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Gluten, Transglutaminase, Celiac Disease and IgA Nephropathy

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Abstract

Both, celiac disease and IgA nephropathy are autoimmune diseases that are IgA mediated and share multiple clinical, pathophysiological, genetic, nutritional and immunological aspects. In view of recent observations and wider understanding of the central role played by the intestinal ecosystem in celiac disease and IgA nephropathy development, the present review highlights those shared aspects, concentrating on potential nutritional therapeutic strategies in IgA nephropathy.

Keywords: Gut-kidney axis; Celiac disease; IgA nephropathy; Berger's disease; IgA deposit; tissue transglutaminase; Gluten

Introduction

The gut-kidney axis is a part of a much wider network, centered in the gut and irradiating to remote organs, conveying the messages of loss of tolerance and autoimmunogenesis [1-4]. This axis appears crucial in IgA nephropathy (IgAN) physiopathology [5]. This review highlights the shared molecular mechanisms between celiac disease and IgAN. Before relating these two diseases, it is logical to introduce the two entities apart.

Celiac disease

Celiac disease is an autoimmune inflammatory disorder of the small intestine, triggered by the ingestion of prolamins contained in wheat, barley or rye, in genetically susceptible individuals. In high risk populations, the average risk of CD can reach 5-10%; however, its incidence in the general population is 1-1.5%.

There is an increased risk of complications such as haematological and gastrointestinal malignancies, osteoporosis/penia and other extra intestinal manifestations, decreased height, malnutrition and nutritional deficiencies, fertility impairment, stillbirth, dismaturity, psychosocial retardation, impairment of quality of life, increased mortality and additional autoimmune conditions, if left untreated. Thus, early diagnosis and subsequent adherence to a gluten-free diet is highly recommended. The epidemiology and phenotype of CD are constantly changing. It has been shown that the classic intestinal clinical picture of malnutrition, chronic diarrhoea and nutritional deficiencies are disappearing and extra intestinal presentations are emerging. Skin, endocrine, skeletal, hepatic, haematological, thrombophylic, gynaecological, fertility, dental and behavioural abnormalities are often described. Nowadays, we are witnessing an epidemiological shift in the disease phenotype toward a more advanced age, and increased prevalence of latent, hypo symptomatic or asymptomatic behaviour [6,7]. All these changes make the diagnosis of the disease more difficult and the reliance on symptomatology more remote [8].

Pathophysiologically, CD is an autoimmune disease where the enzyme tissue transglutamimnase (tTg) is the auto antigen. By post translational modification of the absorbed gliadin peptide, deamidating or crosslinking, those peptides are becoming immunogenic/toxic, resulting in mucosal inflammation and damage [9,10]. Several well established serological markers are available for screening, diagnosing and follow-up: anti endomysium, anti-deamidated gliadin and anti tTg autoantibodies. However, two novel ones, the anti-neo-epitope tTg and anti-neo-epitope microbial Tg were recently described with good performances [11-13].

Several of the extra-intestinal manifestations of CD involve the kidney. Urolithiasis and crystal-induced kidney disease, nephrogenic ascites, increased risk of end-stage renal disease and membranoproliferative glomerulonephritis type 1 were associated with CD. The present review will concentrate on CD and IgAN.

IgA nephropathy

IgAN or Berger's disease is the most common form of primary glomerulonephritis in the developed world and it is an important cause of end-stage kidney failure. The presence of mesangial IgA became a major criterion for the diagnosis of IgAN, while features of the disease include mesangial cell proliferation, matrix expansion and clinical symptoms of renal injury, such as haematuria and proteinuria. The disease is characterized by the accumulation in mesangial areas of complexes containing polymeric IgA1. The mechanisms involved in the pathogenesis of IgAN are only now emerging and seems to be linked to abnormalities of the IgA system [14-16]. Current studies indicate an ordered sequence of multi-hits as fundamental to disease occurrence. Altered glycan structures in the hinge region of the heavy chains of IgA1 molecules act as auto-antigens, potentially triggering

