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Food antigens and Transglutaminase 2 in IgA nephropathy: molecular links between gut and kidney

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Abstract

The transglutaminase 2 (TG2) is one of the enigmatic enzymes with important functional diversity. It plays an important role in several pathologies such as celiac disease (CD). In patients with active CD, the abnormal retrotranscytosis of IgA/gliadin complexes is mediated by Transferrin Receptor 1 (TfR1). This triad association takes also place in IgA nephropathy (IgA-N). IgA-N is characterized by the formation of nephrotoxic complexes of IgA1 and soluble CD89 (sCD89). These complexes are abnormally deposited in the kidney. Using a humanized mouse model of IgA-N (α1KI-CD89Tg), we showed that IgA1-sCD89 complexes engender mesangial cell activation and proliferation with TfR1 and TG2 up-regulation, associated with IgA-N features. This TG2-TfR1 interaction enhances mesangial IgA1 deposition promoting inflammation. Humanized α1KI-CD89Tg mice deficient for TG2 show a decrease in TfR1 expression in kidney leading to reduced IgA1-sCD89 deposits and an improvement in IgA-N features. Moreover, TG2 is active and overexpressed in the intestine of IgA-N mice and gliadin participates to this renal pathology. In kidney as in intestine, the TG2 has a crucial role in the cooperation between TfR1-IgA and a central role in the pathogenic amplification.

Introduction

The transglutaminase 2 (TG2) is one of the enigmatic enzymes with important functional diversity. This protein plays an important role in several pathologies such as cancer, neurologic disorders and celiac disease (CD). During CD, TG2 regulates the disease at different levels: deamidation of the gliadin, the retrotranscytosis of IgA through the epithelial layer and is also recognized by IgG and IgA as an auto-antigen. Interestingly, in IgA nephropathy (IgA-N), a disease characterized by IgA deposition in kidney, similar mechanisms are involved. In this review, the molecular mechanisms involving TG2, IgA and TfR1 will be explored in intestine and kidney to decipher pathological mechanism in IgA nephropathy.

IgA and its receptors

IgA is the most abundant antibody isotype produced in our body (Macpherson et al., 2008). Human IgA exists in two subclasses, termed IgA1 and IgA2. In the secretions, IgA is formed as dimers linked by the J chain and associated to the secretory component, which is a part of the extracellular domain of the polymeric Ig receptor (pIgR) generating secretory IgA (Brandtzaeg et al., 1999; Kaetzel, 2005). Quantitative studies of the origin of S-IgA in human external secretions have convincingly demonstrated that the majority of IgA is produced locally by plasma cells, densely distributed in the mucosal subepithelium. This locally produced IgA is selectively transported by the pIgR. S-IgA provides mucosal immune protection and the maintenance of appropriate bacterial communities (Cerutti and Rescigno, 2008). IgA

constitutes the second Ig class in the bloodstream (R. C. Monteiro and J. G. J. van de Winkel, 2003) and is mainly composed of monomers. IgA-induced effector cell functions in the immune system are dependent on IgA receptors since IgA poorly activates complement (R. C. Monteiro and J. G. J. van de Winkel, 2003). Several IgA receptors have been described: the first one, the pIgR is involved in the IgA secretion across mucosal epithelium. The second type, designated FcαRI (or CD89), is capable of binding both human IgA1 and IgA2 subclasses as well as C reactive protein (Lu et al., 2011; R. C. Monteiro and J. G. Van De Winkel, 2003; Woof and Mestecky, 2005). The CD89 is expressed on myeloid cells and controls the balance between immune cell activation and inhibition depending on the molecular size of IgA. While monomeric IgA binding to CD89 induces cell inhibition, IgA-immune complex binding induces cell activation through a dual role of the ITAM motif of the CD89-associated FcRγ chain. Other IgA receptor types are the Fcα/μR (Cho et al., 2006; R. C. Monteiro and J. G. Van De Winkel, 2003; Woof and Mestecky, 2005) and the FcRL4 (Wilson et al., 2012). The non-homologous IgA receptors are the asialoglycoprotein receptor (ASGP-R2) (Rifai et al., 2000; Stockert et al., 1982), the C-type lectin receptor DC-SIGN (or CD209) (Diana et al., 2013), the Dectin-1 on intestinal M cells (Rochereau et al., 2013), the recently identified β1-4galactosyltransferase (Molyneux et al., 2017) and the transferrin receptor 1 (TfR1, or CD71) (R. C. Monteiro and J. G. J. van de Winkel, 2003; Moura et al., 2001). This last receptor is ubiquitous and its main function is iron uptake via transferrin binding and internalization. Interestingly, TfR1 binds to IgA1 to promote erythroblast proliferation (Coulon et al., 2011).

