Coeliac Disease, a model of food-induced inflammatory disease

Celiachia, un modello di patologia infiammatoria indotta da alimenti

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Background/aim.

Epidemiological studies, have associated the increase in chronic inflammatory diseases, such as diabetes, atherosclerosis, asthma, chronic liver disease, autoimmune diseases, degenerative diseases and inflammatory bowel diseases to the spread of the so-called " Western diet". The Mediterranean diet has increasingly been regarded as the gold-stantard diet for human health.

The nutrients exert their effects on tissue inflammation, either by direct action on the cells, or because they regulate the composition of the intestinal microbiota. The enterocyte and the intestinal immunocompetent cells, are equipped with complex systems to "feel" the food and to respond to them. Even cereals (and in particular wheat) can cause intestinal inflammation, for example in celiac disease. The intestinal damage from gluten (the complex of soluble alcohol proteins in wheat) in celiac disease consists of inflammation and remodelling of the mucosa, with flattening of the villi and hypertrophy of the crypts. There are two main types of inflammatory response to gluten peptides in celiac disease (1): there is the adaptive response mediated by CD4 + T cells to some peptides: the 33 mer of A-Gliadin, resistant to gastric digestion, is a prototype endoluminal and parietal intestinal. The peptide is deamidated by tissue transglutaminase (tTG) and presented by class II histocompatibility antigens, DQ2 and DQ8, to CD4 + T cells, with Th1-type response, mediated by gamma interferon and other proinflammatory cytokines. Then there is the response, not mediated by T cells, to other peptides: the

peptide 31-43 of A-gliadin (P 31-43) is the prototype. P 31-43, which is part of peptide 31-55, is resistant to gastric and intestinal digestion and causes inflammation with multiple mechanisms, the best known of which consists of a stress / innate and proliferative response, mediated by EGF and IL15 (2). Peptide P31-43 is also a growth factor for various cell lines and for the enterocyte of celiac, as it is able to activate the EGF-EGFR system, the most powerful mitogen present in our body. The gliadin-induced proliferation of celiac crypt is not only dependent on EGF but also on IL15. The proliferation of crypt enterocytes and the innate immune response to celiac gliadin are regulated by a cooperation between EGF and IL15. P31-43 induce also a stress/innate immune response involving interferon α (IFN-α) (3). Thus a double action of gliadin is delineated in the induction of the mucosal damage of celiac subjects. On the one hand, gliadin can activate the T-mediated response and on the other it can induce an innate/ inflammatory response. The combined effects of this double action induce the typical lesion of the celiac mucosa. But what causes the sensitivity to gliadin peptides in celiac cells is not really clear.

In this study, we describe a stressed/inflamed celiac cellular phenotype in enterocytes and fibroblasts probably due to an alteration in the early-recycling endosomal system. Moreover we show that celiac cells are more sensitive to the gliadin peptide P31-43 and IL15 than controls. This phenotype is reproduced in control cells by inducing a delay in early vesicular trafficking.

Methods. For organ culture studies, biopsy fragments from duodenum were obtained from CD patients with villous atrophy controls, affected by gastroesophageal reflux, and CD patients on GFD (Gluten free diet). Fibroblasts were cultured from skin and intestinal biopsies obtained from CD patients, (GFD, GCD) and controls. We used double immunofluorescence staining, western blotting and immunoprecipitation to evaluate EGFR and EEA1 levels and co- localization in fibroblasts and biopsy fragment from patients with CD and controls. We transfected cells with siHRS and mRNA analysis was

perfomed to evaluate the levels of EEA1.

Results. We found in CD biopsies and fibroblasts an increase of markers of the innate immune response (EGFR, IL15-R α, MXA) and of the inflammatory response (NFkB). CD cells (enterocytes and fibroblasts) presented a constitutive alteration in the intracellular vesicular system at the level of the early-recycling compartment. In fact, in CD enterocytes and fibroblasts, the numbers of early vesicles were increased, and the EGF/EGFR trafficking was delayed in the early endocytic vesicles; moreover, the decay of the EGFR was prolonged, and TfR levels were increased. We induced a delay in early endocytic trafficking by transfecting cells with siHRS in control cells and rendered them more sensitive to gliadin treatment using as read out STAT5 and NFkB levels.

Conclusions. In the present study we show that cells from celiac disease patients present a delay of the endocytic trafficking and are more sensitive to the wheat gliadin peptide P31-43 than control cells. We also found that inducing delays in early vesicular trafficking leads to a celiac-like cellular phenotype, carachterized by inflammation and activation of innate immunity, thus implicating the early-recycling endosomal system in celiac disease. This constitutive lesion might mediate the stress/innate immune response to gliadin, which in turn triggers the gliadin-specific T-cell response.

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3) Nanayakkara M, Lania G, Maglio M, Auricchio R, De Musis C, Discepolo V, Miele E, Jabri B, Troncone R, Auricchio S, Barone MV.P31-43, an undigested gliadin peptide, mimics and enhances the innate immune response to viruses and interferes with endocytic trafficking: a role in celiac disease.Sci Rep. 2018 8:10821