New advances in coeliac disease: serum and intestinal expression of HLA-G

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Abstract
Coeliac disease (CD) is a common autoimmune disorder characterized by an immune response to ingested gluten and has a strong HLA association with HLA-DQ2 and HLA-DQ8, but as human HLA-DQ risk factors do not explain the entire genetic susceptibility to gluten intolerance. Our aim was to investigate whether HLA-G, a gene located in the MHC class I region, and with important role in the induction of immunotolerance, may contribute to CD susceptibility. We demonstrated the expression of soluble HLA-G (sHLA-G) forms in intestinal biopsy and in serum of patients with CD. Indeed, all patients tested showed a positive expression of HLA-G in intestinal mucosa with different grade of immunoreaction. The serum levels of sHLA-G found in coeliac patients depend on the association with other diseases of autoimmune nature or genetics, and also depend on the transgressions in the diet with gluten ingested. The enhancer expression of sHLA-G in CD could be due as part of a mechanism to try restore the tolerance process towards oral antigens in a disease caused by loss of tolerance to dietary antigens and counteract the inflammation. In summary, in this paper, we demonstrate the association of CD with sHLA-G expression.

Introduction
Coeliac disease (CD) is a common autoimmune disorder that has genetic, environmental and immunologic components (1–2). CD is characterized by an immune response to ingested wheat gluten and related proteins of rye and barley that leads to inflammation, villous atrophy and crypt hyperplasia in the intestine (2, 3). A defect in antigen processing by epithelial cells, together with the intrinsic properties of the gliadins, as well as the HLA-DQ haplotype of the individual are considered the principal factors involved in the pathogenesis of CD (3). Moreover, it has been shown that the disease is associated with the expression of HLA-DQ2 and HLA-DQ8 (4, 5). In addition, transglutaminase 2 (TTG2) may play an important role in CD development, acting as a deamidating enzyme and as a target auto-antigen in the immune response (6, 7). Exposure to gliadin and related prolamins in humans with an appropriate HLA-DQ haplotype is necessary but not sufficient for developing this disease. An additional risk factor for CD is an anomalous innate immune response. Induction of T cell activation by gluten probably constitutes a key event in the development of the disease (8). Concerning the innate immune response that preceded T cell activation, the resident professional antigen-presenting cells play an essential role for antigen recognition and T cell activation. Indeed, in coeliac patients the activation of the adaptive immune system likely occurs upon encounter of gliadin in the small intestine (9).

In addition to this hypersensitivity to gliadin mediated by T cells, cytokine secretion also contributes to the observed lesion in this pathology (10, 11). In fact, cytokines play a central role in the development of an immune response through their regulatory effect on immune cells, such as Th1 and monocytes. For example, IL-10 in conjunction with transforming growth factor-α lead to the enhanced secretion of IgA by activated B cells and inhibit the synthesis of pro-inflammatory cytokines tumour necrosis factor-β, IL-1β and IL-6 by monocytes (11).

This immune-mediated pathology is predominantly characterized by a de-regulated immune response at the gut level dominated by T cells of the Th1 type, although humoral (Th2)
immune activation is also detected in CD. In coeliac lesions, gluten-reactivity T cells predominantly recognize gluten peptides in which glutamine residues have been converted to glutamic acid by deamination mediated by tissue TTG2 (12). Activation of CD4+ T cells probably represents a key event in the development of the disease. The presentation of either non-classical MHC class I-mediated antigens or non-MHC-restricted antigens may occur in the gut of coeliac patients.

On the other hand, CD is associated with the HLA-DQ heterodimer encoded by DQA1*0501 and DQB1*0201 alleles, although this gene do not explain the entire genetic susceptibility to gluten intolerance (13). Therefore, it has been suggested that other genes might predispose to CD. Human histocompatibility leukocyte antigen gene HLA-G is a molecule of immune tolerance implicated in several inflammatory diseases (14, 15). Consequently, it is interesting to study the effect of this molecule in the development of CD. In this study, we investigated the possible implications of HLA-G in CD.

