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Chapter 1

Differential Hallmarks of Celiac Versus Non-Celiac Gluten Sensitivity

Mahesh Mohan and Karol Sestak

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Abstract

Non-celiac gluten sensitivity (NCGS) is an intestinal tissue transglutaminase (TG2)- and IgE-independent form of GS. NCGS is approximately 6× more prevalent than the classical celiac disease (CD), and its incidence is on the rise. Because of its high relative prevalence and striking resemblance to other forms of GS, there is a greater need to develop new and accurate diagnostic assays to facilitate its definitive diagnosis. As the presence of serum anti-gliadin antibodies (AGA) in the absence of TG2 antibodies is suggestive of NCGS, several reports have recommended AGA immunoassays for differential diagnosis. Although AGA immunoassays are in general suitable for diagnostic purpose, to corroborate NCGS and to distinguish it from CD, a simultaneous use of CD-specific diagnostics, i.e., TG2 antibody-based assay, is also required. Due to lower accuracy of AGA assays than those of TG2-based ones, there will always be a chance (estimated to 5–10%) of misdiagnosing NCGS. Moreover, AGA-based diagnostics would not take into consideration the fact that NCGS is potentially triggered by not only gluten but also other molecules such as fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs). Therefore, a second generation of assays needs to be developed to differentiate NCGS from CD with high accuracy.

Keywords: celiac, gluten, NCGS, tissue transglutaminase, differential diagnosis, gut microbiome, gluten-free, diet, IBS, chronic inflammation, small intestine, GI tract

1. Introduction: NCGS, CD, and irritable bowel syndrome

Similarities between non-celiac gluten sensitivity (NCGS) and irritable bowel syndrome (IBS) were first noted in 1978 when it was reported that an adult female patient with IBS but not

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celiac disease (CD) showed dramatic relief of chronic diarrhea and abdominal pain symptoms after administration of gluten-free diet (GFD) [1–6]. More recent studies corroborated that some but not all IBS patients show significant onset of clinical diarrhea upon mucosal challenge with gluten [7, 8]. There is an emerging consensus that tissue transglutaminase (TG2) antibody-negative and anti-gliadin antibodies (AGA)-positive (TG2−AGA+) IBS patients with DQ2/8-negative haplotype qualify as NCGS candidates [3]. Such an assumption can be confirmed by placing suspect NCGS patients on GFD with subsequent relief of clinical/immunological symptoms. Conversely, if AGA test is used alone, without other corroborative/exclusionary assays, its predictive value for NCGS is poor [4]. Taken together, it appears that NCGS and IBS patients share several clinical and histopathological symptoms. NCGS should therefore be differentiated from IBS based on complete CD/NCGS serology, and diagnosis can be confirmed by performing a mucosal gluten challenge. To simplify and to expedite diagnostic steps, new molecular assays need to be developed to differentiate NCGS from IBS and CD.

2. Composition of host gut microbiome and NCGS/CD

Given the unprecedented rise of food allergies and autoimmune disorders in urban populations during recent decades, several studies have indicated that a potential causative association exists between some of these disorders and composition of the host's gut microbiome [9, 10]. Since both CD and NCGS are inflammatory disorders of not only gastrointestinal (GI) tract but also other organs, including dysfunction of the gut-brain axis [11, 12], studies aimed at identification of specific hallmarks of gut dysbiosis of these disorders are the focus of current investigations.

It has been reported that bacteria involved in gluten metabolism predominantly belong to phylum *Firmicutes*, in particular, those from the genus *Lactobacillus*, followed by *Streptococcus*, *Staphylococcus,* and *Clostridia* [13, 14]. Recently, it was shown that GFD treatment significantly altered proportions of these bacterial groups and that restoration of normal bacterial flora took many months and possibly years [14, 15]. It was also shown that increased presence of some of the bacterial species involved in gluten metabolism leads to enteritis [13]. Our group recently demonstrated that *Streptococcaceae* and *Lactobacillaceae* families were enriched in GS rhesus macaque model of CD, while *Coriobacteriaceae* predominated in healthy animals [14]. In the future, studies to elucidate specific dysbiotic pathways that distinguish NCGS from CD need to be done.

