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Natural killer T cells and ulcerative colitis

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ABSTRACT

Ulcerative colitis (UC) is one of the two major forms of inflammatory bowel disease (IBD). Both innate immunity and adaptive immunity are aberrant in IBD. The pathogenesis of UC includes abnormal inflammation and immune responses of the digestive tract. Natural killer T (NKT) cells participate in the innate and adaptive immune responses, together with a vast array of cytokines. Recent studies suggested that IL-13, IL5 and IL-4 are involved in the occurrence and the development of UC. Manipulating NKT cells may be a potential strategy to reconstruct the abnormal immune responses in UC. In this review, we explore the roles of NKT cells and cytokines in UC. Additionally, neutralizing antibodies and inhibitors of cytokines produced by NKT cells or their receptors are also discussed as novel therapeutic choices for UC.

1. Introduction

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is an inflammatory, chronic and progressive disease. Patients undergo remission and relapse alternately during disease development [1,2]. The incidence of IBD has increased during recent decades [3]. Currently, the pathogenesis of IBD is still unclear. Genetics, environment, lifestyle and intestinal microflora can all influence the development of UC. In addition, the relative balance between effector T cells and regulatory T cells also play important role in intestinal immunity and inflammation [4]. The main pathogenesis of UC is closely related to the abnormal immune responses to innocent commensal bacteria [5]. Unlike CD, inflammation is limited to the superficial mucosa and submucosa of the colon and rectum in patients with UC.

Studies have shown that UC is a disease mediated by Th2 cytokines such as IL-13, IL-5 and IL-4 [5,6]. And these Th2 cytokines are produced partly by NKT cells [7,8]. NKT cells are a unique subset of lymphocytes, which express molecules of conventional T cells and of natural killer (NK) cells [9]. NKT cells participate in tumor surveillance, immune responses to infectious pathogens, prevention of autoimmune diseases and self-tolerance maintenance. However, NKT cells are also involved in some detrimental immune responses together with their secreted cytokines. For example, IL-13 and IL-4 can induce airway hypersensitivity, as well as the disruption of epithelial cell tight junctions [10]. Furthermore, NKT cells show both protective and destructive functions in IBD. On the one hand, NKT cells play a protective role in the dextran sulfate sodium (DSS)-induced colitis model when NKT are stimulated with α-galactosylceramide (α-GalCer) [11]. On the other hand, NKT cells participate in several detrimental inflammation and immune responses in the gut, such as the development of oxazalone-induced colitis by producing IL-13 [12]. NKT cells can also produce many cytokines to affect vivo tissues. In the pathogenesis of UC, NKT cells can secrete Th2 cytokines, resulting in mucosal inflammation and destruction [13]. In addition, NKT cells have been reported to inhibit development of a CD4 T-cell lineage Th17, which is associated with mucosal immunity and autoimmune disorders. The purpose of this review is to demonstrate the current knowledge concerning NKT cells, UC and their association. So far, UC is an inflammatory disease that is still not medically curable. Anti-inflammatory steroids are used commonly to control and maintain the remission. In this review, we also discuss the use of different approaches to suppress the production of Th2 cytokines in UC treatment.

Abbreviations: α-GalCer, α-galactosylceramide; CD, Crohn's disease; DSS, dextran sulfate sodium; IBD, Inflammatory bowel disease; MHC, major histocompatibility complex; MMP-1, matrix metalloproteinase-1; NK, natural killer; STAT6, signal transducer and activator of transcription 6; TCRs, T-cell receptors; UC, ulcerative colitis; C-X-C motif, chemokine; CXCL, chemokine ligand

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2. The profile of natural killer T cells

