Constitutive differential distribution, activity and expression of type 2 transglutaminase in cells derived from celiac patients and from healthy subjects

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Type 2 transglutaminase (TG2) has an important pathogenetic role in celiac disease (CD), an inflammatory intestinal disease caused by the ingestion of gliadin-containing cereals. TG2 deamidates specific glutamines of gliadin peptides in the intestinal mucosa, thus enhancing gliadin immunogenicity. A strong autoimmune response to TG2 also characterizes CD development. Recent studies have demonstrated the occurrence of some constitutive differences between cells from CD and control subjects, mainly regarding a general higher level of phosphorylation and an alteration of vesicular trafficking in CD cells. Moreover, we observed that anti-TG2 antibodies specifically derange, in skin control fibroblasts, the uptake of the α-gliadin peptide 31-43, which is responsible for the innate immune response. However, anti-TG2 antibodies fail to protect CD fibroblasts from 31-43 internalization and consequential effects. To define the contribute of TG2 to the constitutive different phenotype of celiac cells, we investigated TG2 subcellular distribution in skin fibroblasts from CD and control subjects and also analysed how 31-43 modulated TG2 expression and activity. We used confocal microscopy and differential centrifugation to study TG2 subcellular localization. A microplate colorimetric assay was employed to evaluate TG2 in situ activity, whereas TG2 expression was quantified by Western blot and PCR. We found that TG2 was more abundantly associated with cell membrane surface and early endosomal and autophagic compartments in CD fibroblasts than in control cells. We also observed that 31-43 activated TG2 more in control than in celiac cells and induced TG2 expression in celiac cells, but not in control ones. Differences in TG2 localization and in the way 31-43 modulates TG2 activity and expression in control and CD cells suggest that TG2 participates in defining the constitutive celiac cellular phenotype.
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