INTERPLAY BETWEEN TYPE 2 TRANSGLUTAMINASE, AUTO-ANTIBODIES AND GLIADIN PEPTIDES IN CELIAC DISEASE

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Background

The Ca^{2+}-dependent enzyme type 2 transglutaminase (TG2) catalyses post-translational modifications that play a key role in the pathogenesis of celiac disease (CD), an intestinal inflammatory disorder triggered by the ingestion of cereals containing gluten proteins, mainly gliadins. In CD, a strong auto-immune response toward TG2 is also present and auto-antibodies seem to exert per se several biological effects on cells. Furthermore, antibodies against TG2 are able to reduce, in Caco-2 cells, the uptake and the biological activity of peptide 31-43 (p31-43), a peptide able to induce an innate immune response. On these basis, our aim is to better investigate the interplay between p31-43, auto-antibodies and TG2 in cell line models as well as in a model of primary skin-derived CD fibroblasts.

Main achievements

We obtained results about the biological effects of p31-43 and anti-TG2 antibodies in intestinal Caco-2 cells, indicating their functional interaction with TG2 function(s). Both p31-43 and anti-TG2 antibodies caused an increase of Ca^{2+} ions mobilization from intracellular stores and TG2 activation in Caco-2 cells (Caputo et al. Plos One 2012; Caputo et al. Amino Acids 2013). P31-43 also induced an ER-stress response in these cells (Caputo et al. Plos One 2012). On the other hand, anti-TG2 antibodies were able to induce a phosphoproteome modulation inside Caco-2 cells (Paolella et al. Plos One 2013). Moreover, the ability of anti-TG2 antibodies to derange the uptake of p31-43 by cells, interacting with cell surface-TG2, was not observed in CD primary skin derived-fibroblasts, whereas antibodies still exerted their protective role in skin-derived fibroblasts of normal subjects (Paolella et al. Amino Acids 2017). Finally, we attempted to identify a potential p31-43 receptor in Caco-2 cells, however we could not isolate any membrane proteins able to interact with p31-43, and we suggested that the mechanism of entrance of p31-43 into cells was dependent by a direct interaction with membrane lipids (Paolella et al. Cell Biol Intern 2018).

Future perspectives

In the light of the observation that anti-TG2 antibodies were unable to reduce p31-43 uptake by CD fibroblasts, while they protected normal fibroblast from p31-43 entrance, we will focus our next research to the study of constitutive differences concerning TG2 between normal and CD cells, using the model of skin fibroblasts. We will analyze TG2 expression and activity, both basal and in the presence of p31-43 or anti-TG2 antibodies. We will also characterize the subcellular distribution of TG2 in normal and CD cells and how protein turnover can be altered by antibodies or peptides. Next, we will study basal Ca^{2+} homeostasis in fibroblasts and how p31-43 or antibodies can modulate Ca^{2+} availability into cells and which deposits are involved. We will also analyze how peptides and antibodies modulate the unfolded protein response and the ER-stress into normal and CD fibroblasts.

Publications

1. *Caputo I, Secondo A, Lepretti M, Paolella G, Auricchio S, Barone MV, Esposito C (2012) Gliadin peptides induce tissue transglutaminase activation and ER-stress through Ca^{2+} mobilization in Caco-2 cells. PLoS One 7(9):e45209. https://doi.org/10.1371/journal.pone.0045209.*
2. *Paolella G, Caputo I, Marabotti A, Lepretti M, Salzano AM, Scaloni A, Vitale M, Zambrano N, Sblattero D, Esposito C (2013) Celiac anti-type 2 transglutaminase antibodies induce phosphoproteome modification in intestinal epithelial Caco-2 cells. PLoS One 8(12):e84403. https://doi.org/10.1371/journal.pone.0084403.*

3. *Caputo I, Lepretti M, Secondo A, Martucciello S, Paolella G, Sblattero D, Barone MV, Esposito C (2013) Anti-tissue transglutaminase antibodies activate intracellular tissue transglutaminase by modulating cytosolic Ca^{2+} homeostasis. Amino Acids 44(1):251-60. https://doi.org/10.1007/s00726-011-1120-y.*

4. *Vangone A, Abdel-Azeim S, Caputo I, Sblattero D, Di Niro R, Cavallo L, Oliva R (2014) Structural basis for the recognition in an idiotype-anti-idiotype antibody complex related to celiac disease. PLoS One 30; 9(7):e102839. https://doi.org/10.1371/journal.pone.0102839.*

5. *Paolella G, Lepretti M, Barone MV, Nanayakkara M, Di Zenzo M, Sblattero D, Auricchio S, Esposito C, Caputo I (2017) Celiac anti-type 2 transglutaminase antibodies induce differential effects in fibroblasts from celiac disease patients and from healthy subjects. Amino Acid 49(3):541-550. https://doi.org/10.1007/s00726-016-2307-z.*

6. *Martucciello S, Paolella G, Esposito C, Lepretti M, Caputo I (2018). Anti-type 2 transglutaminase antibodies as modulators of type 2 transglutaminase functions: a possible pathological role in celiac disease. Cell Mol Life Sci 75(22):4107-4124.doi:10.1007/s00018-018-2902-0.*

7. *Paolella G, Lepretti M, Martucciello S, Nanayakkara M, Auricchio S, Esposito C, Barone MV, Caputo I (2018) The toxic alpha-gliadin peptide 31-43 enters cells without a surface membrane receptor. Cell biol Intern 42(1):112-120. https://doi.org/10.1002/cbin.10874.*

External collaborations

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