The Role of the Microbiota in Inflammatory Disease: The Celiac Disease Model.

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Introduction

Celiac disease (CD) is a life-threatening enteropathy which follows an autoimmune etiology. The CD victim is found to develop sensitivity to gluten and related prolamines. CD pathogenesis is multifactorial, and genetic predisposition due to possession of HLA-DQ2 and or HLA-DQ8 alleles of the Major Histocompatibility Complex (MHC) loci is a primary cause. It is a severely debilitating inflammatory disease and the primary treatment includes withdrawal of gluten from the diet. The clinical pathology includes intraepithelial lymphocytosis and influx of lymphocytes to the lamina propria leading to villous atrophy and crypt hyperplasia due to an overproduction of the pro-inflammatory cytokine IFN-Ɣ. Recent studies by advanced techniques have found an important association between CD pathogenesis and dysregulation of multiple immune regulatory pathways [1].

Celiac disease is widespread in the western hemisphere and gradually emerging as a threat in the east with a prevalence of 1% in both the regions of the world. 90% CD patients are reported to carry the HLA-DQ2/HLA-DQ8 alleles. 40% of the western population possess this genotype however only 1% develop the disease. This led to the speculation and discovery of other factors responsible for causing the disease. These include environmental, epigenetic and non-HLA genetic factors and association of dysbiosis of the gut microbiota. It is believed that a complex interaction among these components leads to disease manifestation.

Dysbiosis of microbiota is a frequently observed phenomenon in CD patients and recent reports indicate a crucial role of the microbiota in CD pathogenesis. A study reported by Caminero et al. found that certain gut-associated bacteria like *P. aeruginosa* and *Lactobacillus sp*. has the capacity to modify gluten peptides and enhance or reduce their immunogenicity and potential to activate T-cells, thereby modulating risk of CD in genetically susceptible individuals [2]. Tian et al. who studied the oral microbiota in patients with active and refractory CD and compared them with that of healthy controls reported the increased number of salivary *Lactobacillus sp*. and suggested this was responsible for higher gluten-degrading activity of CD subjects as opposed to normal subjects [3]. Gutierrez et al., studied from fecal samples of CD patients versus normal subjects the quantification and contribution of glutenase involved in degrading gluten and concluded from their study that microbial activity can modify digestion of the remaining fraction of 33-mer peptides that result from gluten digestion in humans [4]. These findings suggest the significant role played by oral and gut-associated bacteria in enzymatically degrading gluten to immunogenic forms which provide the immunogenic trigger in CD subjects.

Recent studies have found a link between infection exposure and CD pathogenesis. For example, *Candida albicans* infection has been proposed as a factor involved in stimulating the onset of CD in genetically predisposed individuals [5]. There has been constant debate whether or not *Helicobacter pylori* infection affects CD onset and pathogenesis [6]. More studies have reiterated the assumption that the microbiota is involved as cause or consequence of CD and clearly demonstrated the role of the microbiota and dysbiosis of the microbiome in association with CD and which contribute mainly in steps of gluten digestion and degradation, modulating the outcome of the clinical impact of gluten either by augmenting or abrogating the symptoms. More research and a deeper understanding of the complex connection between microbiota and innate and adaptive immunity network can resolve the problems of CD prevention and outcome and pave new paths for novel therapeutic approach. Enrichment or depletion of required microbial components that contribute to pathogenesis in CD can be a useful tool to combat the pathophysiology of CD. For example, *P. aeruginosa* isolated from human CD cases when injected into mice duodenum exhibited elastase activity that degraded gluten into peptides which were depicted to trigger gluten-specific T cells [2]. Reducing the load of this bacteria may induce tolerance in CD subjects. On the other hand, *Lactobacillus sp.* from non-CD subjects degraded peptides that resulted from gluten digestion due to human and *P. aeruginosa* proteases. These approaches can be used to deal with CD therapy in a patient-specific manner as these can alleviate the need for many CD subjects to be prescribed a totally GFD restriction. Probiotic use can be an additional treatment for CD patients and researchers have demonstrated the efficacy of probiotic bacteria in alleviating the symptoms of gluten intolerance. Gallpeau et al. showed that elafin (a serine protease inhibitor produced by small intestinal epithelial cells) expression in the small intestinal epithelium was lower in patients with active CD compared with control patients without CD. In *in vitro* experiments, elafin significantly slowed the kinetics of the deamidation of the 33-mer peptide to its more immunogenic form. Treatment of gluten-sensitive mice with elafin was delivered to the intestine of the gluten-sensitive mice by the *Lactococcus lactis* vector normalized inflammation, improved permeability, and maintained ZO-1 expression [7]. McCarville et al. showed a commensal strain of Bifidobacterium longum that produces serine protease inhibitor can be used to attenuate gliadin-induced immunopathology and influences microbiota composition in NOD/DQ8 mice [8].

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