Animal models of celiac disease. Usefulness and limitations.

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Introduction and Objective

Celiac disease is a chronic enteropathy caused by inappropriate immune response against peptides of gluten present in dryland cereals, mainly affecting genetically predisposed individuals who express HLA-DQ2 and HLA-DQ8, although gluten is also able to activate innate immunity. The lack of an animal model that reproduces completely the disease hinders the progress towards the research on the CD pathogenesis. Gluten intolerance is a very important public health problem because it is clearly a disease underdiagnosed.

The aim of this literature review is to find the most suitable animal model in order to clarify the disease pathogenesis process and to find new therapeutic targets.

Figure 1. Immunopathogenesis of MHC-II dependent CD. The activation of T cells responsive to gluten in the small intestine triggers an inflammatory response dominated by Th1 cytokine profile, predominantly IFN-γ and other pro-inflammatory cytokines (TNF-α, IL-15) with proportional decline of immunoregulatory cytokines (IL-10, TGF-β). This imbalance causes histological changes at the level of the intestinal wall.

Figure 2. Normal duodenal mucosa of a CD control patient (A) and a patient with CD (B) showing villus atrophy and hyperplasia of the crypts. (Arranz E et al. Inmunopatogenia de la enfermedad celiaca, 2012)

Table 1. Animal models for the study of gluten sensitivity: Usefulness and limitations.

<table>
<thead>
<tr>
<th>Species/Model</th>
<th>Gluten Free Diet</th>
<th>Transgenic</th>
<th>Small Intestinal</th>
<th>Intestinal Inflammation</th>
<th>Intestinal Repair</th>
<th>Protocol for Induction</th>
<th>Anti-IFN-γ</th>
<th>Anti-TGFβ</th>
<th>Anti-IL-10</th>
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Therapeutic Approach

1. Use of probiotics and intestinal microbiota to enhance the intestinal permeability.
2. Promote the function of the intestinal barrier: some drugs act protecting the integrity of the tight junctions in the small intestine.
3. Prevention of the formation of immunogenic peptides: using polymers that bind to gliadin preventing recognition of MHC-II.
4. Oral enzyme therapy: the prolyl-endopeptidases (PEP) are able to easily split immunostimulatory gluten peptides rich in proline. Identify a gluten threshold dose well tolerated by most patients when consuming a PEP specific dose.
5. Block the presentation of the peptide HLA-DQ.
6. Inhibitors of tissue transglutaminase (TG2) with activity limited towards the intestinal lining.
7. Blockade of gliadin transcellular transport.
8. Anti IL-15 and anti-IFN-γ neutralizing antibodies are promising candidates for future therapies.
9. NKG2D antagonists alters the growth and functions of reactive CD8⁺ T cells.

Final Conclusions

Transgenic animals are not the most appropriate model for CD, because they do not reflect reality. Instead, Macacus rhesus is the most suited model for spontaneous CD, but very few laboratories are approved by the ethics committee. New insights involving the swine SLA-II, particularly mutations into the SLA-DQA and SLA-DQB, point out the possibility of a new CD model, but more research efforts would be needed to elucidate its suitability. Actually, there is no animal model so far that encompasses all the features in order to study the CD, but further studies are needed to find an effective therapeutic strategy.