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Intraepithelial Lymphocytes in Celiac Disease: License to Kill Revealed

Infiltration of lymphocytes in the small intestinal epithelium is a hallmark of active celiac disease. In this issue of *Immunity*, two papers uncover mechanisms controlling the cytolytic potential of these cells and provide evidence that lymphocyte killing of enterocytes is an important part of the celiac disease pathogenesis.

Celiac disease is a prevalent disorder caused by an inappropriate immune response to dietary gluten proteins. The lesion, localized in the small intestine, is characterized by villous atrophy, crypt cell hyperplasia, and infiltration of inflammatory cells in the lamina propria and in the epithelium. The pathological changes are dependent on gluten consumption, and the disease is effectively treated by a life-long gluten exclusion diet. The disorder has a very strong HLA association. The presence of the HLA-DQ2 or DQ8 molecules is necessary but not sufficient for disease development, and there is evidence for involvement of additional genetic factors. The DQ2 and DQ8 molecules bind and present gluten peptides to $CD4^+$ T cells of the lamina propria. There exist several distinct gluten peptides that are recognized by $CD4^+$ T cells. The great majority of these peptides are only or better recognized after conversion of certain Gln residues to Glu (i.e., deamidation), a process mediated in vivo by the enzyme tissue transglutaminase. The key genetic role of HLA suggests that the DQ restricted T cells play a critical position in shaping the anti-gluten response leading to celiac disease (Sollid, 2002).

The increased number of intraepithelial lymphocytes (IEL) is typical of active celiac disease. The majority of these cells are $TCR\alpha\beta^+$ $CD8^+CD4^-$ and a significant proportion are $TCR\gamma\delta^+$ $CD8^-CD4^-$. IEL express a variety of NK lineage receptors (Jabri et al., 2000; Roberts et al., 2001). It has previously been demonstrated that IEL have a cytolytic potential (Lundqvist et al., 1996; Oberhuber et al., 1996), but until now it has been unknown what controls their cytotoxicity. The papers by Meresse et al. and Hüe et al. bring interesting new knowledge on the function of IEL in celiac disease and shed light on the role of NK lineage receptors in immune-mediated disorders. The papers demonstrate that the enterocyte expression of the nonconventional HLA molecule MIC is upregulated in active celiac disease. MIC molecules are known to be induced in enterocytes by stress (Groh et al., 1996), and Hüe et al. demonstrate that the expression of MIC by enterocytes is increased in intestinal biopsies cultured in vitro with gluten or certain gluten peptides. The same MIC-inducing effect is observed by adding recombinant IL-15 to the biopsy cultures, and an antibody to IL-15 is able to block the effect of gluten, suggesting that IL-15 is centrally involved in the upregulation of MIC. MIC serves as a ligand for the activating NKG2D receptor that signals through the associated DAP10 adaptor protein. NKG2D is expressed on most NK cells, $CD8^+$ $TCR\alpha\beta^+$ and $TCR\gamma\delta^+$, but normally not on $CD4^+$ T cells (Bauer et al., 1999). Whereas Meresse et al., but not Hüe et al., find that expression of NKG2D by IEL is increased in active celiac disease, both papers report that IEL can lyse epithelial cells via NKG2D. Moreover, Meresse et al. report that IL-15 arms NKG2D-mediated cytolysis by freshly isolated IEL. IL-15 seems to be a key mediator in these events as stimulation of freshly isolated IEL with IL-15 leads to increased expression of both NKG2D and DAP10, as well as to increased phosphorylation of ERK. As demonstrated by Meresse et al., ERK and JNK are both kinases involved in the NKG2D signaling, and their observations suggest that IL-15 primes the NKG2D signaling pathway. Importantly, the same authors also find that freshly isolated IEL from active celiac disease patients mediate TCR-independent lysis through NKG2D without the need for IL-15 prestimulation. In essence, the two papers make the case that the villous atrophy of active celiac disease is caused by IEL-mediated killing of enterocytes, and that the MIC-NKG2D interaction rendered active by IL-15 exposure is critical for this enterocyte killing.

The papers by the Jabri and Caillat-Zucman groups along with two other recent papers (Groh et al., 2003; Ogasawara et al., 2004) indicate that NGK2D plays a key role in immune-mediated diseases. Groh et al. found that $CD4^+CD28^-$ T cells in peripheral blood and synovial tissues of rheumatoid arthritis patients express NKG2D and are able to recognize MIC molecules aberrantly expressed on synoviocytes of affected joints. Ogasawara et al. found that autoreactive $CD8^+$ T cells infiltrating pancreas islets of NOD mice express NKG2D, and that NKG2D blockade prevents autoimmune diabetes. Thus, while NKG2D may exert beneficial functions during infections and against tumor cells, it may also serve as an immune activator that can tip the balance in favor of autoimmunity and chronic inflammation. The observation by Meresse et al. that NKG2D can mediate cytolysis independent of TCR ligation in recently activated T cells is particularly relevant in this context. Their observation suggests that self-perpetuating loops of immune activation can be established. With regard to the situation in celiac disease, it still remains to be determined which antigenic stimulus is responsible for the recent in vivo activation of the intraepithelial T cells that seems to be required for TCR-independent lysis, and whether this antigen stimulation is unique to celiac disease patients.

Another issue not fully explained by the findings of work by the Jabri and Caillat-Zucman groups is how the IEL cytotoxicity relates to HLA-DQ2/DQ8, whose presence is mandatory for celiac disease development. The gluten peptide (gliadin p31-49), which was the most active in inducing MIC in the Hüe et al. study, does not appear to be recognized by DQ restricted, gluten-

reactive T cells of the gut (Arentz-Hansen et al., 2000). A length variant of the same peptide (gliadin p31-43) has previously been found to induce innate immune activation in intestinal biopsies of celiac disease patients cultured in vitro with gluten (Maiuri et al., 2003). Strikingly, Maiuri et al. observed effects of this peptide in biopsies of celiac disease patients, but not of healthy DQ2 positive individuals. Taken together, these observations suggest that the activation of the innate immune system, including the overexpression of IL-15 (Mention et al., 2003), migration of lymphocytes to the epithelium, and killing of enterocytes, somehow is controlled by DQ2 or DQ8 restricted $CD4^+$ T cells in the lamina propria. Interestingly, Hüe et al. observed strong expression of MIC by mononuclear cells in the lamina propria along with the increased MIC expression in the epithelium. Their observation raises the possibility that the threshold for activation of $CD4^+$ T cells in the lamina propria, if they express NKG2D like $CD4^+$ T cells of synovial tissues in rheumatoid arthritis (Groh et al., 2003), can be lowered by gluten exposure. The NKG2D-MIC axis may possibly exert an important role also at the level of lamina propria T cells. An important future goal will be to understand in detail the connection between IEL functions and the activation of DQ restricted, gluten-reactive T cells in the lamina propria of celiac disease patients.

All the papers reporting on the role of NKG2D in immune-mediated diseases suggest that NKG2D may be a good target for therapeutic intervention. It will be exciting to see whether these interesting findings eventually can be extended to the clinic.

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Selected Reading

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