

short communication

Key words

IL-22 • celiac disease

Is IL-22 involved in celiac disease?

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Summary

Celiac disease is caused by a specific immune response to antigens present in wheat gluten and related proteins of rye and barley in genetically susceptible individuals.

Several studies have been conducted to define the nature and role of systemic cytokine levels in the pathophysiology of celiac disease. In order to identify the potential role of the Th17 subset in the pathogenesis of the celiac disease, we analyzed the serum levels of IL-22 in affected patients. Our data show that higher IL-22 serum levels are found in cases than in the controls, with a difference near to the limits of significance.

Introduction

Celiac disease, also known as gluten-sensitive enteropathy and nontropical sprue, is caused by a specific immune response to antigens present in wheat gluten and related proteins of rye and barley in genetically susceptible individuals ^{1,2}.

The immune response, adaptive as well innate, may be focused on a limited region of the alpha gliadin component of gluten and is characterized by the presence of anti-gluten and anti-transglutaminase 2 antibodies. It appears that the generation of epitopes for recognition by CD4+ T cells requires deamidation of the protein by tissue transglutaminase ¹. The lymphocyte infiltration in the epithelial membrane and the lamina propria and the expression of multiple cytokines and other signaling proteins leads to local inflammation, villous atrophy, and crypt hyperplasia in the small intestine. Although considered a primary gastrointestinal disease, celiac disease is known to have widespread systemic manifestations, including bone and skin disease, anemia, endocrine disorders, and neurologic deficits ². Several studies have been conducted to define the nature and role of systemic cytokine levels in the pathophysiology of celiac

disease. An involvement of T-cells, both Th1 and Th2, has been described and a defect in Tregs function has been suggested in the pathogenesis of the disease ³⁻⁶.

In a previous study, we showed that the proinflammatory cytokine IL-18 serum concentrations was correlated with the clinical status of celiac patients, resulting increased before and significantly reduced after gluten-free diet ⁷. A distinct lineage of T-helper cells, namely Th17, induced by IL-23 and producing IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (IL-25), IL-17F, IL-22 and IL-26, is emerging as responsible for pathogenic effects in autoimmune disorders. Some authors demonstrated the co-existence of both Th1 and Th17 responses in the active celiac disease lesion and their up-regulation in case of reactivation of proinflammatory pathways after re-exposure to gliadin in patients before gluten-free diet treated ^{6,8}. Moreover, it was demonstrated that celiac disease has a different cytokine expression compared with the other clinical gluten-induced condition, known as "gluten sensitivity"; this suggests that celiac disease, but not gluten sensitivity, is associated with an autoimmune Th17 mediated process ⁸.

Materials and methods

In order to identify the potential role of the Th17 subset in the pathogenesis of the celiac disease, we analyzed the serum levels of IL-22, one of the cytokines secreted by these cells, in affected patients and compared the results with a group of healthy donors. More recently, it has been reported that IL-22 may be also produced by Th22 and Th1 at different stages and in different microenvironments during an immune response⁹. IL-22 serum levels were measured by immunoenzymatic methods, using a commercially available kit (R&D System Europe, Abingdon, UK).

Serum samples were obtained from 27 celiac patients (20 females, 7 males), mean age 31.4 year, range 3-53. All patients at diagnosis were positive for anti-gliadin IgG and IgA antibodies (AGA), anti-endomysium, anti-tissue transglutaminase (anti-tTG) and all were histologically positive with villous atrophic pattern (grade 3 C of Marsch mod. Oberhuber classification)^{10,11}; 43 healthy donors sex and age-matched were enrolled as controls. Each subject gave a written informed consent.

Results and conclusions

The statistical analysis, performed by the Kolmogorov-Smirnov test, showed that higher IL-22 serum levels were present in cases than in the controls with difference near to the limit of significance ($p = 0.0737$) (Fig. 1).

No correlations between IL-22 serum levels and age of the subjects and anti-tTG titers were found.

Therefore, the presence of a Th17 response in the active stage of the disease is apparent, supporting the data already obtained using RT-PCR analysis of gene expression^{5,8}.

These findings highlight that the role of Th17 cells, already described in the pathogenesis of many autoimmune and allergic disorders¹², is also detectable in celiac disease. However, these preliminary data need further investigation to better clarify how each subset of T cell participate in the celiac disease development.

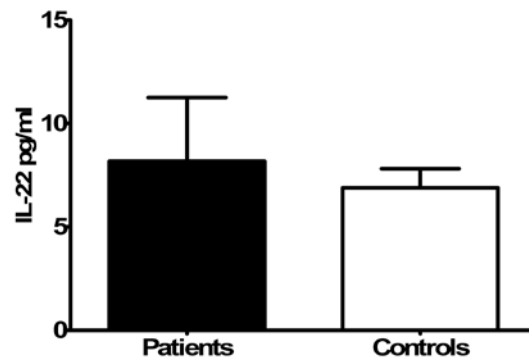


Fig. 1.

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