the production of glycan-specific autoantibodies. Recognition of novel epitopes by IgA and IgG antibodies leads to the formation of immune complexes galactose deficient-IgA1/anti-glycan IgG or IgA [17]. Immune complexes of IgA combined with FcαRI/CD89 have also been implicated in disease exacerbation [18-20]. These nephritogenic immune complexes are formed in the circulation and deposited in renal mesangium. Deposited immune complexes ultimately induce glomerular injury, through the release of pro-inflammatory cytokines, secretion of chemokine and the resultant migration of macrophages into the kidney. The TfR1/CD71 receptor has a pivotal role in mesangial cells as a receptor for hypogalactosylated IgA [21]. Activation of this receptor after the binding of polymeric IgA1 lead to mesangial cell proliferation and pro-inflammatory cytokine production [22]. Emerging data indicate that mesangial-derived mediators that are released following mesangial deposition of IgA1 lead to podocyte and tubulointerstitial injury via humoral crosstalk [23,24].

Clinically, IgA nephropathy usually progresses slowly over many years, but the course of the disease in each person is uncertain. The classic presentation is episodic haematuria, which usually starts within a day or two of a non-specific upper respiratory tract infection. These infections have in common the activation of mucosal defences and hence IgA antibody production. No cure exists for IgAN, but angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists can slow its course [25]. Potential therapies include: bacterial protease [26], Glycan-targeted drugs, anti-B cell therapies and complement inhibitors [27].

There are other diseases associated with glomerular IgA deposits, the most common being IgA vasculitis (known as Henoch-Schönlein purpura), which is considered by many to be a systemic form of IgAN.

Similarities and Dissimilarities between Celiac Disease and IgA Nephropathy

Due to recent expanding knowledge on the two entities, on the central role played by nutrients, microbiome, IgA metabolism and functions and the mucosal and systemic immune systems[1-4,17,28-30], cross-talks between the two diseases, were discovered [16,18,29-33]. Table 1 summarizes the epidemiological, clinical and pathophysiological aspects of CD and IgAN. The geographical distribution of the two diseases does not exactly overlap. CD is more frequent in Europe due to the wheat consumption and IgAN in Asia. However, in China where IgAN can represent until 40% of kidney biopsies, the wheat is the main cereal for the west/north region and CD frequencies were underestimated [34,35]. The predisposition genes are located in the same loci for both diseases. Associated infections are common in CD and IgAN. To note, CD and IgAN are both considered now as auto-immune diseases with reactivity against tTG in CD [9] and against hypogalactosylated IgA1 in IgAN [36].

Moreover, molecular mechanisms are shared between the two diseases: CD patients exhibit overexpression of TfR and tTg on enterocytes leading to the retrotranscytosis of IgA bearing gliadin (a component of gluten) [37,38]. In kidney, TfR and tTg overexpression results in increase of IgA deposits [18,21,39]. The binding of IgA1 complexes on TfR at the cell surface of mesangial cells induces the overexpression of TfR [39] and tTG [18]. In absence of tTG, the IgA deposits are dramatically reduced and *in vitro* IgA1 binding on mesangial cells is diminished [18]. A deleterious loop following IgA1 binding on mesangial cells lead to TfR and tTG production, these proteins in turns amplifying the IgA1 deposition.