NKT cells express cell-surface molecules of both T cells, such as T-cell receptors (TCRs) and CD3, and NK cells, including NK1.1 (in mice) [14]/CD161 (in human), Ly49 and NKG2D [15]. These cells participate in innate and adaptive immunity. NKT cells are present mainly in the liver and thymus, and they are also present in the intestinal tissue of both mice and humans. However, it is difficult to determine the accurate percentage of lymphocytes in lamina propria and intraepithelial layer that are NKT cells due to the absence of the identified markers of NKT cells. Recently, IL-13Rα2 was proposed to be a surrogate marker of the NKT cell and became an alternative approach to NKT cells quantitation in UC [16]. There are diverse subgroups of NKT cells. Investigators distinguish the type of NKT cells based on the TCR repertoire on the surface of the cells. Thus, these cells are divided into invariant NKT cells and variant NKT cells, which are also referred to as type I NKT cells and type II NKT cells, respectively [17]. Type I NKT cell expresses a TCR that comprises invariant α-chains (Vα14-Jα281 in mice and Vα24-Jα18 in humans) combined with restricted β-chains [18]. Both kinds of NKT cells are thymus-dependent, as conventional T cells. The positive and negative selection of type I NKT cells are mediated by CD1d+ thymocytes [19] and dendritic cells [20]. At the same time, there are insufficient tools to study type II NKT cells. Therefore, studies of type II NKT cells usually use 24αβ NKT cells instead, which are transgenic murine cells that express the TCR derived from type II NKT cells [21]. 24αβ NKT cells are positively selected by hematopoietic cells expressing CD1d, and they are also negatively selected when presented with abundant self-antigens [22] (Fig. 1). Multiple mechanisms for NKT cell activation have been described [23]. Both types of NKT cells are CD1d-restricted cells. CD1 is a family of nonpolymorphic cell surface glycoproteins encoded outside the major histocompatibility complex (MHC), but with a distant relation to MHC class I molecules [24]. CD1d is a member of the CD1 family and comprises a light chain (β-microglobulin) that is non-covalently linked to a heavy chain [25]. Moreover, CD1d is expressed on the surface of many kinds of human antigen-presenting cells, such as monocytes, B cells, epithelial cells and macrophages [26,27]. CD1d molecules are synthesized in the endoplasmic reticulum, and subsequently are transported to the cell surface via the Golgi network. Interestingly, activation of NKT cells in humans via CD1d antigen presentation is limited to a restricted subset of glycosphingolipids. The best-known glycosphingolipid is synthetic glycolipid α-GalCer [28]. α-GalCer was originally derived from a marine sponge, and it is the most efficient compound to activate type I NKT cells [29]. Type I NKT cells are activated by α-GalCer presented by intestinal epithelial cells in human and mice [30]. Type II NKT cells are CD1d-restricted, but do not recognize α-GalCer [31]; they recognize sulfatide (3-sulfated galactosylceramide and lyso-sulfatide glycolipid) instead [32,33]. However, recently it was reported that type I NKT cells could be activated directly through the engagement of toll-like receptor 4 (TLR4), a molecule that is expressed on the surface and localized in the early endosome of type I NKT cells [34]. Upon activation, NKT cells secrete a cocktail of effector molecules. Type I NKT cells can rapidly produce IL-4 and IFN-γ in vivo following the administration of α-GalCer [35], while direct engagement of TLR4 by either endogenous or exogenous ligands leads to enhanced IFN-γ but reduced IL-4 production [34]. In addition, type I NKT cells also produce diverse other cytokines, such as IL-2, IL-5, IL-6, IL-10, IL-13, IL-17, IL-21, TNF-α, TGF-β and GM-CSF [9,36–40]. Studies of 24αβ NKT cells demonstrated that type II NKT cells produced high level of IFN-γ but minimal level of Th2-related cytokines [41], differing from the reports of patients with UC in which type II NKT cells produced the Th2 cytokine IL-13 [13].