Because of its low polymorphism and restricted tissue distribution, HLA-G has been considered a non-classical gene or class Ib. HLA-G is highly expressed by human cytotoxic lymphocyte and natural killer (NK) cells that constitute the maternal–foetal interface (16, 17). The HLA-G gene transcripts for at least seven different HLA-G mRNAs: four membrane-bound HLA-G isoforms, namely HLA-G1, -G2, -G3 and -G4, and three soluble proteins, namely HLA-G5, -G6 and -G7 (18). The presence of soluble HLA-G (sHLA-G) in the cerebrospinal fluid of multiple sclerosis (19) and allograft acceptance after transplantation (20, 21) suggests a tolerogenic function for this molecule against innate and adaptive cellular immune responses. Interestingly, it has been suggested that HLA-G antigens may play a protective role in inflammation (14). Thus, sHLA-G molecules inhibit lytic activity of NK cells, induce apoptosis of CD8+ CTLs and affect CD4+ alloprriferation (22, 23). In this sense, the immune modulatory properties of sHLA-G explain its potential interest in CD. Our aim was to investigate whether HLA-G, a gene located in the MHC class I region, may contribute to CD susceptibility.

**Methods**

**Patients**

This study was performed after approval of the Ethics Committee. Biopsies of small intestine were obtained following gastrointestinal endoscopy on consenting patients being investigated for CD (the patients were followed at the Virgen de las Nieves Hospital of Granada, Spain). Two biopsies from each patient were for histological analysis and one biopsy was investigated for CD (the patients were followed at the Virgen de las Nieves Hospital of Granada, Spain). Two biopsies from each patient were for histological analysis and one biopsy was employed by immunohistochemistry analysis. Twenty-four patients had features typical of active CD and nine patients in whom CD was excluded were included in the control non-coeliac group (patients with irritable bowel syndrome (n = 2), malabsorption syndrome (n = 2) and Crohn’s disease (n = 5)).

**Serological and histological analysis**

The diagnosis of CD is established by means of serologic screening tests accompanied by biopsy of the small intestine and confirmation of a clinical response to gluten elimination from the diet. Subjects were prospectively screened for CD using anti-endomysial antibodies (AEIMAs), anti-gliadin antibodies (AAGs), tissue transglutaminase antibodies (TTGAs) and CD-specific HLA typing. The best single measure for screening is IgA anti-recombinant human tissue transglutaminase, measured by means of ELISA, which has high sensitivity and specificity for CD (24).

**Immunohistochemistry analysis**

Samples fixed in formalin and paraffin embedded were used for immunohistochemistry. HLA-G was detected using a mAb MEM-G/1 (Exbio, Prague, Czech Republic), which reacts with denatured HLA-G heavy chain, and 5A6G7 (Exbio) that recognized sHLA-G isoforms. An IgG1 isotypic mAb (Sigma) was used as negative control. Immunohistochemical staining was performed using the UltraTech HRP Streptavidin–Biotin Universal detection system (Immunotech, France). After deparaffinisation and rehydration, sections were microwaved in 10 mM citrate buffer (pH, 6.0) for antigen retrieval. Sections were cooled in PBS, and the endogenous peroxidase activity was quenched with 3% hydrogen peroxide in distilled water. Sections were then treated with the protein-blocking agent, incubated sequentially with the primary antibody, and then with a biotinylated secondary antibody and with the streptavidin–peroxidase reagent. The immunoreaction was visualized with chromogen working solution AEC (3-amino-9-ethyl-carbazole) (Immunotech). Finally, the sections were counterstained with haematoxylin. A positive control and a negative control tissue were always considered.

**ELISA**

Microtiter plates were coated with the 5A6G7 mAb (10 µg ml⁻¹) as a capture antibody for the detection of sHLA-G in serum. The labelling was performed with the sHLA-G-Kit (Exbio). Optical densities were measured at 450 nm (Organon Teknika®, Turnhout, Belgium). The concentrations of sHLA-G were determined from the value of optical density according to the standard curves (Exbio).

**Statistical analysis**

All results are expressed as mean ± SEM. Data were evaluated for statistical significance using the STATGRAPHICS Plus 5 program. A non-parametric test (Kruskal–Wallis test) was used to determine the differences among groups. Kolmogorov–Smirnov test was used to compare the distribution between groups. P-values <0.05 were considered significant.

