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Functional Involvement of CD44 Variant 7 in Gut Immune Response

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Abstract
A major problem in inflammatory bowel disease (IBD) is the accumulation of highly activated T-helper cells that are refractory to apoptosis induction. Hence, persistent inflammatory lesions are prevalent and are the basis of chronic disease. In IBD upregulation of costimulatory molecules on lamina propria lymphocytes has been described leading to apoptosis resistance. CD44 is a cell adhesion molecule and a signalling receptor that functions as a costimulatory molecule in T-cell activation. Several variant isoforms of CD44 (CD44v) are expressed by alternative splicing of variant exons encoding extracellular regions. Particularly isoforms containing CD44v7 are expressed on T cells and macrophages in T-helper-1 (Th1)-mediated chronic inflammation and autoimmune diseases. In this review recent data on the functional involvement of CD44v7 isoforms in IBD are discussed. In a mouse model of experimental colitis blockade or deletion of CD44v7 protects mice from severe intestinal inflammation by inducing apoptosis in lamina propria mononuclear cells. Recently, we observed that in lamina propria mononuclear cells from the inflamed but not uninflamed mucosa of patients with Crohn's disease, blockade of CD44v7 isoforms also induces apoptosis. The finding that obstruction of CD44v7 isoforms can antagonize Th1-cytokine-dependent immune pathology identifies CD44v7 as a target in the treatment of inflammatory diseases such as IBD, rheumatoid arthritis, multiple sclerosis and other autoimmune diseases in which CD44v7 isoforms are upregulated.

Introduction

The mucosal immune system is comprised of anatomically defined lymphoid microcompartments, such as Peyer's patches in the small intestine, appendix, and solitary follicles in the large intestine and rectum, nasal mucosa and tonsils, which serve as principal mucosal inductive sites where immune responses are initiated. It also contains diffuse accumulations of large numbers of lymphoid cells that are either distributed in the lamina propria or interspersed among epithelial cells in mucosal tissues and glands, and form the effector sites where immune responses are expressed [1, 2]. Three major adaptive effector mechanisms participate in the immune

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defense of mucosal surfaces. Secretory IgA antibody formation and antigen-specific cell-mediated cytotoxicity are the primary mechanisms involved in antimicrobial defense in the mucosal epithelium. The induction of IgA production to protein antigens is highly dependent on T-helper cells [3, 4]. In addition, mainly through the production of regulatory cytokines, regulatory T cells contribute as a third form of mucosal defense. The tissue microenvironment, the cytokine milieu and the antigen itself influence the further differentiation of CD4+ naïve T cells to T-helper (Th)-0 cells that produce both interferon (IFN)-γ and interleukin (IL)-4 and further to a Th1- or Th2-directed immune response. Mucosal uptake of antigens may result in the development of immunity or tolerance, or even both, the decision being taken in the epithelium or underlying lymphoid tissue and it is mainly determined by the nature and presentation of the antigen. Besides the strength of the T-cell receptor signal or antigen density, the second signal in T-cell activation is provided by engagement of one or more T-cell surface receptors with their ligands on antigen-presenting cells. At present, the role of these pairs of costimulatory molecules, like CD28-B7 and CD154-CD40, in regulating Th1 versus Th2 immune responses in vivo is not known in detail [5].

CD44 as a Cell Adhesion Molecule and a Signalling Receptor

One of the lymphocyte markers which is supposed to work as a costimulatory molecule is the transmembrane glycoprotein CD44. The role of CD44 as a hyaluronan receptor has been known for many years and defines CD44 as a cell adhesion molecule [6]. However, there is also substantial evidence that CD44 is a potent signalling receptor. Early studies using anti-CD44 monoclonal antibodies to trigger the receptor established that CD44 is a costimulatory molecule on T cells [7–10]. For example, stimulation through CD44 has been reported to enhance T-cell proliferation and IL-2 production independent of CD28 [7, 8, 10, 11]. Furthermore, it has been shown that ligation of the costimulatory molecule CD40 rapidly upregulates CD44 expression on T cells [11]. In addition to T cells, stimulation through CD44 enhances macrophage production of proinflammatory mediators, including IL-12, IL-1β, and tumor necrosis factor-α (TNF-α) [12, 13]. In the last decade, it has been reported that anti-CD44 antibodies have potent anti-inflammatory activity in vivo [14–16], most probably resulting from an antibody-mediated (anti-panCD44 antibody IM7) shedding of CD44 from leukocytes, thus preventing cell recruitment and activation [17]. Although IM7 has been taken under consideration for clinical immunotherapy in autoimmune disease and cancer, recent data pointed out its harmful side effects, such as systemic shock [18].

