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Celiac Disease: Molecular Insight and Future Challenges

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Abstract

CD is an autoimmune enteropathy resulting in lifelong immune disorder of the small intestine where inflammation is triggered by ingestion of gliadin fraction of wheat gluten and similar alcohol-soluble proteins (prolamines) of barley and rye in genetically susceptible subjects. In current situation, there is an urgent need for the development of non-dietary therapies by multidisciplinary research direction involving collaborative efforts between biologist, engineers, chemist and clinicians. This can be achieved by molecular understanding of gluten-induced pathogenesis in CD. Over the past decades, three pathogenically critical molecules - gluten, TG2, and HLA-DQ2 - have served as focal points of interest. This mini review summarizes current understanding about the CD from the molecular basis and address future challenges.

Introduction

Celiac disease (CD) is a multifactorial and polygenic disorder that is caused by an immune response to ingested cereal gluten proteins of wheat (gliadins and glutenins), barley (hordeins), and rye (secalins) [1,2] CD is increasingly considered a systemic disorder although the main pathological lesion is located in the proximal small intestine. In the most developed lesion, there is loss of intestinal villi and infiltration of mononuclear cells, both in the epithelium and the lamina propria.

In normal physiological conditions, enzymes (gastric, pancreatic and small intestinal brush-border enzymes) digest and convert dietary proteins into amino acids and small peptides. In terms of CD, toxic peptides are rich in the proline content consequently they are more resistant to digestion and non-digested peptides (proline and glutamine rich fragments) accumulate in the small intestine. These peptides are referred to as toxic/immunogenic peptides. The pathological conditions associated with CD begin with the alteration of the barrier function of the intestinal mucosa, allowing dietary gluten peptides to reach the immune system. This suggests that CD is the result of an inappropriate T cell-mediated immune response against ingested gluten.

In addition, patients ingesting gluten also have circulating disease-specific autoantibodies derived from B cells that recognize the enzyme transglutaminase 2 (TG2) as well its product and complexes [3-5]. Strikingly, both the intestinal lesions and the autoantibodies are reversibly dependent on oral gluten exposure [6]. A molecular understanding of gluten-induced pathogenesis will therefore likely provide new insights into how the intestinal epithelium and its underlying immune system interact with each other with implications beyond CD. Figure 1 below shows flow diagram of gluten-induced pathogenesis leading to tissue damage in CD.

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Molecular Insight

In the context of CD, three pathogenically critical molecules - gluten, TG2, and HLA-DQ2 (Figure 2) - have served as focal points for intensive collaborative efforts between biologists, chemists, engineers, and clinicians.

Dietary gluten

It is comprised of a number of homologous proteins called gliadins and glutenins in wheat, hordeins in barley, and secalins in rye. Each of these proteins harbors multiple disease-specific T-cell epitopes. These epitopes have relatively higher abundance of Pro and Gln residues. As a consequence, the concentration of certain antigenic peptides builds up in the upper intestinal lumen after ingestion of dietary gluten. This proteolytic resistance of gluten causes HLA-DQ2 mediated inflammatory T cell response in certain individuals with genetic background. Decoding

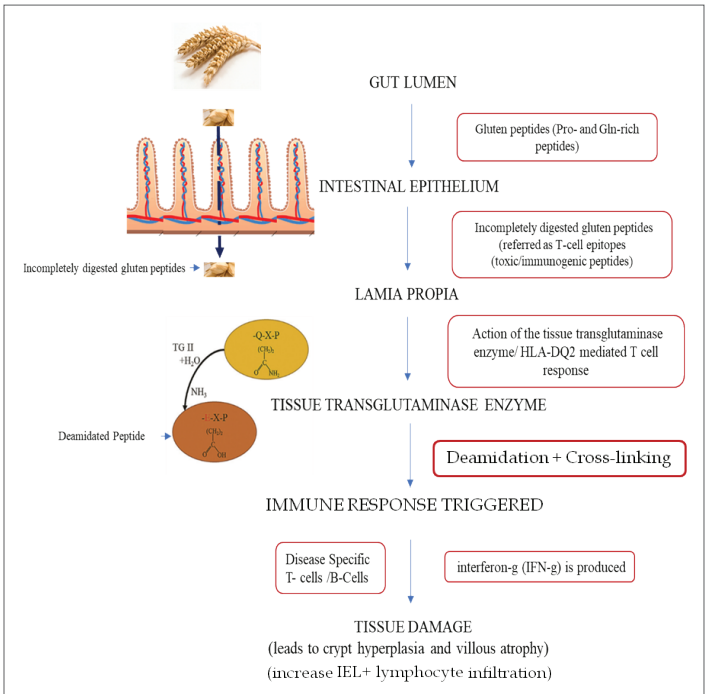

Figure 1: Showing flow diagram of gluten-induced pathogenesis leading to tissue damage (Adapted from [7])

