

Role of the innate immune system in the pathogenesis of gluten sensitivity

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Background: Gliadin is recognized as the environmental trigger that is responsible for the autoimmune process associated with Celiac Disease (CD). Reaction to gluten can involve an allergic (wheat allergy), non-allergic [gluten sensitivity (GS)], or an autoimmune [celiac disease (CD)] mechanism. While in recent years we have showed significant progress on our understanding of the immunological aspects of CD pathogenesis, no major achievements have been made in dissecting the early steps that allow gliadin to cross the intestinal epithelial barrier to be recognized by the intestinal immune system. Recent evidences suggest that early changes in intestinal permeability (IP) may play a pivotal role in the pathogenesis of CD also through a Toll Like Receptor signaling pathway (TLRs) involvement. Conversely, no data are currently available on the role of intestinal barrier dysfunction in the pathogenesis of GS.

Aims: To investigate the changes in IP, TJ protein genes expression and TLRs in GS.

Methods: After obtaining informed consent, biopsy samples were obtained from 12 GS patients, 24 patients with active CD, 3 patients with CD in remission, and 14 healthy controls (age range: 5 years -50 years). Quantitative gene expression of tight junctions proteins Claudin (CL) 1, CL2, CL3, CL4, ZO-1 and of TLR1, TLR2 and TLR4 were performed by Real-time PCR. IP was evaluated by means of the lactulose/mannitol test (LA/MA).

Results: Expression of CL4 was increased three folds in GS subjects compared to both CD patients and healthy controls, while no changes in CL1, CL2, CL3, and ZO-1 expression were detected. Up-regulation of CL4 did not influence IP, since GS patients IP (0.014 ± 0.015) was similar to that detected in healthy controls (0.019 ± 0.018). Conversely, in CD patients an over-expression of both CL1 and CL2 was observed, while no significant changes in CL3, CL4, and ZO-1 were detected. The increased expression of CL1 and CL2 was associated to an increase in IP (0.052 ± 0.048). In CD patients in remission both IP (0.014 ± 0.004) and CL1 and CL2 expression returned to normal levels. To evaluate if the innate immune system is involved in the pathogenesis of GS, TLRs expression was measured in a random subgroup of CD (N=10), GS (N=4) patients and normal subjects (N=4). TLR1 resulted significantly increased in CD respect to the GS and normal controls ($p < 0.05$) while an over expression of TLR2 and TLR4 was detected in both CD and GS groups compared to normal controls.

Conclusions: Compared to CD patients, GS subjects showed normal IP and CL1 and CL2 expression. These results show that the pathogenesis of GS is different from that of CD and does not involve the loss of intestinal barrier function. The over expression of TLRs both in CD and GS could suggest an important role of innate immune system in both conditions. Gluten Sensitivity appears to be a new chapter in the book of "Food intolerance" to be investigated.