Whereas the standard form of CD44 shows a broad expression on various cells of epithelial and hematopoietic origin, alternative splicing of at least ten exons, encoding variant extracellular regions, generates a large number of isoforms [19]. Expression of these so-called variant isoforms is strictly controlled [20] and confined to specific states of lymphocyte activation, hematopoiesis and tumor progression [21–24].

Specific Expression of CD44 Variant Isoforms v6 and v7 on Activated Lymphocytes

In the mouse model for experimental colitis, it has been shown that isoforms containing CD44v6 and v7 are hardly expressed on resting lymphocytes in the spleen, lymph nodes, peripheral blood or Peyer's patches [21]. After in vitro stimulation via a T-cell mitogen or a nominal antigen, however, there was upregulation of CD44v6 and v7. Expression patterns of these splice variants defined the molecules as activation markers in gut-associated lymphoid tissue. Particularly at inflammatory sites on lamina propria lymphocytes CD44v6 and v7 isoforms are strongly upregulated. In addition, since CD44v6 and v7 expression during activation was transient, it was tempting to speculate that these two variant isoforms are functionally active in lymphocyte activation [25].

Blockade of CD44 Variant Isoforms Cures Experimental Colitis in the Mouse

In experimental colitis CD44v7 expression is upregulated on mononuclear cells of intestinal inflammatory lesions in Th1-polarized inflammation. Unlike in vitro stimulation, expression of CD44v7 was not transient, but persistent [26]. Based on these data, it was demonstrated that administration of a monoclonal antibody against CD44v7 [27], but not anti-CD44v6, cures most mice with 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis. The colitis induced by the haptenizing agent TNBS has been described as Th1-cytokine-driven inflammation [28]. In this model after an initial increase in the Th1 cytokine IFN-γ, the therapeutic effect of anti-CD44v7 anti-

body treatment was accompanied by an increased production of IL-10 and a decreased production of IL-12 in lamina propria lymphocytes as well as systemically [29]. Furthermore, co-administration of a neutralizing antibody to IL-10 (2A5.7) completely abrogated the therapeutic effect of anti-CD44v7 antibody in TNBS colitis, which indicates the central role of IL-10 in CD44v7 regulation. It has been suggested that the CD44v7-specific antibody functions by regulating an overshooting Th1 reaction in chronic inflammation [30].

CD44v7 Is Essential for a Th1-Type Immune Response

To further define the role of CD44v6 and v7 in colitis, mice bearing a targeted deletion of exons v6 and v7 of CD44 were generated without affecting the expression of the other exons. Under normal conditions, these mice have no altered phenotype or changes in the distribution of cell subpopulations in the lymphatic systems. Mice with TNBS-induced colitis are protected from severe inflammation and wasting disease by deletion of CD44v7 alone and v6/v7. Adoptive transfer of bone marrow cells clearly shows that expression of CD44v7 on hematopoietic cells but not on intestinal epithelia is necessary to establish intestinal inflammation [26]. Moreover, crossing CD44v6/v7 mutants with IL-10-deleted mice, which develop chronic enterocolitis [31], is protective against experimental colitis for an observation period of more than 1 year [26].