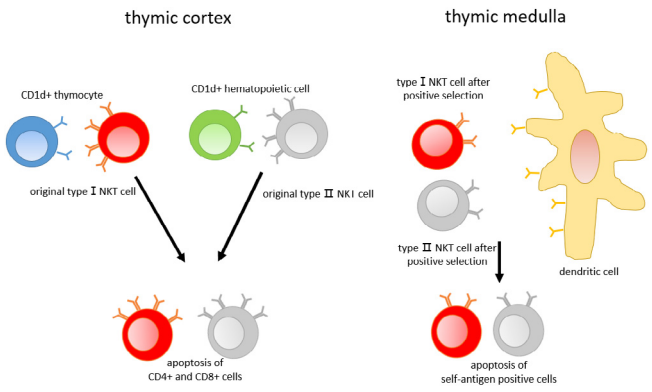

Fig. 1. The positive and negative selection of both types of NKT cells present in thymic cortex and thymic medulla, respectively. The positive and negative selection of type I NKT cells are mediated by CD1d+ thymocytes and dendritic cells. The positive selection of type II NKT cells are mediated by CD1d+ hematopoietic cells, and are negatively selected with abundant self-antigens.

3. Natural killer T cells participate in UC

Type I NKT cells play roles in intestine mucosal immunity, while the function of type II NKT cells is currently unclear. Comparison of mice lacking type I NKT cells with mice lacking type I and type II NKT cells, indicated that type II NKT cells are regulatory cells that might suppress anti-tumor immunity [42–44]. Type II NKT cells also regulate the responses of type I NKT cells by modulating dendritic cell function [45,46]. Activation of type II NKT cells by sulfatide suppresses the proliferative and cytokine responses of type I NKT cells [43]. Previous studies indicated that NKT cells show a dual effect in the intestinal mucosa. Type I NKT cells make both protective and pathogenic contributions to disease. In contrast, type II NKT cells appear to promote intestinal inflammation [41]. The beneficial immune responses in which type I NKT cells engage include the response to tumors, host protection from a variety of infectious agents (including bacteria, parasites, and viruses), the prevention of autoimmune diseases and the maintenance of self-tolerance. In many other conditions, type I NKT cells participate in the development of certain detrimental immune responses, such as the development of oxazalone-induced colitis [47].

Genetic, environmental and microbiological factors can influence the development of UC. To better understand the immune responses that might be involved in the pathogenesis of human IBD, investigators used murine models of intestinal inflammation initially. NKT cells have received some attention in certain IBD models. Confusingly, NKT cells have been found to correlate with a protective role in Th1-mediated CD and a deleterious one in Th2-mediated UC [48].

A well-known model used for UC research is oxazolone colitis. After the intrarectal administration of the haptenating agent oxazolone, the colon develops inflammation rapidly [49]. Moreover, this model is a short-lived colitis (lasting less than 5 days) that is characterized by the particular superficial inflammation of the colon associated with edema, ulceration of the epithelia cell layer, and neutrophil accumulation, similar to human UC. In addition, the lamina propria T cells of mice with oxazolone colitis produced much more IL-4 and IL-5 compared with the controls [50]. IL-4 is the hallmark cytokine that directs Th2 development [51]. Produced by mast cells, basophils, NKT cells and Th2 cells themselves, IL-4 is required for Th2 development. Mice deficient in IL-4 and its receptor fail to develop a potent population of effector Th2 cells [52–54]. IL-4 is mainly involved in promoting naïve helper T cells to differentiate into Th2 cells. And then, Th2 cells secret abundant IL-4 via positive feedback. Besides, IL-4 also has many other biological functions, such as stimulation of the proliferation of activated B cells and T cells, upregulation of the expression of MHC class II molecules and promotion of IgE production [55]. Administration of antibodies against IL-4 prevented the development of colitis, showing that this kind of Th2 response had an initial function in the pathogenesis of oxazolone colitis [50]. This strongly suggested that oxazolone colitis is a Th2-mediated