3. Host luminal shedding of fecal microRNAs

Recently, a novel concept concerning the capability of intestinal epithelial cells to release luminal regulatory microRNAs (miRNAs) was described [16]. It was demonstrated that

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these fecal miRNAs could potentially enter bacterial cells and regulate their replication and growth. In this context, it is possible that inflammation-induced miRNAs could enter commensal bacteria and posttranscriptionally suppress or promote their growth by binding to specific sequences on bacterial genes [16]. This in turn, depending on the outcome, may give pathogenic bacteria an opportunity to expand leading to dysbiosis. [16]. These findings have therapeutic implications as oral supplementation of stable miRNA mimics capable of targeting specific dysbiotic or probiotic members of the gut microflora relevant to disease relapse and/or remission may be implemented. In our recently published studies, we hypothesized that GS disorders including CD and NCGS have their own unique signatures of dysbiosis. In addition, it is also likely that regulatory miRNAs secreted by host epithelial cells in response to dysbiotic events are also disease specific. Recently, we identified and reported several miRNAs (miR-203, miR-204, miR-23b, and miR-29b) with perfect complementarity between miRNA seed nucleotides (5′ prime nt position 2–7) and 16S rRNA sequence of dysbiotic bacterial species in the rhesus macaque model of CD (**Figure 1**) [14].

Dysbiotic bacterial species that could be potentially regulated in this fashion by inflammatory miRNAs included members of the *Streptococcaceae* and *Lactobacillaceae* families that are known to play roles in metabolism of gluten [13]. As biological and regulatory functions of miRNAs include host cell effects such as expression of epithelial tight junction proteins, more work remains to be performed to characterize regulatory relationships and pathways pertinent to miRNA molecules that influence dysbiotic gut microbiota in NCGS and CD individuals.

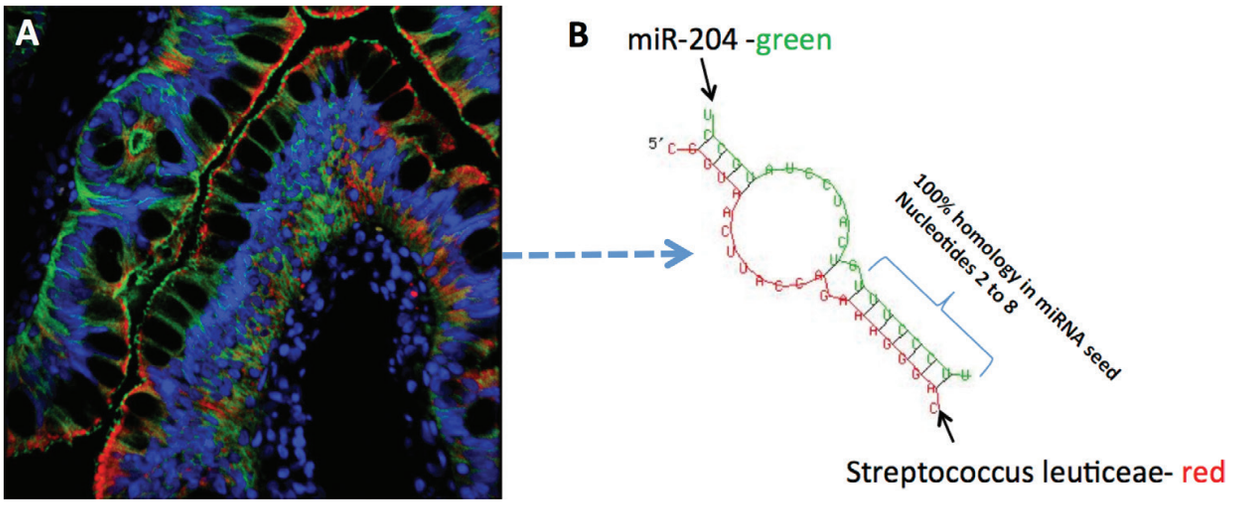


Figure 1. Small intestinal epithelial cells of gluten-sensitive rhesus macaque (A) were visualized by immunofluorescent triple labeling of cytokeratin-1 (red), tight junction protein claudin-1 (green), and nuclear DNA (blue) antigens. Epithelial cells of gluten-sensitive but not healthy, normal primates produced regulatory fecal microRNAs (miRNA) species complementary with dysbiotic bacterial species such as *Streptococcus leuticeae* (B) and others. It was proposed that intensity of such interactions can shape the gut microbiome dysbiosis either toward remission or relapse [14, 16].