**Results**

Coeliac children presented impaired growth, chronic diarrhoea, abdominal distention, poor appetite and hypotonia. The mean weights and heights of the subjects with CD were not significantly different to the reference sex and age matched population (mean weight 13.43 ± 6.14, mean height 90.79 ± 20.05, mean age 3.74 ± 3.07), and the body mass index (BMI) in the coeliac patients was underweight for age with BMI less than fifth percentile (25). The diagnosis of CD is established by means of serologic screening tests accompanied by biopsy of the small intestine and confirmation of a clinical response to...
Immunohistochemistry of HLA-G

The expression of HLA-G antigen in the biopsies of active coeliac patients was analysed. Our results provide the first evidence of HLA-G expression in coeliac patients. Indeed, all patients tested showed a positive expression of HLA-G with different grade of immunoreaction, as demonstrated by immunohistochemistry using antibody 5A6G7, which allows to discriminate between sHLA-G protein from membrane-bound HLA-G forms. Our results demonstrated no cell-surface HLA-G expression in CD. Interestingly, we have only detected the presence of the sHLA-G isoforms and not the membrane-bound HLA-G forms as it demonstrates not to find immunoreactivity when used antibody that recognize the membrane-bound HLA-G forms (Fig. 1B).

The expression of HLA-G was restricted to the inner surface of Lieberkuhn crypts (Fig. 1A), and in patients with other diseases associated, the expression of sHLA-G was also found in the apical surface of the intestinal mucosa (Fig. 1C). In addition, there was no evidence of HLA-G expression in intestinal biopsies of non-coeliac patients.

ELISA results

In view of the above results, we decided to further analyse sHLA-G in serum of coeliac and non-coeliac patients by ELISA. We established the following groups of patients for ELISA analysis: coeliac patients with other associated diseases, as syndrome de down or autoimmune thyroiditis (CD1, n = 7); coeliac patients with transgressions of the diet (CD2, n = 7) and gluten-free diet coeliac patients for >5 years without transgression of the diet (CD3, n = 7) and non-coeliac patients (C, n = 9).

The levels of sHLA-G in serum were higher in CD1 patients (400 U ml⁻¹ ± 50), the coeliac patient group 2 (CD2) presented medium values of sHLA-G (55.52 U ml⁻¹ ± 12.5) and the coeliac patient group 3 (CD3) presented low or very low levels of sHLA-G (<10.5 U ml⁻¹ ± 2.5). Therefore, the results in the CD3 group were likely due to the length of time

Table 1. Clinical data of coeliac patients

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<th>Height (cm)</th>
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<th>AEMA</th>
<th>ATGA</th>
<th>HLA-DQB1</th>
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AAG, anti-gliadin antibody expressed as milligrams per litre; AEMA, anti-endomysial antibody; ATGA, anti-transglutaminase antibody expressed as units per millilitre and Down s, down syndrome.
on a gluten-free diet. The C group presented very low levels of sHLA-G (1.5 U ml⁻¹ ± 0.3). There were significant differences between the patients of the group CD1 and the other two groups (CD2 and CD3), as well as between the patients of CD1 group and non-coeliac patients (C) (Fig. 2). Although not statistically significant, there were also differences between the patients of group CD2 and the non-coeliac patients.

It is interesting to underline the behaviour of one of the patients (JP), father of a coeliac child (MBP). This patient was considered as non-coeliac, presenting a normal biopsy and normal serological test values for endomysial antibodies (EMAs) and TTGAs. However, the patient presented low immune reactivity in the intestinal biopsy for sHLA-G and positive values of sHLA-G in serum (25 U ml⁻¹).

**Immunohistochemistry of IL-10**

Finally, we have determined IL-10 production in patients with CD. Immunohistochemistry for IL-10 was performed on formalin fixed tissues and the immune reactivity was semi-quantitatively scored. A strong IL-10 immunoreactivity was observed in the lamina propria in coeliac patients (Fig. 3). This cytokine was expressed mainly in areas infiltrated by inflammatory cells.

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**Fig. 1.** Expression of sHLA-G in coeliac patients’ intestinal biopsy. Magnification: ×200. (A) sHLA-G expression in active coeliac patients staining with 5A6G7 (arrow). (B) Negative results on the membrane staining with the MEM/G1 antibody. (C) sHLA-G expression in apical surface of the intestinal mucosa and crypts of Lieberkühn (arrows).

**Fig. 2.** Serum sHLA-G levels in coeliac (n = 24) and control patients (n = 5) by ELISA. Expressed as units per millilitre. C, control group; CD1, coeliac group 1; CD2, coeliac group 2 and CD3, coeliac group 3. a: versus control group, P < 0.001; b: differences between coeliac groups, P < 0.001.

**Fig. 3.** IL-10 immunoreactivity in the lamina propria cells in coeliac patients (asterisk). Magnification: ×200.
Discussion

In this study, we demonstrate an association of CD with HLA-G expression. To our knowledge, this is the first study to describe the expression of sHLA-G in biopsy samples and in serum from patients with CD. Conversely, membrane HLA-G molecules were not expressed in coeliac patients. The lack of membrane HLA-G expression may be linked to a specific regulatory process in the alternative splicing of the primary HLA-G transcript, which could favour selection of the soluble isoforms.