disease, like UC. However, the initial model lasted just 3–4 days and resulted either in rapid recovery or death of the mice. To establish a more long-lived, chronic model, investigators presensitized mice by skin painting 5 days before intrarectal administration of oxazolone [12]. The histopathology of this pro-longed model is similar to that seen in human UC, suggesting a similar pathological mechanism between both types of colitis. This chronic model showed that the initial IL-4 response was superseded after approximately 4–5 days with an increasing IL-13 response [12]. Consistent with this, lamina propria mononuclear cells from UC patients produce higher IL-5 and IL-13, but not IL-4, compared with CD [13]. Since the disease development could be prevented by the administration of the IL-13 neutralization agent, IL-13Rα2-Fc, IL-13 response might represent the intrinsic pathogenesis of this colitis [12]. Hence, UC is associated with an atypical Th2 response mediated by IL-13, rather than a typical Th2 response mediated by IL-4 [13]. In addition, NKT cells might be the source of IL-13 in oxazolone colitis because they could produce IL-13 upon activation by α-GalCer. Furthermore, CD1d−/− mice, as well as wild-type mice injected with anti-CD1d antibodies, were completely protected from oxazolone colitis. Moreover, Jα18−/− mice, which lack type I NKT cells, but not type II NKT cells, were protected from oxazolone colitis, which suggested that type I NKT cells, rather than type II NKT cells, are important for the occurrence of this kind of colitis. However, the cells secreting IL-13 are different in mice and human [12]. Type I NKT cells are the source of IL-13 in mice; whereas, in humans, IL-13 is generated by type II NKT cells [13].

As mentioned above, NKT cell participate in some detrimental immune responses. In the murine model of human UC, it was strongly suggested that the pathogenesis of this colitis result from the generation of NKT cells secreting IL-13. Oxazolone is a unique type of haptenating agent that can give rise to a lipid moiety presented to NKT cells by antigen-presenting cells with CD1. In the intestines, the CD1 antigen-presenting cells can also be gut epithelial cells [30]. The initial toxic effects of the agent results in a flooding of the lamina propria with oxazolone and oxazolone-modified bacterial antigens and then induces an immune response that leads to further inflammation mediated by NKT cells [12]. Subsequently, the NKT cells proliferate and differentiate in to Th2 type cells. As Th2 type cells, they begin to produce IL-13, which acts as an autocrine factor that causes NKT cells to become cytotoxic effector cells with the capacity to cause tissue injury. Such cytotoxicity could contribute to the ulceration of the mucosa and the observed alteration of the epithelial barrier [56]. Similarly, NKT cells from the lamina propria of UC patients were cytotoxic for epithelial cells and this cytotoxicity was heightened by IL-13 [13]. Furthermore, not only NKT cells, but also IL-13 itself is responsible for the impaired epithelial barrier function. IL-13 can impair the intestinal epithelial barrier function by affecting apoptosis, tight junctions and restitution of the epithelia [57]. Addition of IL-13 to epithelial monolayer cultures resulted in an increased expression of the pore-forming tight junction protein, claudin-2. Consistently, lamina propria tissue from UC patients also had a similar alteration of claudin-2 expression. Additionally, one recent research revealed that signal transducer and activator of transcription 6 (STAT6) played important roles in altering epithelial barrier function by influencing induction of claudin-2 [58]. And increased expression of this protein is associated with increased epithelial barrier permeability [56]. Thus, both NKT cells and IL-13 are crucial for the development of human UC.