TG2, IgA and TfR1 in the intestinal pathophysiology of celiac disease

TG2 as an auto-antigen

Celiac disease (CD) is an autoimmune inflammatory disease of the small intestine triggered by a dysregulated response to gluten. Patients suffering with CD exhibit increased circulating IgA and IgG antibodies against gliadin (one component of gluten), endomysium (a substrate of TG2) and TG2. Celiac autoantibodies are produced in the small intestinal mucosa, and it has been recognized that the small intestinal epithelial membrane of CD patients contains deposited IgA (Picarelli et al., 1996). Moreover, TG2 was shown to cross-link IgD, leading to B cell receptor activation and auto-reactivity against TG2 (Iversen et al., 2015).

TG2 and IgA retrotranscytosis

TG2 also participates to the induction of the immune response against gliadin in CD. The 31-49 gliadin peptide is protected from lysosomal degradation in intestinal cells from CD patients but not in healthy controls. IgA-complexes containing 31-49 peptide are observed in both serum and intestinal fluids from CD patients. TfR1, an IgA receptor, is overexpressed at the apical face of intestinal biopsies during the active phase of CD. Intact gliadin 33-mer or p31-49 peptides complexed with IgA are retrotranscytosed from the apical to the basolateral side of enterocytes (Matysiak-Budnik et al., 2008). Moreover, we established gluten sensitivity in mice which developed characteristics of CD, associated with overexpression of TfR1 and TG2, as well as overproduction of IgA (Papista et al., 2012). TG2 activity is required in the retrotranscytosis since the inhibition of TfR1 or TG2 in intestinal epithelial cells can block the p31-49 peptide/IgA transport across the cell monolayer (Lebreton et al., 2012).

TG2 and deamidation of gliadin

One of the enzymatic function of TG2 is the deamidation of specific glutamines. TG2 can catalyze the deamidation of gliadin, leading to the generation of immunodominant peptides recognized by T cells in CD (Shan et al., 2002). Moreover, the microbial TG can also catalyze this reaction (Lerner et al., 2016).

To summarize, TG2 plays different roles in the intestine of CD patients leading to reaction to gliadin and intestinal inflammation: This enzyme catalyzes the deamidation of gliadin, participates with the TfR1 to the retrotranscytosis of IgA bearing gliadin peptides and is also recognized as an auto-antigen (Figure 1, intestinal part).

TG2 and its partners in IgA nephropathy

TG2 on mesangial cells

IgA nephropathy (IgA-N), a leading cause of renal failure, is characterized by the deposition of hypogalactosylated IgA1 complexes in the renal mesangium. IgG anti-hypogalactosylated IgA1 autoantibodies have been identified within circulating IgA immune complexes (IC) associated with disease progression (Suzuki et al., 2011). We and others have shown that that other types of IgA-IC, namely IgA-soluble CD89 complexes (IgA-sCD89), are essential for disease initiation, present in the mesangium and involved in disease pathogenesis (Berthelot et al., 2012; Berthelot et al., 2015; Launay et al., 2000; Vuong et al., 2010), Berthelot, Robert et al. 2015). Despite its major role in IgA-N physiopathology, CD89 is not expressed by mesangial cells and thus cannot be the receptor responsible for IgA deposition in the mesangium. We have identified an IgA receptor implicated in mesangial deposition: the transferrin receptor

(TfR1/CD71) (Moura et al., 2001). TfR1 binds IgA1 but not IgA2. TfR1 is highly expressed and co-localizes with deposited IgA in patient's biopsies (Haddad et al., 2003). IgA glycosylation and size (altered in IgA-N patients) are essential for binding to TfR1 (Moura et al., 2004). The proliferation of mesangial cells is induced via the PI3K/Akt pathway, which produce inflammatory cytokines via the MAPK/Erk pathway (Tamouza et al., 2012). The humanized mouse model of IgA-N expressing both human IgA1 and CD89 (the α1KI-CD89Tg mice) showed rapid IgA1 deposits associated with proteinuria and hematuria. Using this model, we reported the major role of TG2, as a critical factor to promote IgA-N (Berthelot et al., 2012). Knock-out mice for TG2 exhibited less IgA deposits in kidney and a decrease of hematuria. In vitro experiments with human mesangial cells showed that the binding of IgA-sCD89 complexes on these cells, via the TfR1, induced their activation and the TG2 overexpression at the cell membrane (Figure 1, kidney part). This expression of TG2 stabilized the IgA deposits by increasing IgA binding to TfR1 (Berthelot et al., 2012). When IgA deposits are cleared using an IgA1 protease, TG2 and TfR1 expression are no more detectable (Lechner et al., 2016). TG2 is also expressed on other kidney cell types as tubular cells (Ito et al., 2018) which could also impact IgA-N progression. Moreover, TG2 concentration in urine from IgA-N patients correlated proteinuria and distinguished active and non-active patients (Moresco et al., 2016).