Why and at which stage is the region encoded by CD44v6 and v7 important in intestinal inflammation? According to the expression profile and proliferation studies, CD44v7 functions as a costimulatory molecule and might be a receptor molecule on antigen-presenting cells for an as yet unidentified ligand. We have shown recently that CD44v7 is upregulated by CD40 ligation [32], which promotes clonal T-cell expansion, and delays activation-induced cell death [33–35]. The ability of CD40 ligation to modulate an immune response towards cell proliferation and apoptosis may depend on the availability of additional coreceptors or ligands that are transiently upregulated during T-cell activation, e.g. CD44v7. Most interestingly, analysis of cell death in the inflamed lesions revealed that mononuclear cells in the CD44v7- and CD44v6/v7-deleted infiltrates had higher rates of apoptosis as compared to those from wild-type mice. The increase in apoptotic markers, measured as active caspase 3, p85 PARP, and TUNEL activity is restricted to inflamed lesions in CD44v7 (and v6/v7) null mice, indicating that blockade of CD44v7 may be a highly specific therapeutic approach in inflammatory bowel disease [26]. Recent data in murine models of experimental autoimmune encephalomyelitis and rheumatoid arthritis unequivocally demonstrate that not the standard region of CD44, whose expression is unaffected by the mutation, but rather the region encoded by exon v7, is causally involved in autoimmune or chronic inflammation [for review see 36].

Blockade of CD44v7 Induces Apoptosis in Patients with Crohn's Disease

In the pathogenesis of inflammatory bowel disease, such as Crohn's disease or ulcerative colitis, dysregulated CD4+ T-cell activation and proliferation in the intestinal mucosa is a key component [37]. Crohn's disease is characterized by a Th1-directed immune response with increased CD4+ T-cell production of IFN-γ and activated macrophages that secret TNF-α and IL-12 [38]. Data obtained in animal models of experimental colitis and humans suggest that Crohn's disease can result from a defect in counter regulating the immune response, e.g. by TGF-β, to normal mucosal antigens, which initiates and/or sustains chronic inflammation [39]. Although both CD44v6 and CD44v7 are upregulated upon mitogenic stimuli in vitro, we have found an increased expression of CD44v7 but not CD44v6 in the peripheral blood and inflamed mucosa of patients with Crohn's disease, but not ulcerative colitis [32, 40]. Since deletion of CD44v7 protects mice from colitis by induction of apoptosis of activated T cells and macrophages, blockade of CD44v7 might be a new approach to re-induce programmed cell death of activated cells in chronic inflammatory conditions in humans. Indeed, we demonstrate that in patients with Crohn's disease blockade of CD44v7 with a monoclonal antibody induces apoptosis in the lamina propria mononuclear cells of inflamed mucosa, but not in the non-inflamed mucosa of Crohn's disease or control tissue. This effect is not detected in the lamina propria of patients with active ulcerative colitis or acute diverticulitis. In addition, apoptosis induction is also obtained using a recombinant CD44 variant fusion protein containing CD44v7.

Finally, the apparent influence of CD44v7 on IL-10 production needs to be discussed further. We have described in the mouse model that IL-10 becomes significantly upregulated by curative treatment with anti-