4. Dietary gluten and neurodevelopmental disease markers

The first report suggesting an association between increased occurrence of neurodevelopmental disorders and consumption of gluten-containing cereal grains dates back to 1966 [17]. In the same year, it was reported that some but not all GS patients develop neurological dysfunctions referred to as gluten ataxia, gluten neuropathy, or gluten encephalopathy [18, 19]. Since then, several studies have suggested that symptoms of the autism spectrum disorders (ASD) could be improved upon changes in diet. One of these diets is GFD [20]. Despite its widespread use, the efficacy of GFD for the treatment and prevention of ASD has not been conclusively proven. More recently, a case report involving NCGS patients with gluten psychosis was reported [21]. The molecular mechanisms underlying ASD/psychosis vs. dietary gluten relationship are highly complex and understudied [22, 23]. Therefore, a transition from the "clinical phenomena" to "basic research" type of studies is needed. We propose that perturbation levels (measured by the extent of mRNA expression) of ASD predisposition genes need to be elucidated in preclinical, humanlike models first in the context of experimental introduction/withdrawal of dietary gluten.

For this and other purposes, we developed the rhesus macaque (*Macaca mulatta*) model of GS [14, 24–30]. The presence of AGAs, gluten-sensitive enteropathy (GSE), increased intestinal permeability, and genetic predisposition were all documented. Consistent with human disease, GSE in macaques is characterized by a wide range of severity, ranging from the subclinical to severe form that includes decreased absorption of nutrients, decreased xenobiotic metabolism, cancer predisposition, diarrhea, dermatitis, decreased diversity of gut microbiome, as well as the perturbations in expression of several neurodevelopmental disorder-associated genes including those of ASD and down syndrome. One of these genes that showed significant upregulation in GS rhesus macaques was the Ca^{2+}-dependent activator protein for secretion 2 (*CADPS2*). In humans, the *CADPS2* gene is located within the autism susceptibility locus 1 on chromosome 7q. It was shown that *Cadps*2-knockout mice exhibit cellular and behavioral traits consistent with ASD [31]. The CADPS2 protein regulates exocytosis of synaptic vesicles in neurons and neuroendocrine cells. In accordance with these findings, analysis of the ASD-associated genetic predisposition factors by a group at Harvard School of Medicine revealed that ASD is not restricted to not only humans but also apes, monkeys, and dolphins [32]. Remission and relapse stages of GSE can be accomplished in GS macaques by feeding gluten-free and gluten-containing diets, respectively. Similar to human gluten-sensitive patients, AGA and GSE are reversibly dependent in GS macaques by exposure to dietary gluten [24, 33, 34]. Thus, an extensive use of GS rhesus macaque model in experimental and translational studies involving neurodevelopmental disorder-associated genes and their corresponding pathways is desired—as a new preclinical tool for not only ASD research but also for the development of NCGS vs. CD differential diagnostics.

5. NCGS vs. CD microbial signatures

Based on the assumption that CD is caused by an autoimmune reaction to TG2, while NCGS is caused by chronic bacterial intestinal infections, a recent study by Columbia University

researchers focused on the identification of differential, bacterial byproduct-specific diagnostic markers to distinguish the two conditions [35]. Their findings suggested that enteropathy could occur in individuals who report GS in the absence of CD, while it is associated with increased serum antibodies recognizing bacterial lipopolysaccharide (LPS) and/or its CD14 ligand [35]. Although several antibodies were evaluated for their potential to be used as differential diagnostic tools including anti-LPS, anti-flagellin, and anti-soluble CD14 (sCD14), the best predictive values were attributed to antibodies targeting LPS and sCD14. These results corroborated that NCGS and CD have common and differential features that can be further exploited for the development of more sensitive and accurate differential diagnostic assays.

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