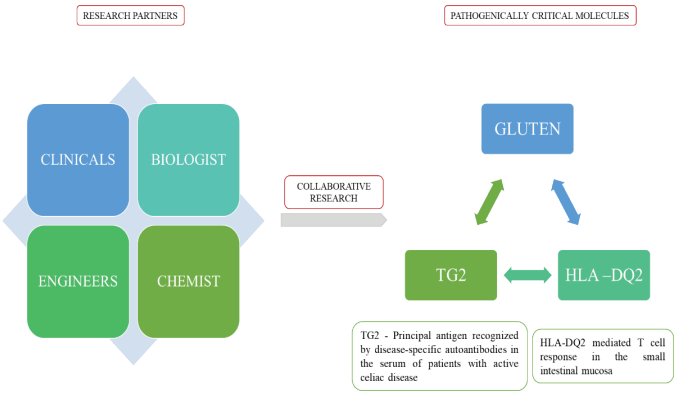

Figure 2: Clinicians, biologists, chemists. Principal autoantigen & Pathogenically critical molecules in the area of CD and research collaboration (Adapted from [7])

this fundamental characteristic will consequently support the interface of chemistry-immunology. Advances has further supported the discovery, scale up, and ongoing clinical development of latiglutenase, an experimental oral enzyme therapy comprised of a fixed dose mixture of two proteases [8]. More recently, a monoclonal antibody capable of sensitively and specifically detecting a protease-resistant and highly immunogenic gluten peptide has been commercialized, and subsequently used to develop assays for detecting inadvertent gluten consumption, thereby highlighting a potentially practical means for improved dietary compliance by CD patients [9]. The current dietary compliance for gluten-free products is limited to maximum 20 ppm set by the European regulation [10].

Transglutaminase 2 (TG2)

It is a non-essential ubiquitous protein in mammals. Its relationship to CD pathogenesis became evident in the last two decade mainly due to two major findings. Firstly, TG2 was identified as the principal antigen recognized by disease-specific auto antibodies in the serum of patients with active CD. Secondly, it was observed that, in order for the T cell epitopes from gluten to be recognized as high affinity ligands by HLA-DQ2, they must undergo post-translational modifications at selected Gln residues via TG2-catalyzed deamidation.

However it is to be noted that the relationship between these two in terms of mechanism currently remains to be fully established. However, together they laid the hypothesis that pre-systemic inhibition of TG2 in the small intestine may represent a viable non-dietary modality for CD therapy. A number of investigators have independently lead inhibitors against this cysteine protease-like enzyme. However, identification of appropriate cellular and animal models for pharmacological evaluation of these inhibitors is challenging and needs further research. However, an unexpected finding that enabled progress in this regard was the observation that an allosteric disulfide bond maintains extracellular TG2 in a catalytically inactive state in the intestine [11]. This in turn led to a search for molecular factors capable of inducing TG2 activity. A growing number of inflammatory signals have been identified that induce extracellular TG2 activity in the small intestine although their relevance to CD remains to be definitively established.

Future Directions

In past two decades, the role of gluten and HLA-DQ2 (or infrequently HLA-DQ8) as the most important environmental and genetic causes has been understood to some extend [12]. It is also understood that other genetic and environmental factors can play significant roles in the onset of CD. Recent studies also suggest that in celiac patients, multiple gluten-related immunogenic pathways are dependent on microbial transglutaminase [13]. Recent studies suggest that microbial transglutaminase is a potential inducer of tight junction permeability, and many characteristics of tissue transglutaminase, if imitated by microbial transglutaminase, may have devastating effects on the celiac population [12]. Nonetheless, any of these genetic clues could present an entirely new window into the onset, severity, or clinical heterogeneity of CD. With respect to environmental factors beyond dietary gluten, the list of potential culprits is seemingly endless. Perhaps the most significant translational advances in the foreseeable future will likely be the development of prototypical animal models for CD.

Recent studies have shown that the new insight into the pathogenesis of CD is shifting toward an important role of B-cells in addition to $CD4^+$ T-cells [14]. Current knowledge about the host microbiome characterization and the better understanding of toxic peptides at molecular and structural level had added new and relevant information to better understand the mechanism that could initiate the $CD4^+$-T-cells response and induce the loss of oral tolerance to the gluten. Overall, these results are of potential consequences for therapeutic approaches targeting on plasma-cell depletion and on modified propyl-endopeptidase enzymes [15]. Amongst human autoimmune diseases, the environmental trigger has been identified and characterized chemically [1,16]. As referred to our earlier discussion, T cell epitopes in gluten have also been extensively characterized, however the mechanism by which they gain access to sub-epithelial antigen presenting cells is not fully understood [11,17,18]. This is a key area of interest so as to further develop insight about CD. Elucidation of the mechanism will allow researcher to understand the process for the transport of intact peptides from the gut lumen to the subepithelial vasculature. This would definitely have broader physiological implications beyond CD.

In conclusion, notwithstanding the fact that CD remains an example of a lifelong chronic disorder for which no drug therapies are available, it has been a vivid example of the power of collaborative research at the chemistry-biology interface. One can only hope that, over the next decade, the celiac patient will start to reap the benefits of the scientific advances that have emerged as a result of this collaborative spirit.

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