TG2 and gliadin in IgA-N

In IgA-N, many links between intestinal mucosa and IgA deposits in the kidney were described as genetic, intestinal IgA production, immune responses to mucosal antigens, gut microbiota (Chemouny et al., 2018; Coppo, 2018; De Angelis et al., 2014; Floege and Feehally, 2016). Food antigens, including milk proteins, bovine serum

albumin, soybean proteins and gluten have been described to form IgA complexes in IgA-N (Coppo, 1988; Feehally et al., 1987; Fornasieri et al., 1987; Kloster Smerud et al., 2010; Laurent et al., 1987; Nagy et al., 1988; Rostoker et al., 1988; Sancho et al., 1983; Sato et al., 1987; Smerud et al., 2009; Yap et al., 1987), which in some cases can be deposited in the mesangium of IgA-N patients (Russell et al., 1986; Sato et al., 1990; Sato et al., 1988). The role of gluten in IgA-N was assessed by in vitro studies showing the direct interaction of gliadin with IgA partners and with mesangial cells (Amore et al., 1994; Coppo et al., 1992). 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 (Papista et al., 2015).

A gluten free diet during three generations in the mouse model of IgA-N, resulted in a massive decrease of IgA1 deposits in kidney associated to the decrease of inflammation and hematuria (Papista et al., 2015). This decrease was gluten specific, as shown by its re-introduction in the diet being followed by the re-appearance of mesangial IgA1. The diminution of IgA1 deposits with gluten free diet was associated with down-regulation of mesangial TG2 and TfR1 expression in mouse kidneys. In the small intestine, as previously demonstrated, gluten free diet resulted in an improvement of morphology and a resorption of inflammation. The number of B cells producing IgA was also decreased with the diet. Using a substrate peptide specific for TG2 (Itoh et al., 2013), we were able to detect an increased activity of TG2 in the intestine of α1KI-CD89Tg mice compared to non-gluten reactive mice (Figure 2) showing that, similarly to CD, TG2 is activated in the intestine of IgA-N.

In human, Costa et al reported a patient case suffering with celiac disease and IgA nephropathy. They detected TG2 deposits both in kidney and in duodenum (Costa et

al., 2018). The risk of CD in IgA-N patients is increased compared to healthy population and associated with a worse renal function (Nurmi et al., 2018). In the same way, the risk of IgA-N in CD is increased (Collin et al., 2002; Welander et al., 2013; Wijarnpreecha et al., 2016). Glomerular IgA deposits can be found in CD patients without clinical signs of renal disease (Pasternack et al., 1990). IgA-N patients exhibits abnormal increased intestinal permeability (Davin et al., 1988; Rostoker et al., 1993), associated to bad renal outcome (Kovacs et al., 1996) and intestinal inflammation (Rantala et al., 1999; Rostoker et al., 2001). These studies showed the clinical associations between IgA nephropathy and celiac disease.

Gluten free diet was tested for IgA-N patients. When CD was clearly associated to IgA-N, five cases showed the efficacy of gluten free diet for clinical remission of IgA-N (Costa et al., 2018; Habura et al., 2019; Koivuviita et al., 2009; La Villa et al., 2003; Woodrow et al., 1993). However, the results of trials on non-selected IgA-N 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 (Yagame et al., 1988). 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 (Coppo et al., 1990). In the mouse model, effects of gluten free diet were observed after a long period of time (Papista et al., 2015). Clinical trials for gluten free diet in IgA-N patients should be assessed over a longer time period. This diet could be more efficient for IgA-N patients exhibiting gluten reactivity, as not all patients are positive in serological tests.