	Celiac disease	**IgA nephropathy**
Incidence	1-1.5%	0.5-1%
Gender predominance	female	male
Geoepidemiology	North West to South East gradient	East South to West North gradient
Environmental factors	gluten, mTg, infection, stress, formula feeding, increased diversity of dysbiota	upper respiratory/urinary/ gastrointestinal infection
Associated Infections	EBV, HCT, tuberculosis	Staphylococcal & streptococcal infections, HIV, malaria, Chlamydia, Lyme disease
HLA predisposition	Loci: DQ-A1, DQ-B1 Serotype: DQ-2, DQ-8	Loci: DQ-A1, DQ-B1, DR-B1**58**
Autoantibodies	tTg, DGP, EMA, neo-epitope tTg, neo-epitope mTg	IgG and IgA anti galactose-deficient IgA1
Autoantigen	tTg	galactose-deficient IgA1
Inducer enzyme (PTMP)	tTg, mTg deamidation/cross-linking	tTg
Adaptive/innate immunity	+++	+++
Target/ associated organs	small bowel/joint, bone, endocrine, heart, lung, liver, kidney, skin, nerves, etc.	kidney/skin, joint, intestine in HSP associated with IgA nephritis
Therapy	Gluten free diet	Angiotensin converting enzyme inhibitors, Angiotensin II receptor antagonists, Immunosuppressors[25]

Table 1: Similarities and dissimilarities between Celiac disease and IgA nephropathy.

Gluten and IgA Nephropathy

Food antigens, including milk proteins, bovine serum albumin, soybean proteins and gluten have been described to form IgA complexes [40-43], which in some cases can be deposited in the mesangium of IgAN patients [44-46]. The role of gluten in IgAN was mainly assessed by *in vitro* studies with the direct interaction of gliadin and IgA partners and mesangial cells. We studied in vivo the effects of a gluten free diet using a humanized mouse model for IgAN, the α1KI-CD89Tg mice [32], which expressed both human IgA1 and CD89 presenting some features of IgAN.

In vitro

Gliadin interacts with IgA1 by a lectin manner [47] leading possibly to the formation of IgA aggregation. Moreover, gliadin binds also directly to mesangial cells *in vitro* [48] increasing polymeric IgA

binding to mesangial cells. The binding of gliadin results in mesangial cell activation and production of proinflammatory cytokines [47].

Moreover, gliadin directly interacts with CD89 and participates in the formation of IgA-sCD89 complexes. Purified gliadin bound to recombinant sCD89 in a dose-dependent way, as shown by ELISA and surface acoustic wave (Figure) [32].

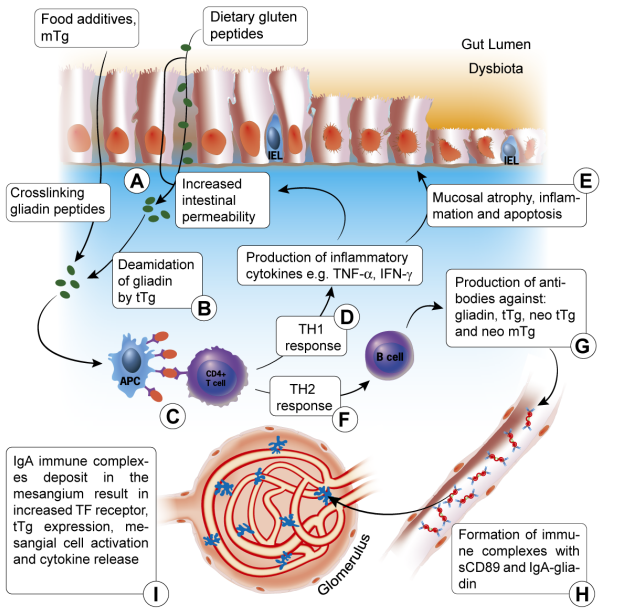

Figure 1: Summary of the involvement of gluten in IgA nephropathy pathogenesis.

Animal models

Ingestion of dietary components eliciting antigen response classically induces the IgAN disease in mice [49]. These models are based on oral immunization with the dietary component followed or not by intravenously challenge. The oral immunization with gliadin in BALB/c mice resulted in kidney IgA deposition better than soya immunization [47] showing that oral breakdown tolerance can lead to IgAN.

