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The microbiota as a component of the celiac disease and non-celiac gluten sensitivity

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SUMMARY

Dietary gluten present in wheat, rye and barley induces several gastrointestinal disorders, including celiac disease and non-celiac gluten sensitivity (NCGS). Celiac disease is an immune-based enteropathy triggered by ingestion of gluten in genetically susceptible individuals resulting from the interaction between genetic and environmental factors. Although gluten has been recognized as the main environmental trigger of the disease, a specific role for the intestinal microbiota in celiac disease development has been suggested. NCGS individuals develop adverse reactions after the exposure to gluten. Due to the similarities in clinical outcomes and the absence of diagnostic biomarkers, it is challenging to differentiate NCGS from celiac disease. The aetiology of NCGS remains unknown, although the involvement of innate immune mechanisms has been suggested. Since the influence of intestinal microbiota on immune cell homeostasis and on education of both innate and adaptive immune system is well known, the role of host-microbe interactions in the non-celiac gluten sensitivity have been hypothesized.

This review aims to summarize the current knowledge of the contribution of microbiota to the pathogenesis and/or onset of celiac disease. In addition, a brief overview of the possible role of the microbiota components on the NCGS is presented.

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1. Introduction

Gluten-related disorders are the umbrella term for all conditions related to gluten ingestion, such as celiac disease and non-celiac gluten sensitivity (NCGS). The prevalence of these diseases has increased over the past 50 years, being an emerging health problem worldwide. Currently, celiac disease is considered the most common food intolerance, prevalence being approximately 1–2% of the population [1]. In contrast, the prevalence of NCGS has been estimated to be as high as 6% of the general population, depending on the population studied [2]. The biological basis of gluten induced symptoms in the absence of celiac disease is unknown but it has been suggested to be related to immune responses to components of wheat apart from gluten, such as wheat amylase-trypsin inhibitors (ATIs) and fermentable oligo-, di-, monosaccharides and polyols (FODMAPs) [2,3].

The main genetic component of celiac disease, HLA-DQ2/DQ8 heterodimers, is well-known. Although these HLA-DQ genes underlie the disorder, only a small percentage of carriers develop the disease and thus, other genetic and environmental factors must be involved in the onset of celiac disease. This review aims to summarize the current knowledge of the contribution of microbiota to pathogenesis and/or onset of CD. In addition, a brief overview of the possible role of the microbiota components on the development and/or onset of NCGS will be provided.

2. Celiac disease

Celiac disease is an immune-based enteropathy triggered by ingestion of wheat, rye and barley derived gluten in genetically susceptible individuals. Upon exposure to gluten, inflammatory cascade is induced in the small intestinal mucosa leading to villous atrophy, crypt hyperplasia and increased numbers of lymphocytes in the lamina propria. Disruption of intestinal villus structure leads to impaired epithelial barrier function resulting in nutrient malabsorption that may cause severe symptoms such as anaemia, osteoporosis and, in case of children, to growth retardation. The clinical picture of the celiac disease is highly variable and individual-specific. Classical symptoms of celiac disease include different gastrointestinal symptoms such as abdominal pain and diarrhoea. However, many CD patients are predominantly symptomatic, showing both gastrointestinal and extra-intestinal manifestations. In asymptomatic patients the diagnosis is often delayed and thus the small-bowel mucosal damage may be severe before the celiac disease is suspected. Therefore, early diagnosis of the disease is crucial for the prevention of persistent villous atrophy predisposing to severe complications. Celiac disease is a life-long disease that cannot be cured but the symptoms can disappear and small bowel mucosal damage, intestinal inflammation and epithelial integrity are improved by commitment to a life-long gluten-free diet.

The main genetic predisposition to celiac disease are the human leucocyte antigen (HLA) DQ2 and DQ8 haplotypes. These HLA-DQ genes account for approximately 40% of the genetic risk of celiac disease [4]. However, although these genes underlie the disorder, only a small percentage of carriers develop disease. In addition, the disease concordance in monozygotic twins has been reported to be only 85% [5]. Thus, other genetic and environmental factors must be involved in the onset of the disorder (Fig. 1). Recent genome wide association studies have reported additional 39 non-HLA regions associated with susceptibility to celiac disease development [4]. Interestingly, most of these regions contain genes with immune related functions, several of which are also involved in shaping the intestinal microbiota. In addition, altered expression of non-specific celiac disease risk-genes affecting the host-microbe interactions has recently been reported. For instance, a decreased TOLLIP mRNA levels were observed in untreated celiac patients when compared to healthy controls [6]. TOLLIP is an intracellular protein that inhibits toll-like receptor signalling and failure to upregulate its transcription has been suggested to contribute to the chronic inflammation in celiac and inflammatory bowel disease patients [6,7]. These results suggest the potential role of disturbed host-microbe interaction in the pathogenesis of celiac disease.

It is assumed that aberrant microbiota diversity and relative abundances of specific bacterial taxa lead to functional imbalance where the mutualistic relationship between the host and his microbes is disturbed. Deviations in the microbiota community structure has been associated with several local and systemic diseases, possibly contributing to the pathogenesis and/or clinical manifestation of these