Conclusions

Molecular mechanisms involving IgA, TG2 and TfR1 are shared between CD and IgA-N (Figure 1). CD patients exhibit overexpression of TfR1 and TG2 on enterocytes leading to the retrotranscytosis of IgA bearing gliadin (Lebreton et al., 2012; Matysiak-Budnik et al., 2008). In kidney, TfR1 and TG2 overexpression results in increase of IgA deposits in IgA-N (Berthelot et al., 2012; Moura et al., 2005; Moura et al., 2004). The binding of IgA1 complexes on TfR1 at the cell surface of mesangial cells induces the overexpression of TfR1 (Moura et al., 2005) and TG2 (Berthelot et al., 2012). In the absence of TG2, the IgA1 deposits are dramatically reduced and in vitro IgA1 binding on mesangial cells is diminished (Berthelot et al., 2012). A deleterious loop following IgA1 binding on mesangial cells lead to TfR1 and TG2 production, these proteins in turns amplifying the IgA1 deposition. The targeting of these molecules could improve disease symptoms.

Conflicts of interest

The authors have declared that no conflict of interest exists.

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Author Contribution Statement

Conceptualization: LA, LB; Formal analysis: LA; Funding acquisition LB; Project administration LB; Supervision: RCM, LB; Writing – original draft: LA, LB; Writing – review & editing: LA, RCM, LB.