At the opposite way, a gluten free diet during three generations in α1KI-CD89Tg mice, a humanized model of IgAN, resulted in a massive decrease of IgA1 deposits in kidney associated to the diminution of inflammation and haematuria [32]. These results were strong and reproducible (n=20 animals, 100% of animals). This decrease was gluten specific, as shown by its re-introduction in the diet during 30 days being followed by the re-appearance of mesangial IgA1 (n=10, 100% of mice). Moreover, the diminution of IgA1 deposits was associated with down-regulation of mesangial tTG and TfR expression in mouse kidneys. In the small intestine, as previously demonstrated, gluten free diet resulted in an improvement of morphology: the crypt hyperplasia diminished, the villus/crypt ratio increased. Moreover, there was a resorption of inflammation with less infiltrated immune cells (T cells and macrophages). The number of B cells producing IgA was also decreased with the diet. Taken together, these results indicated that gluten via the induction of gastrointestinal inflammation and systemic immune responses may favour IgAN development in mice.

It should be noted that the sensitization of mice to gluten by its depletion from the diet during three generations is an experimental design serving to mimic the intolerance of some patients with CD [50]. Although these experiments allowed us to establish a link between gluten and IgAN onset, this strategy could not be applied to patients over generations.

Clinical studies on gluten free diet

Several tests of gluten free diet for IgAN are described in the literature. When CD was clearly associated to IgAN, three cases showed the efficacy of gluten free diet for clinical remission of IgAN [51-53]. However, the results of trials on non-selected IgAN patients were mitigated. A Japanese group observed no difference for the IgA complex production after two weeks of diet with enriched gluten or without gluten [54]. Coppo et al in an uncontrolled study tested a long-term gluten free diet from 6 months to 4 years depending on patient follow-up. The diet was associated to the decrease of circulating IgA complexes and proteinuria after 6 months but serum creatinine was not controlled and progression of the disease was not reversed [55].

To explore the duration of the diet by an experimental strategy, we treated our α1KI-CD89Tg mice, previously fed with a standard gluten-containing chow, with gluten-free diet during 2, 6 or 9 weeks. Gluten-free diet during 6 and 9 weeks of treatment, but not during 2 weeks, induced a significant decrease in hematuria and reduced IgA1 deposits in the mesangium [32]. Nine weeks in mice correspond to approximately 5-7 years in humans. So, a long-term delivery of gluten-free diet introduced in the early stages of IgAN could prevent progression of the disease in selected patients exhibiting high level of IgA anti-gliadin. As shown by the effect of gluten reintroduction in our model, this gluten-free diet should be strict without any gap.

Other diets

Several diets were investigated and suggested for patients with IgAN as Mediterranean diet [56], low-antigen diet [a diet free of foods likely to cause an allergic reaction] [57] and fish oil (KDIGO recommendations) [25].

Intestinal Infections and IgAN

A recent genome-wide association study (GWAS) of IgAN has shown an interesting new association of IgAN and loci associated with risk of inflammatory bowel disease or maintenance of intestinal barrier and intestinal MALT response to pathogens [58]. A defective immune tolerance might favour an abnormal response to micro biota with alterations of the intestinal barrier, increased antigen absorption, MALT activation and subclinical intestinal inflammation. This in turn can favour an abnormal handling of endotoxin by an intestinal barrier leading to increased production of aberrantly glycosylated polymeric IgA1 in the context of systemic micro inflammation eventually producing IgA1 mesangial deposits and nephritis. This may also induce abnormal response to alimentary antigens such as gliadin that together with synthesis of aberrantly glycosylated polymeric IgA1 anti-gliadin results in pathogenic immune complexes which eventually enter the circulation inducing mesangial IgA1-gliadin deposits, as demonstrated in mice [32].

Conclusion

Growing evidences show a crucial role of intestine in aberrant production of hypogalactosylated IgA1 in IgAN. Food plays a potential role in IgAN initiation and progression. Figure 1 summarizes the steps of gluten involvement in celiac disease and IgA nephropathy. Due to the multiple shared aspects between IgAN and CD, gluten and other alimentary components should be further explored to assess new therapeutical strategies for IgAN patients.

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