Gluten For Punishment – The Role of HLA DQ2 in Celiac Disease

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Abstract
Celiac disease (CD) is an inflammatory disease of the gastrointestinal tract. Many people are affected by this disease, but are undiagnosed. They dismiss the digestive and neurological symptoms as nothing more than malaise. Those who are diagnosed need a controlled, gluten-free diet to alleviate symptoms, since there is currently no medical treatment. The HLA-DQ2 allele is the second highest risk factor for CD. HLA-DQ2 is a MHCII molecule, which presents antigens to a specific subset of T cells (T helper). An MHCII molecule is a protein exposed on the membrane of antigen presenting cells; these cells populate several body districts like small bowel mucosa. In a physiological setup, T cells are able to distinguish between “self” and “non-self” antigens, and they can be stimulated only upon recognition of “non-self” antigens bound to a “self” MHCII. Structurally, HLA-DQ2 has a binding groove, composed of two alpha helices and a beta sheet floor, where peptides from undigested gluten (gliadins) bind. Gliadins interact specifically with the binding groove thanks to Tyr-22, Leu-53, Arg-70 and Lys-71, resulting in a HLA-DQ2-gliadin complex. This complex may be recognized by T helper cells as “non-self,” with subsequent activation and initiation of an autoimmune response. The ensuing inflammation causes disruption of the structure and function of the small intestine. By learning about binding of gliadins to MHCII, scientists may find a drug that can block the binding groove from gliadins or modify the gliadins to prevent their interactions with HLA-DQ2.

Role of Major Histocompatibility Complex II Molecule
• HLA, a member of MHC molecules, has 6 genes
  • class I (A, B, C) expressed by all nucleated cells. Present peptides to CD8+ T cells
  • class II (DR, DP, DQ) expressed by Antigen Presenting Cells. Present peptides to CD4+ T cells
• Cells continually breakdown proteins from self or non-self.
• Presents foreign antigens to T cells, which elicits T cell activation leading to an antigen-specific response.
• Presents self proteins to T cells to recognize self and build tolerance
• Lose of tolerance to self can lead to Celiac Disease

Binding Process of Gliadin to DQ2 and Ensuring Immune Response

Role of HLA DQ2 in Immune Response
• Antigen Presenting Cells (APC) continually breakdown proteins of either self or non-self origin, which can be exposed to T cells bound to HLA molecules.
• HLA DQ2 specifically binds a gluten-derived peptide (gliadin)
• The presence of Tyr-22, Leu-53, Arg-70, Lys-71 in this allele allows the proline-rich sequence of gliadin to bind.
• Upon recognition of the DQ2/gliadin complex, CD4+ T cells are stimulated to produce cytokines, promoting inflammatory response and destruction of epithelial lining of the small intestines.
• CD is initiated and sustained.

Unbound HLA DQ2
HLA DQ2-Gliadin Complex

Interactions of T cell response and intraepithelial lymphocytes (IEL)

Role of HLA DQ2 in CD
• Normal Healthy Villi
• Inflamed Villi

In normal small intestines, tiny hair like structures called villi line the internal intestinal wall. Healthy villi absorb nutrients into your intestines to create healthy digestive system. In Celiacs, there is an immune response to gluten that results in an inflammatory response.

Peoples affected by Celiac Disease have incredibly short villi covering their intestines, and so nutrients are not absorbed properly into their system because there is not enough surface area available for proper nutrient absorption. In affected individuals, inflammation is also evident, resulting in the shortening of the villi.

Data Supports HLA DQ2 Results in CD

Description of Data
• Various types of DQ were studied to determine cause of CD
• Subjects have been “typed” based on their DQ (and DR) alleles
• The ability to initiate a T cell response as function of the expressed DQ allele was analyzed by co-culturing patient APCs and CD4+ T cells in the presence of gliadins
• T Cell response to various DQ and gluten peptide combinations was measured
• If peptides can bind to APC, T cells will respond by increasing in numbers
• T cell response observed in cultures where DQ2+ APCs were present was dramatically higher as compared to APCs expressing any other DQ (length of the bars in the graph). This suggests that the DQ2/gliadin complex leads to CD

Table: Celiac Disease (CD) is a disease of the gastrointestinal tract. Many people are affected by this disease, but are undiagnosed. They dismiss the digestive and neurological symptoms as nothing more than malaise. Those who are diagnosed need a controlled, gluten-free diet to alleviate symptoms, since there is currently no medical treatment. The HLA-DQ2 allele is the second highest risk factor for CD. HLA-DQ2 is a MHCII molecule, which presents antigens to a specific subset of T cells (T helper). An MHCII molecule is a protein exposed on the membrane of antigen presenting cells; these cells populate several body districts like small bowel mucosa. In a physiological setup, T cells are able to distinguish between “self” and “non-self” antigens, and they can be stimulated only upon recognition of “non-self” antigens bound to a “self” MHCII. Structurally, HLA-DQ2 has a binding groove, composed of two alpha helices and a beta sheet floor, where peptides from undigested gluten (gliadins) bind. Gliadins interact specifically with the binding groove thanks to Tyr-22, Leu-53, Arg-70 and Lys-71, resulting in a HLA-DQ2-gliadin complex. This complex may be recognized by T helper cells as “non-self,” with subsequent activation and initiation of an autoimmune response. The ensuing inflammation causes disruption of the structure and function of the small intestine. By learning about binding of gliadins to MHCII, scientists may find a drug that can block the binding groove from gliadins or modify the gliadins to prevent their interactions with HLA-DQ2.

Conclusions
Life used to be simple: Celiac Disease (CD) was a rare disease, diagnosed in 1 in 1,000 individuals. Patients were HLA-DQ2+ of HLA-DQ8+ and could be treated effectively with a gluten-free diet. That was about it. Now we know that CD affects ~1% of the population in Western Europe and the USA, most of which remain undiagnosed. Although good insight has been gained on the immunopathology of CD—inflammation in both lamina propria and epithelium—it remains unclear what triggers the development of CD and why not every patient is equally affected. In addition, with the recognition of Refractory CD (RCD) and RCD-associated lymphoma that do not respond to a gluten-free diet, CD has become a far more complicated disease.

Delving deeper in the structural and cellular mechanisms leading to inappropriate T cell response and resulting inflammation will help establish therapeutic protocols easier for the patients to follow.