant peptides that induce IFN-γ secretion in vitro, as expected in CD (Senger et al, J Immunol. 2005, 175, 8087). However, we still observed the absence of enteropathy in this model. Exacerbation of the intestinal gliadin-specific immune response by co-administration of Lactobacillus casei also does not cause any mucosal damage (D'Arienzo et al, Immunol Lett 2008, 119, 78). Interestingly, we found that mucosal immunization toward gliadin, followed by COX inhibition, decreases villus height in DQ8 mice (D'Arienzo et al, Eur J Immunol 2009; 39:3552). COXs are enzymes involved in the synthesis of prostaglandins from arachidonic acid. In particular, prostaglandin E2 (PGE2) enhances the production of anti-inflammatory cytokines and/or inhibits the production of pro-inflammatory cytokines in in vitro models of T-lymphocyte stimulation.

Main achievements

1. In the absence of mucosal immunization gliadin challenge with indo still triggered

a CD-like enteropathy after a 10-day treatment. In particular, mice showed a significant reduction of villus height, increased crypt depth, increased number of lamina propria (LP) activated macrophages and high basal levels of intestinal IFN-γ. Furthermore, enteropathy onset was characterized by: increased levels of oxidative stress markers, activation of matrix metalloproteinases, caspase-3 activity and a significant increase of tissue transglutaminase (tTG) protein levels. After a 30-day treatment enteropathic mice also developed serum antibodies toward gliadin (IgA) and tTG (IgG).

2. In enteropathic DQ8 mice we detected a decline of detoxifying mechanisms thus leading to accumulation of oxidative stress markers. Pre-treatment with the bioactive compound conjugated linoleic acid (CLA) prevented this accumulation, as well as signs of the gliadin-induced enteropathy.
3. Enzymatic transamidation of wheat gliadin by microbial transglutaminase inhibits IFN-γ secretion in gliadin-specific splenic CD4+ T cells isolated from DQ8 mice immunised with native gliadin. Notably, splenic CD4+ T cells from mice immunised with transamidated gliadin produced significant levels of IL-10 when challenged in vitro with native or transamidated gliadin.

Future perspectives

1. In vivo efficacy of dietary polyphenols in DQ8 mice (in collaboration with Laboratório Associado para a Química Verde -Tecnologias e Processos Limpos (REQUIMTE), Universidade do Porto, Portugal, project n. PTDC/BBB-BQB/3326/2012). In analogy with our previous findings with CLA, the main goal of this proposal is to define the metabolic and beneficial influence of polyphenol extracts in the mouse model of gliadin-specific enteropathy. The polyphenolic supplementation will be provided per os as a 2-week pre-treatment.
2. Down-regulation of immunogenic and cytotoxic properties of gliadin through its enzymatic transamidation or via the activation of the Nrf2 pathway (Progetto Fellowship N. 006_FC_2018). In humans, the protective role of Tregs against autoimmune disorders has been largely studied, including CD. CD is a T cell-mediated, tissue-specific autoimmune disease. On the other hand, various studies showed that the number of regulatory Foxp3+ T cells was increased in the LP of CD patients. Furthermore, the effects of gluten on intestinal antioxidant and detoxifying defenses have been recently described in DQ8 mice (Bergamo et al, Eur J Nutr. 2016; 55: 729). On the basis of these findings we plan: -to prove that immunization with transamidated gliadin is able to down-regulate the intestinal gliadin-specific Th1 response in sensitized DQ8 mice; -to verify the anti-inflammatory/immunomodulatory ability produced by co-administration of antioxidant molecules and Nrf2 activators (CLA) in mice immunized with native gliadin. This work represents an innovative approach to recover gluten tolerance

based on the use of modified antigen molecules. Furthermore, we will investigate a new therapeutic target (Nrf2) to mitigate the pro-inflammatory activity of gluten in sensitive animals.

Publications

1. *Bergamo P, Maurano F, Mazzarella G, Iaquinto G, Vocca I, Rivelli AR, De Falco E, Gianfrani C, Rossi M. Immunological evaluation of the alcohol-soluble protein fraction from gluten-free grains in relation to celiac disease. Molecular Nutrition & Food Research. 2011; 55(8):1266-70.*
2. *D'Arienzo R, Stefanile R, Maurano F, Mazzarella G, Ricca E, Troncone R, Auricchio S, Rossi M. Immunomodulatory effects of Lactobacillus casei administration in a mouse model of gliadin-sensitive enteropathy. Scandinavian Journal of Immunology. 2011; 74(4):335-41.*
3. *Bergamo P, Gogliettino M, Palmieri G, Cocca E, Maurano F, Stefanile R, Balestrieri M, Mazzarella G, David C, Rossi M. Conjugated Linoleic Acid protects against gliadin induced depletion of intestinal defenses. Molecular Nutrition & Food Research. 2011; 55 Suppl 2:S248-56.*
4. *Lombardi E, Bergamo P, Maurano F, Bozzella G, Luongo D, Mazzarella G, Rotondi Aufiero V, Iaquinto G, Rossi M. Selective inhibition of the gliadin-specific, cell-mediated immune response by transamidation with microbial transglutaminase. Journal of Leukocyte Biology 2013; 93(4):479-88.*
5. *Mazzarella G, Bergamo P, Maurano F, Luongo D, Aufiero VR, Bozzella G, Palmieri G, Troncone R, Auricchio S, David C, Rossi M. Gliadin intake alters the small intestinal mucosa in indomethacin treated HLA-DQ8 transgenic mice. American Journal of Physiology Gastrointestinal Liver Physiology. 2014; 307(3):G302-12.*
6. *Ogita T, Bergamo P, Maurano F, D'Arienzo R, Mazzarella G, Bozzella G, Luongo D, Sashihara T, Suzuki T, Tanabe S, Rossi M. Modulatory activity of Lactobacillus rhamnosus OLL2838 in a mouse model of intestinal immunopathology. Immunobiology. 2015;220:701-710.*
7. *Bonavita R, Isticato R, Maurano F, Ricca E, Rossi M. Mucosal immunity induced by gliadin presenting spores of Bacillus subtilis in HLA-DQ8 transgenic mice. Immunol Letters. 2015; 165:84-89.*
8. *Bergamo P, Palmieri G, Cocca E, Ferrandino I, Gogliettino M, Monaco A, Maurano F, Rossi M. Adaptive response activated by cis9, trans11 Conjugated Linoleic Acid reduces pathological signs in an animal model of gliadin-induced enteropathy. European Journal of Nutrition. 2016;55:729-740.*
9. *Rossi S, Luongo D, Maurano F, Bergamo P, Rossi M. Immunomodulatory activity of recombinant a-gliadin conjugated to cholera toxin in DQ8 transgenic mice. Immunology Letters. 2017; 187:47-52.*
10. *Luongo D, Bonavita R, Rossi S, Rotondi Aufiero V, Feliciello N R, Maurano F, Iaquinto G, Mazzarella G, Rossi M. Tailoring the immune response to wheat gliadin by enzymatic transamidation. Cytokine. 2019; 117:23-29.*

External collaborations

- *Osawa R, Ajinomoto Foods Europe SAS, France*
- *Campbell G, School of Applied Sciences, University of Huddersfield, Huddersfield, UK*
- *Sashihara T, Meiji Corp, Ltd, Japan*
- *de Freitas V, University of Porto, Faculty of Sciences, Department of Chemistry and Biochemistry, Portugal*