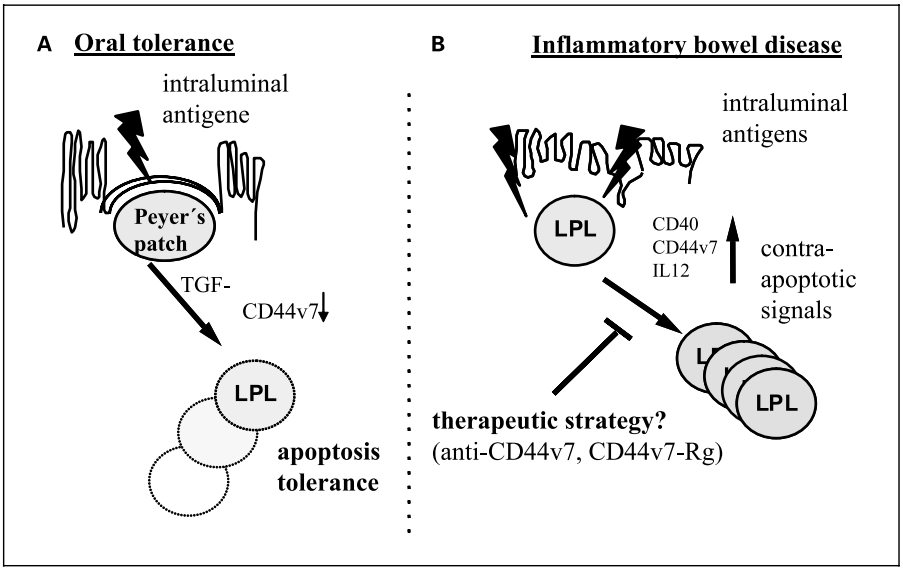

Fig. 1. A In the normal gut mucosa Peyer's patch lymphocytes express small levels of CD44v7. Antigen exposure induces oral tolerance, mediated by regulatory cytokines such as TGF-β and apoptosis of effector cells. B In chronic inflammatory bowel disease costimulatory molecules such as CD40 and CD44 that give contra-apoptotic signals, are upregulated on lamina propria mononuclear cells sustaining the chronic inflammation in the gut. LPL = Lamina propria lymphocytes.

CD44v7 [29]. In a clinical study an increased number of IL-10-producing peripheral blood mononuclear cells in patients with inflammatory bowel disease has been described after in vitro culture with anti-CD44v7 [32]. Interestingly, anti-CD44v7-stimulated T cells as well as B cells and monocytes produce IL-10 [32]. In line with these findings, it has been described that Fas-mediated apoptosis of lymphoid cells leads to rapid production of anti-inflammatory cytokines such as IL-10. In these studies, the apoptotic cells containing IL-10 were responsible for the activation of immune deviation through interaction with antigen-presenting cells [41, 42]. Thus, apoptotic cell death of immune effector cells and tolerance are linked through the production of an anti-inflammatory cytokine in order to minimize dysregulated immune reactions, e.g. a Th1-cytokine response that might compromise organ integrity [43, 44]. Since apoptosis induction might restore immunological tolerance in intestinal mucosa, neutralizing CD44v7 might provide a promising therapeutic approach in inflammatory bowel disease (fig. 1).

Conclusion

The ubiquitously expressed CD44 standard molecule is the major cellular receptor for hyaluronic acid and a signalling receptor in T-cell activation. The present data on CD44 variant isoforms, which are expressed in a highly restricted manner, suggest a specific involvement of the variant isoform CD44v7 in the gut immune system. CD44v7 is essential for Th1-cytokine-mediated experimental colitis in distinct mouse models and upregulated in the inflamed mucosa in Crohn's disease. In the inflamed mucosa neutralization of the costimulatory molecule CD44v7 by a monoclonal antibody or a recombinant fusion protein induces apoptosis in human as well as mouse lamina propria mononuclear cells. Thus, CD44v7 appears to endow lamina propria mononuclear cells with resistance towards apoptosis leading to sustenance of the chronic inflammation in the gut. Many questions remain regarding the varied functions of the CD44 antigen, its multiple isoforms, and its multiple ligands. While hyaluronan polymers are components of the extracellular matrix and a substrate for CD44-mediated cell adhesion, hyaluronan fragments are signalling molecules which activate the immune system at the site of inflammation [45]. These hyaluronan fragments are themselves capable of activating NF-κB [46] and are present at abnormally high levels in chronic inflammatory conditions such as rheumatoid arthritis [47, 48]. Therefore, binding of matrix components via CD44 variant isoforms might mediate the specific activation signal in chronic inflammation [49]. Furthermore, proteolytic release of the CD44 intracellular domain may lead to direct influence of transcriptional activation of tumor-associated genes [50]. The role of CD44 in apoptosis is controversially discussed. Recent data indicate that deletion of the hyaluronan binding region induces prolonged inflammation in the lung by accumulation of hyaluronan fragments and decreased clearance of apoptotic neutrophils [51]. Others, however,

have shown that binding of CD44 to hyaluronan generates an anti-apoptotic effect [52]. Also we have shown that CD44v7 isoforms protect gut mononuclear cells from undergoing programmed cell death in chronic inflammation [26]. Differential regulation of cell activation and cell death via CD44 and its variant isoforms maybe the result of different ligand interactions, which may cause conformational changes. These changes will have an impact on the interaction with other surface molecules, which still need to be identified. Future therapeutic strategies may thereby include the exploitation of CD44 variant isoforms and the signalling by matrix components to directly induce apoptosis.

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