The immune modulatory properties of sHLA-G justify its potential interest in the control of inflammatory diseases, such as CD. In this study, we have demonstrated that the plasmatic level of sHLA-G was (i) more elevated in coeliac patients with other associated diseases, as Down syndrome or autoimmune thyroiditis, (ii) elevated or medium in coeliac patients with transgressions of the diet and (iii) low or even negative levels in free-gluten diet coeliac patients for >5 years without transgression of the diet. So far, a gluten-free diet is the only therapy that can be provided to coeliac patients. Moreover, sometimes it is difficult to follow a completely gluten-free diet and some patients continue to include gluten in their diet. As a result, in some individuals, the recovery of the intestinal mucosa becomes extended and may take >18 months (27).

On the other hand, CD can be defined as ‘silent’ in an apparently healthy subject. Many of them have a normal or minimally abnormal intestinal mucosal architecture and no typical HLA predisposing genotype (DQ2 or DQ8) and they are negative to EMAs and/or anti-human TTGAs. Interestingly, in our study, one silent patient was positive for sHLA-G expression at serum and mucosa level. Although this result is preliminary and a higher number of cases are required, it suggests that sHLA-G expression can be considered as a useful marker in a silent coeliac patient.

The increased prevalence of autoimmune diseases in coeliac patients, including insulin dependent diabetes mellitus and autoimmune thyroid diseases, has been widely reported (27, 28). Our results showed a correlation between increased levels of sHLA-G and CD associated with other autoimmune diseases. In agreement with that, the connection between CD and other autoimmune disorders might be dependent on a genetic linkage of these pathologies through HLA genes.

The soluble form of HLA-G is of special interest because its molecule plays an important role in the induction of immune tolerance (29). An immune-suppressive function of HLA-G might thus contribute to control CD4+ and CD8+ activities, consequently, playing an important role in adaptive immunity (30, 31). In this sense, sHLA-G has the function to inhibit the proliferation of activated T cells, and to induce apoptosis of T cells dose dependently, reinforcing the immune inhibitory role of sHLA-G capable to be secreted during CD as part of a mechanism to restore the tolerance process towards oral antigens. Concerning the adaptive response in CD, a powerful anti-inflammatory response to gliadin might occur during the development of the disease. In coeliac patients, gluten intake seems to cause an overreaction in intra-epithelial T lymphocytes, with uncontrolled production of HLA-G and IL-10. This may cause recruitment of intra-epithelial lymphocytes, leading to a vicious circle with amplified immune activity and maintenance of intestinal lesions.

Cytokines may play important roles in inducing HLA-G expression. In fact, it has been demonstrated that IL-10, up-regulate HLA-G expression (32). Therefore, we cannot exclude that in particular stimulatory situations, secreted cytokines induce HLA-G expression. Here, we consider the possibility that the production of sHLA-G is affected by macrophage secreted cytokines. Macrophages can control immune responses by secreting anti-inflammatory cytokines such as IL-10. The role of IL-10 in inducing HLA-G protein expression has been already demonstrated in monocytes and purified trophoblast cells (32, 33). Moreover, an association between IL-10 and HLA-G expression was demonstrated in cutaneous lymphomas (32) and in ulcerative colitis (15).

In conclusion, the enhancer expression of sHLA-G in CD could be due as part of a mechanism to try restore the tolerance process towards oral antigens in a disease caused by loss of tolerance to dietary antigens. A powerful anti-inflammatory response to gliadin might occur during the development of the disease with uncontrolled production of HLA-G and IL-10 that counteract the inflammation or/and may cause recruitment of intra-epithelial lymphocytes, maintaining the intestinal lesions. Moreover, the expression of sHLA-G may become an immunohistologic parameter for the diagnosis of CD. This has an important relevance in patients with typical or non-classical symptoms, even clinically silent, who remain undiagnosed and are exposed to the risk of long-term complications and do not display clinical manifestations of the CD.

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Abbreviations

AAG anti-gliadin antibody
AEMA anti-endomysial antibody
BMI body mass index
CD coeliac disease
EMA endomysial antibody
sHLA-G soluble HLA-G
TTGA tissue transglutaminase antibody
TTG2 transglutaminase 2

References

HLA-G expression in coeliac disease