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Figure 1

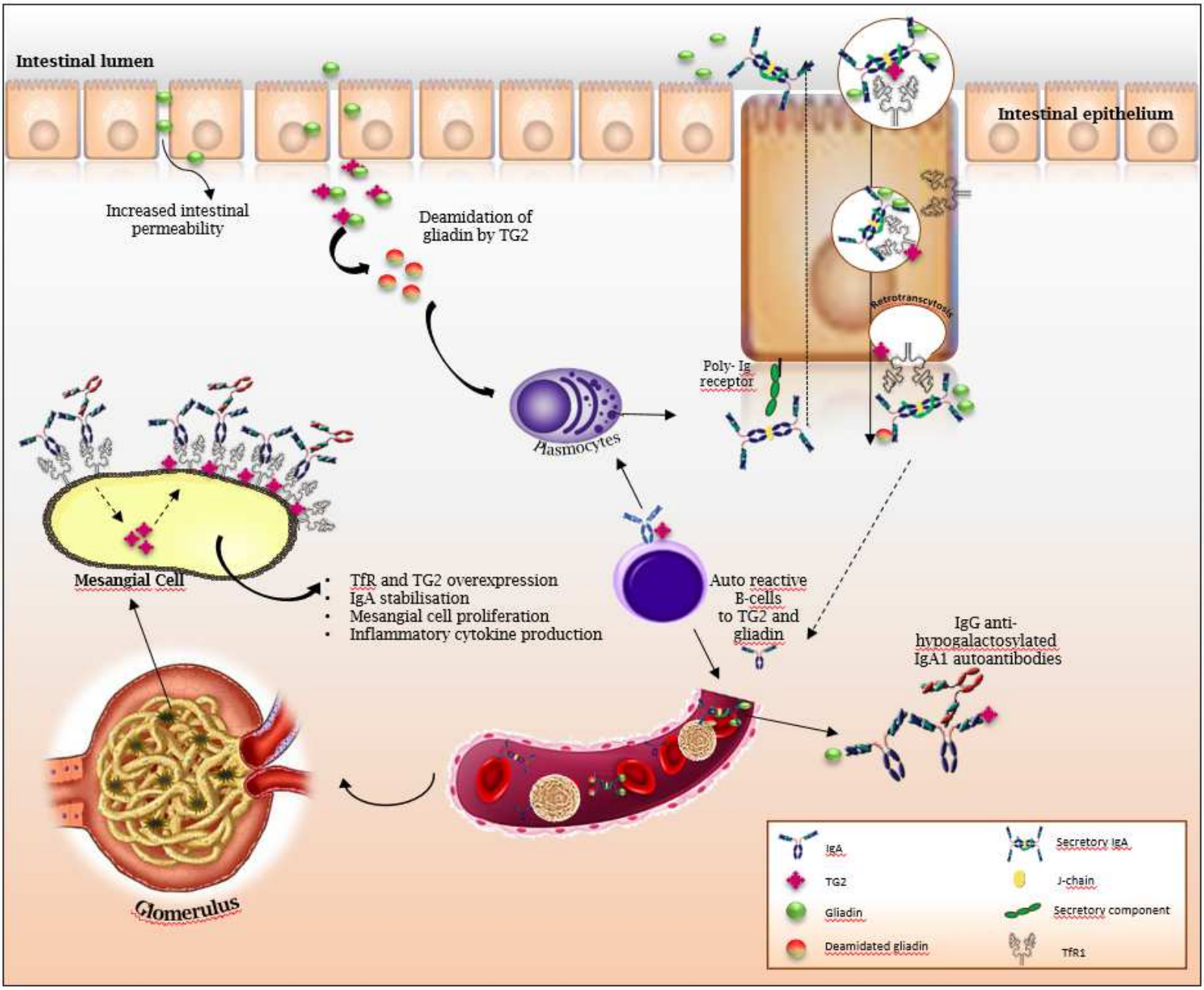

Figure 1 : Pathological mechanisms involving TG2, IgA, and TfR1, starting in the intestine to finish into kidney. Gliadin can enter in the body through the epithelial barrier due to increased intestinal permeability and/or retrostranscytosis of secretory IgA via TfR1 and TG2. This entry also induces the B cell response and the production of anti-gliadin and TG2 antibodies. Circulating IgA complexes containing gliadin can be deposited in the kidney at the surface of mesangial cells via TfR1 and TG2.

Figure 2

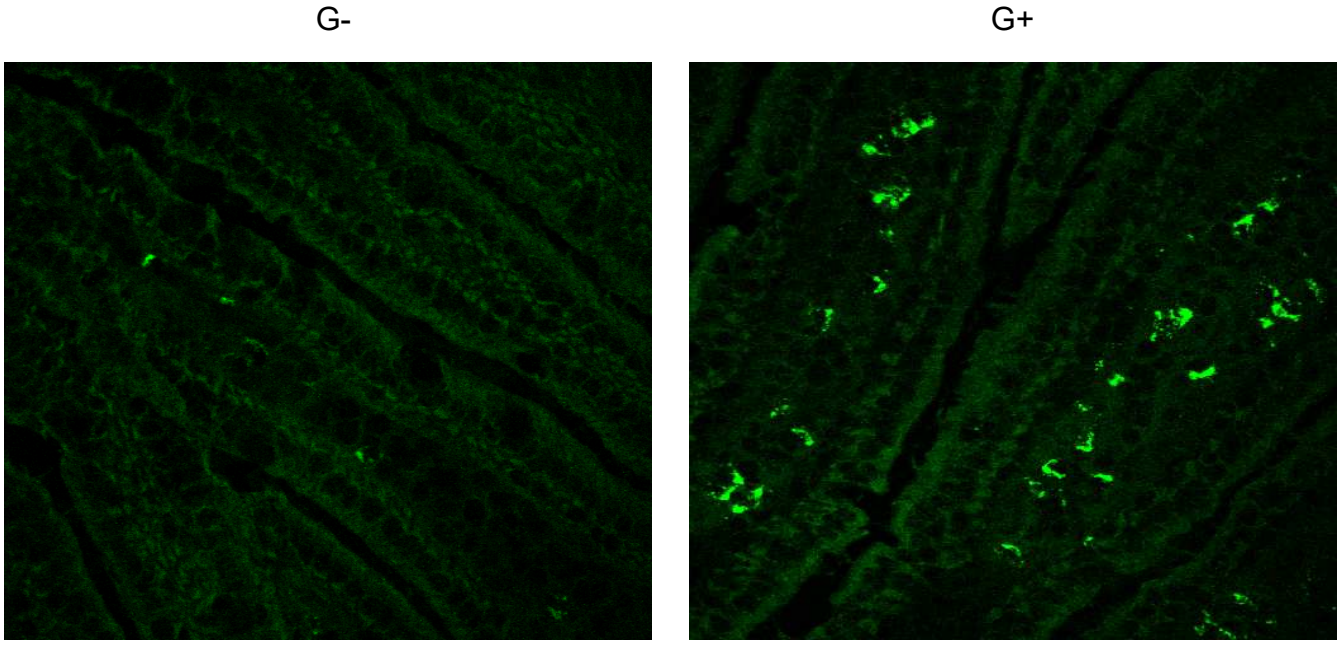

Figure 2: TG2 activity in intestine from gluten sensitized mice. TG2 activity on intestinal fresh frozen slides was detected using peptide T26. G-: α1KI-CD89Tg mice with gluten free diet. G+: α1KI-CD89Tg mice with normal diet