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The Role of Natural Killer Receptors in Celiac Disease

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Abstract

Celiac disease (CD) is a chronic enteropathy that develops in genetically-predisposed individuals after the ingestion of gluten. The small intestinal damage observed in CD patients is characterized by villous atrophy, crypt hyperplasia and massive infiltration of the mucosa with inflammatory cells. The molecular mechanisms that trigger and amplify inflammatory signals in CD are not fully understood. There is evidence that excessive activation of some subsets of Natural Killer (NK) cells occurs in CD and can contribute to the perpetuation of gluten-driven immune response and intestinal damage. On the other hand, the active phases of the disease are also marked by reduced mucosal presence of a specific subpopulation of NK cells expressing activating receptors and producing IL-22, a cytokine involved in the maintenance of intestinal barrier and immune homeostasis. In this article, we shortly revise the current literature on the role of NK cells in CD.

Keywords: Chronic inflammatory; Hyperplasia; Viral infections

Introduction

Celiac disease (CD) is a T cell-dependent chronic inflammatory disorder of the small intestine that affects approximately 1% of the population [1]. CD is triggered by ingestion of gluten, a mixture of proteins found in wheat, barley and rye, which leads to villous atrophy, crypt hyperplasia, massive infiltration of the mucosa with inflammatory cells and consequent malabsorption-related symptoms and signs [2]. The only current treatment of CD is a lifelong exclusion of gluten from the diet [2]. CD almost exclusively develops in HLA-DQ2 and/or HLA-DQ8 positive individuals, which are the restriction elements for CD4+ T cells recognizing gluten peptides [3]. The mechanisms underlying the breakdown of tolerance to gluten and the exact sequence of events leading to tissue damage in CD are not clear. Viruses could act as environmental factors promoting the development and/or propagation of CD-associated detrimental immune response. This relationship is based on the frequent observation that viral infections may precede the onset of CD [4], CD-associated inflammation is associated with increased production of interferon (IFN)-α [5], a cytokine over-produced during viral infections, and *ex vivo* treatment of fetal gut explants with IFN-α induces CD-like intestinal damage [6]. Support to the above hypothesis comes also from the demonstration that activation of various subsets of Natural Killer (NK) cells, a class of innate immune cells that protect host against a variety of viruses by killing infected cells, is either up-regulated or reduced in the active phases of CD [7]. NK cells exert several biological functions, including production of cytotoxic granules (i.e. granzyme B and perforin) and inflammatory or regulatory cytokines and induction antibody dependent cellular cytotoxicity [8]. Cytotoxic functions of NK cells are mainly regulated by the cell surface expression of activating and inhibitory receptors, which interact with ligands on target cells [9]. NKG2D, NKG2C, NKp44, NKp46 and NKp30 are examples of activating receptors while NKG2A in considered an inhibitory receptor [10]. Down-regulation of activating NK cell receptors is one of the strategies used by microbes to escape immune-surveillance, a phenomenon frequently observed in chronic viral infections [11]. Functional impairment of NK cells has been also described in human and experimental immune-mediated diseases (e.g. type I diabetes, encephalomyocarditis) [12], whose pathogenesis is supposed to be viral-mediated. In this context, we have recently shown that the intestinal epithelial compartment of human beings is infiltrated with distinct populations of cells expressing NK receptors and documented a different modulation of such receptors during chronic inflammation [13]. In physiological conditions, NK cells co-expressing NKp44 and NKp46, two activating receptors, produce spontaneously granzyme B and respond to toll-like receptor ligands with enhanced synthesis of granzyme B. These cell subsets are numerically reduced in inflamed duodenum of CD patients but the pathogenic relevance of such a finding remains unclear. Since NKp44/NKp46, double-positive NK cells also produce IL-22, a cytokine involved in the maintenance of intestinal barrier and immune homeostasis, it is conceivable that this defect could contribute to perpetuate the detrimental immune response in CD. At the same time, the fact that exclusion of gluten from diet reverts NKp44/NKp46-double positive NK cell deficiency suggests that such an abnormality is not primarily involved in the initiation of the inflammatory process.

On the other hand, excessive activation of NK cells could kill epithelial cells through the perforin/granzyme pathway further contributing to the small intestinal damage [14,15]. Indeed, the active phases of the disease are characterized by increased induction of activating receptors (i.e. NKG2C, NKp30 or NKG2D) on NK cells [16]. These observations are in line with the demonstration that human major histocompatibility complex class I chain related A and B (MICA and MICB) proteins, nonconventional HLA class I molecules that serve as ligands for the activating NKG2D receptor, are over-expressed in CD patients with villous atrophy [17,18]. MICA/NKG2D interaction is supposed to mediate also killing of epithelial cells in refractory CD, a rare complication of the disease that is resistant to the gluten-free diet

and can associate with the development intestinal T cell lymphoma [18].