Other cytokines secreted by α-GalCer stimulated NKT cells might play different roles in the pathophysiology of UC. IL-22 is a member of the IL-10 family, and is produced partly by NKT cells. Reports have shown that there is abundance of IL-22 in certain inflammatory diseases, such as UC [59]. Furthermore, intestinal epithelial cells and subepithelial myofibroblasts respond to IL-22 stimulation by producing a range of anti-inflammatory, regenerative and tissue-protective proteins and display enhanced migratory capacity. Indeed, a protective role for IL-22 was found in a murine model of Th2-mediated colitis [60]. Furthermore, a certain amount of cytokine IL-21 is also secreted by NKT cells. IL-21 controls the function of both immune and non-immune cells. Besides, overexpression of IL-21 occurs in many chronic inflammatory diseases in humans. Initial studies on IL-21 in IBD revealed that the cytokine is over-produced in the inflamed gut of patients with UC compared with non-inflamed and inflamed controls [61]. As intestinal fibroblasts constitutively express the IL-21 receptor, Thus, IL-21 can enhance fibroblasts production of matrix metalloproteinase-1 (MMP-1), MMP-2, MMP-3 and MMP-9, but not tissue inhibitors of MMP-1 and MMP-2 [62]. MMP is capable of degrading most of the constituents of the extracellular matrix, as collagenases (MMP-2 and MMP-9) are able to degrade collagen [63]. Increased degradation of collagen molecules is observed in UC [64], which suggests that MMPs, whose secretion is promoted by IL-21, are associated with tissue damage in UC. There is experimental evidence that increased MMP-9 expression contributed to the severity of mucosal damage in active UC [65]. However, more experimental data is needed to support the hypothetical association between NKT cell-derived IL-21 and UC. In addition, activated NKT cells could strongly produce TNF-α to mediate immune responses. TNF-α is a 17-kD pleiotropic cytokine that exerts pro-inflammatory effect in UC through increased production of IL-1β and IL-6, expression of adhesion molecules, proliferation of fibroblasts and procoagulant factors, as well as initiation of cytotoxic, apoptotic, acute-phase responses, and inhibition of apoptosis [55,66,67]. TNF-α produced by NKT cells could stimulate chemokine (C-X-C motif) ligand (CXCL) 1, 2, 3 expression by the epithelium and then lead to the recruitment of neutrophils [68]. After that, neutrophils activated by NKT cells became tissue-damaging [68]. Taken together, NKT cells secret cytokines to participate in the pathophysiology of UC via interaction network (Fig. 2).

4. Natural killer T cells and UC therapy

Many drugs have been used to treat UC, including 5-aminosalicylic acid, 6-mercaptopurine, corticosteroids and biologics. Some novel therapeutic choices have been developed recently due to ongoing studies in the field of immune response dynamics. The intervention points of these novel therapeutics do not aim to generally dampen the immunological response, but to block the initiation, perpetuation and the pathological changes that occur in inflammatory diseases. Nevertheless, most of these therapeutics are in preclinical development. Specific antibodies and inhibitors are used to modulate the effects of cytokines

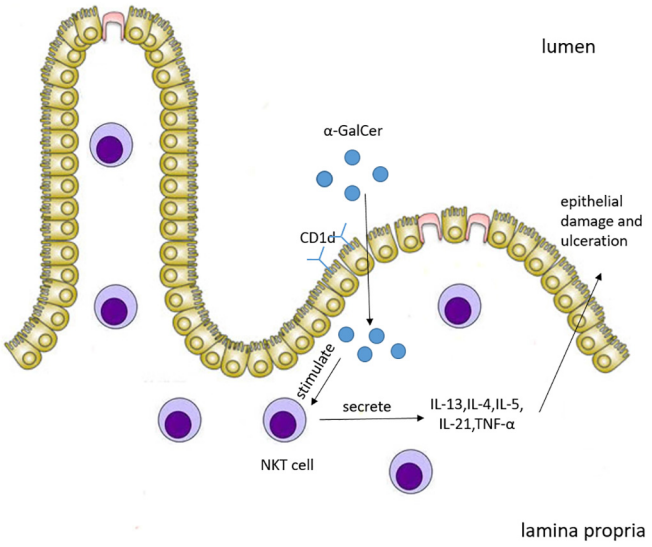

Fig. 2. NKT cells in the lamina propria are activated by glycolipid antigens when presented by CD1d. Activated NKT cells secrete cytokines that participate in the tissue injury observed in UC.

