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Ascorbate-dependent decrease of the mucosal immune inflammatory response to gliadin in coeliac disease patients

Bernardo, D.; Martínez-Abad, B.; Vallejo-Diez, S.; Montalvillo, E.; Benito, V.; Anta, B.; Fernández-Salazar, L.; Blanco-Quirós, A.; Garrote, J.A.; Arranz, E.

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Abstract

Background

The IL-15/NF-κB axis has an important role in coeliac disease (CD) and may represent a molecular target for immunomodulation. Ascorbate (vitamin C) is known to show inhibitory effects on NF-κB. Therefore, we studied if ascorbate supplementation to gliadin gliadin-stimulated biopsy culture could down-regulate the mucosal immune response to gliadin in CD.

Methods

Duodenal biopsy explants from treated CD patients were gliadin challenged in vitro (100µg/ml) with and without 20mM ascorbate. An extra tissue explant in basal culture was used as internal control. Secretion levels of nitrites (3h), and IFNγ, TNFα, IFNα, IL-17, IL-13, and IL-6 (24h) were measured on the supernatants. IL-15 was assayed by western-blot on whole protein duodenal explants.

Results

The addition of ascorbate to in vitro culture gliadin-challenged biopsies blocked the secretion of nitrites (p=0.013), IFNγ (p=0.0207), TNFα (p=0.0099), IFNα (p=0.0375), and IL-6 (p=0.0036) compared to samples from non-ascorbate supplemented culture. Cytokine secretion was downregulated by ascorbate even to lower values than those observed in basal cultures (IFNγ: p=0.0312; TNFα: p=0.0312; IFNα: p=0.0312; and IL-6: p=0.0078). Gliadin-challenge induced IL-15 production in biopsies from treated CD patients, while the addition of ascorbate to culture medium completely inhibited IL-15 production. Moreover, the inhibition of IL-15 by ascorbate took place even in the only treated CD-patient who had basal IL-15 production.

Conclusions

Ascorbate decreases the mucosal inflammatory response to gluten in an intestinal biopsy culture model, so it might have a role in future supplementary therapy in CD.

Key words: Ascorbate. Coeliac disease. Inhibition. IL-15. Therapy.

Introduction

Introduction Coeliac disease (CD) is a common gastro-intestinal disorder caused by a hypersensitivity reaction to wheat gliadin and similar proteins from rye and barley, affecting genetically predisposed individuals (HLA-DQ2/DQ8). The current treatment is a life-long strict gluten-free diet (GFD).[1, 2] The most accepted model of the CD immunopathogenesis is the two-signal model, which establishes that gliadin has a dual effect on the CD duodenum, triggering the development of an innate immune response in the epithelium, and activating an adaptive immune response controlled by gluten-reactive T cells with a Th1 cytokine profile.[3, 4] Innate immunity, and specifically interleukin (IL)-15,[5, 6] plays a key role in the development of CD through a DQ2-independent mechanism.[7] The induction of IL-15 seems to be involved in the initial stages of the disease leading to epithelial stress, increase tight-junction permeability, enterocyte apoptosis and dendritic cell (DC) activation,[5, 6, 8, 9, 10, 11, 12] facilitating the development of the secondary adaptive response.[3] Moreover, the gliadin amplifies the production of inflammatory cytokines

through the nuclear factor (NF)-κB with a positive feedback by IL-15, which is also a potent NF-κB activator.[14] Moreover, DCs are important players in the connection between the innate and the subsequent adaptive immune response,[15] and require NF-κB for their development, survival, function and cytokine production.[16, 17, 18] Thus, the IL-15/NF-κB axis is revealed to have an important role in the pathogenesis of CD and may represent a molecular target for strategies of immunomodulation.[19] NF-κB is a heterogeneous collection of dimeric proteins subjected to a complex regulatory mechanism,[20, 21]...

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[a]Mucosal Immunology Lab, Department of Paediatrics & Immunology, and IBGM, Universidad de Valladolid-CSIC, Valladolid, Spain

[b]Gastroenterology Service, Hospital Clínico Universitario, Valladolid, Spain

[c]Research Unit, Hospital Clínico Universitario, Valladolid, Spain

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