The factors leading to upregulation of MICA proteins to the surface of enterocytes in active CD remain to be clarified. *ex vivo* studies with duodenal explants of CD patients on gluten-free diet show that gliadin induces MICA expression in epithelial cells through a mechanism that is dependent on interleukin (IL)-15 [14,18], a cytokine produced in excess by innate immune cells in this disorder. Consistently, the MICA-inducing effect of gliadin is reproducible by the p31-49 gliadin-derived peptide, which is able to directly activate innate immune response in CD and to induce enterocyte apoptosis, the latter effect being inhibited by a blocking IL-15 antibody [19].

Finally, CD-associated mucosal inflammation is marked by reduced levels of the inhibitory receptor NKG2A [16], which could further contribute to the NK cell-mediated intestinal epithelial injury in this disorder.

Taken together the available literature indicate that NK cells can play a major role in CD pathogenesis. While the abundance of NK cells expressing activating receptors and their ability of kill target cells support their involvement in CD-associated villous atrophy, the defective presence of NKp44/NKp46-double positive NK cells could sustain the expansion of the gluten-induced mucosal inflammation. Further studies are needed to support these hypotheses. At the moment, the limited availability of biological samples (e.g., small number of cells purified from endoscopic biopsy samples) and the lack of a valid animal model of CD-like gluten-driven tissue damage represent the major obstacles to such studies.

References

1. Meresse B, Malamut G, Cerf-Bensussan N (2012) Celiac disease: an immunological jigsaw. Immunity 36: 907-919.
2. Di Sabatino A, Corazza GR (2009) Coeliac disease. Lancet 373: 1480-1493.
3. Lundin KE, Scott H, Hansen T, Paulsen G, Halstensen TS, et al. (1993) Gliadin-specific, hla-dq (alpha 1*0501,beta 1*0201) restricted t cells isolated from the small intestinal mucosa of celiac disease patients. J Exp Med 178: 187-196.
4. Stene LC, Honeyman MC, Hoffenberg EJ, Haas JE, Sokol RJ, et al. (2006) Rotavirus infection frequency and risk of celiac disease autoimmunity in early childhood: a longitudinal study. Am J Gastroenterol 101: 2333-2340.
5. Monteleone G, Pender SL, Alstead E, Hauer AC, Lionetti P, et al. (2001) Role of interferon alpha in promoting T helper cell type 1 responses in the small intestine in coeliac disease. Gut 48: 425-429.
6. Monteleone G, Pender SL, Wathen NC, MacDonald TT (2001) Interferon-alpha drives T cell-mediated immunopathology in the intestine. Eur J Immunol 31: 2247-2255.
7. Vivier E, Raulet DH, Moretta A, Caligiuri MA, Zitvogel L, et al. (2011) Innate or adaptive immunity? The example of natural killer cells. Science 331: 44-49.
8. Vivier E, Tomasello E, Baratin M, Walzer T, Ugolini S (2008) Functions of natural killer cells. Nat Immunol 9: 503-510.
9. Hudspeth K, Silva-Santos B, Mavilio D (2013) Natural cytotoxicity receptors: Broader expression patterns and functions in innate and adaptive immune cells. Front Immunol 4: 69.
10. Lanier LL (2005) NK cell recognition. Annu Rev Immunol 23: 225-274.
11. Muntasell A, Magri G, Pende D, Angulo A, Lopez-Botet M (2010) Inhibition of nkg2d expression in nk cells by cytokines secreted in response to human cytomegalovirus infection. Blood 115: 5170-5179.
12. Filippi CM, von Herrath MG (2008) Viral trigger for type 1 diabetes: pros and cons. Diabetes 57: 2863-2871.
13. Marafini I, Monteleone I, Di Fusco D, Sedda S, Cupi ML, et al. (2016) Celiac Disease-Related Inflammation Is Marked by Reduction of Nkp44/Nkp46-Double Positive Natural Killer Cells. PLoS One 11: e0155103.
14. Di Sabatino A, Ciccocioppo R, Cupelli F, Cinque B, Millimaggi D, et al. (2006) Epithelium derived interleukin 15 regulates intraepithelial lymphocyte th1 cytokine production, cytotoxicity, and survival in coeliac disease. Gut 55: 469-77.
15. Mention JJ, Ben Ahmed M, Bègue B, Barbe U, Verkarre V, et al. (2003) Interleukin 15: a key to disrupted intraepithelial lymphocyte homeostasis and lymphomagenesis in celiac disease. Gastroenterology 125: 730-745.
16. Meresse B, Curran SA, Ciszewski C, Orbelyan G, Setty M, et al. (2006) Reprogramming of CTLs into natural killer-like cells in celiac disease. J Exp Med 203: 1343-1355.
17. Bahram S, Bresnahan M, Geraghty DE, Spies T (1994) A second lineage of mammalian major histocompatibility complex class i genes. Proceedings of the National Academy of Sciences of the United States of America 91: 6259-6263.
18. Hüe S, Mention JJ, Monteiro RC, Zhang S, Cellier C, et al. (2004) A direct role for NKG2D/MICA interaction in villous atrophy during celiac disease. Immunity 21: 367-377.
19. Maiuri L, Ciacci C, Ricciardelli I, Vacca L, Raia V, et al. (2003) Association between innate response to gliadin and activation of pathogenic T cells in coeliac disease. Lancet 362: 30-37.