involved in UC. In addition, blocking cell signaling pathway is another strategy to affect the activation of immune cells [69]. Different antibodies and inhibitors have been developed. Monoclonal antibody of TNF-α has already been used in clinical practice, such as infliximab, a chimeric IgG1 monoclonal antibody to TNF-α, and adalimumab, a fully human IgG1 monoclonal antibody directed against TNF-α [70]. IL-4 and IL-13 participate in UC, specifically in disease perpetuation and manifestation. Administration of anti-IL-4 antibodies to mice could prevent the development of disease in the oxazolone colitis model [50]. IL-13R2α-Fc is a soluble receptor for IL-13 that blocks IL-13's interaction with IL-13R, and administration of this agent could prevent the development of oxazolone colitis [12]. Moreover, a human monoclonal antibody of IL-13, which called tralokinumab, is designed for asthma treatment, and it has been proved that tralokinumab may benefit some patients with UC [71]. Besides, IL-25 could stimulate the production of nuocyte and NKT derived IL-13. Neutralizing antibodies to IL-25 has been proved to slow the ongoing inflammation in UC [72]. IL-5 is another Th2 cytokine that is increased in UC. As IL-5R and IL-5 are instrumental in the activation and proliferation of eosinophils, both are addressed by antibodies to trap the ligand or inhibit signaling [73]. However, these approaches are not disease specific. It remains a challenge to develop tailored therapeutics to prevent the progress of the inflammatory cascade. Use of these inhibitors and antibodies individually have shown encouraging results, and the combined use of inhibitors and antibodies might have significant potential [74]. However, the etiology of UC remains unclear. Once the pathogenic antigens have been further identified, UC may be brought under control by cytokines or anticytokines and then maintained by antigen manipulation [75]. Other therapeutics are being designed to modulate NKT cells themselves. Removing leukocytes from peripheral blood via apheresis is one way to reduce the excessive inflammatory immune responses. Apheresis, a well-established treatment strategy in Japan and Europe for UC, filters out many of the circulating inflammatory cell types that are activated in UC [76]. Thus, removing leukocytes from peripheral blood can reduce excessive inflammatory response in UC. Recently, a unique inhibitory sphingolipid produced by the intestinal microbe *Bacteroides fragilis*, called GSL-Bf717, was reported to impede the proliferation of the invariant NKT cells during neonatal development by supplementing the host's endogenous antigen milieu with unique inhibitory sphingolipids [77]. Thus, it may represent a promising and effective treatment of autoimmune and allergic disorders such as UC by destroying the activation of the type I NKT cells. Unfortunately, most of these therapeutic strategies are at the experimental phase and require clinical trials to ensure their safety and efficacy.

5. Conclusions and prospects

In this review, the roles of NKT cells in the intestine and in the pathogenesis of UC were discussed. Type I NKT cells can make protective or pathogenic contributions to UC. However, type II NKT cells seem to promote intestinal inflammation. Results using oxazolone colitis model suggested that the IL-13 response is the intrinsic pathogenic component of the colitis. The levels of many other cytokines are altered in UC, such as TNF-α, IL-4, IL-5, IL-21 and IL-22, suggesting their roles in the pathogenesis of human UC. Thus, compounds that antagonize cytokines participated in UC might be promising therapy approaches. Therapeutics targeting NKT cells are still under investigation. The development of novel therapies might greatly improve the treatment of UC. However, most therapeutics are in preclinical development. A novel activated-T cell apoptosis-inducing antibody AbGn-168H, also called Neihulizumab, is proposed to apply in the treatment of certain immune disease, such as psoriatic arthritis. Whether it can affect on NKT cells remains to be verified. More clinical evidence is needed to verify the efficacy of tralokinumab in UC. Dupilumab, a fully human monoclonal antibody that blocks IL-4 and IL-13, has shown efficacy in asthma patients, but there is no report on its efficacy in UC. In a word, because of the unclear etiology of UC, none of the approaches described are likely to provide a long-term cure. To develop curable treatment for UC, a deeper understanding of the pathogenesis of UC is required.

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