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Review Article

Potential Role of NK Cells in the Pathogenesis of Inflammatory Bowel Disease

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NK cells are a major component of the innate immune system and play an important role in the tissue inflammation associated with autoimmune diseases such as inflammatory bowel disease (IBD). NK cells are unique in bearing both stimulatory and inhibitory receptors specific for MHC class I molecules, and their function is regulated by a series of inhibiting or activating signals. The delicate balance between activation and inhibition that decides NK cell final action provides an opportunity for their possible modulatory effect on specific therapeutic settings. Intestinal NK cells are phenotypically distinct from their counterparts in the blood and resemble "helper" NK cells, which have potentially important functions both in promoting antipathogen responses and in the maintenance of intestinal epithelial homeostasis. NK cell activities have been found to be significantly below normal levels in both remissive and active stages of IBD patients. However, some proinflammatory cytokines (e.g., IL-15, IL-21, and IL-23) could potently induce NK cell activation to secret high levels of proinflammatory cytokines (e.g., IFN-γ and TNF) and promote the cytolytic activities against the target cells. This paper provides the characteristics of intestinal NK cells and their potential role in the pathogenesis of IBD.

1. Introduction

Inflammatory bowel diseases (IBDs), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory diseases of the gastrointestinal tract. The two conditions share a number of common characteristics. However, notable differences are also observed in these disorders. CD may be patchy, segmental, and typically transmural inflammation in the gut, which is characterized by the aggregation of macrophages that frequently form noncaseating granulomas. On the contrary, UC shows the pathological features of a significant number of leukocyte infiltrations within the lamina propria and the crypts, where they form microabscesses, as well as depletion of mucin by goblet cells [1]. Although their exact etiology is still not completely understood, increasing data have demonstrated that these conditions occur through an inappropriate immune response to a subset of commensal enteric bacteria in a genetically susceptible host, with disease initiated by environmental triggers. Dysfunction of the mucosal immune system evokes intestinal inflammation through the activation of both innate and acquired immunity in the gut. Evidence has demonstrated that both T helper 1 (Th1) and Th2 cells are involved in the induction of chronic gut inflammation [2, 3]. CD is a predominately Th1- and Th17-mediated process, while UC seems to be a Th2-like disorder. In healthy individuals, such immunopathogenesis is avoided by the presence of regulatory T cells that inhibit the inflammatory pathway [4]. Among the innate immune compartments, NK cells are a major component of the innate immune responses against intracellular pathogens and participate in the tissue inflammation associated with autoimmune diseases, including IBD [5–7].

2. Immune Responses of NK Cells

NK cells are important effector cells of the innate immune system required for the first line of defense against transformed and infected cells and play an essential role in linking innate and adaptive immunity through their ability to secrete IFN-γ [5–7]. At the early stage of infection, NK cells are considered as the primary source of IFN-γ, shaping

the adaptive immunity through differentiation of $CD4^+$ T cells to the Th1 subsets [8, 9]. NK cells kill their target cells through two major pathways, both requiring close contact between NK cells and the target cells. In the first pathway, cytoplasmic granule toxins including perforins and granzymes are secreted by exocytosis and together induce apoptosis of the target cells. The second pathway involves the engagement of death receptors in target cells by their cognate ligands in NK cells, resulting in classical caspase-dependent apoptosis [8].

Previous studies [7] both in mouse models of autoimmune diseases and in humans have shown that NK cells have either a disease-promoting or -controlling role. Unlike T cells, NK cells do not express a diverse set of antigen-specific receptors, but they are unique in bearing both stimulatory and inhibitory receptors, and their function is regulated by a series of inhibiting or activating signals. When NK cell inhibitory receptors bind to major histocompatibility complex (MHC) class I molecules, their effector functions (i.e., cytotoxicity and cytokine production) are then blocked. Lower expression of stimulatory receptors could result from specific downregulation of the receptors in such NK cells, or from a failure of these cells to upregulate such receptors during development. Moreover, the activation of NK cells also results from the concerted action of costimulatory molecules already well characterized for their function in T cells. However, evidence indicates that NK cells also regulate the innate and acquired immune responses through their secretion of soluble factors and/or cell-cell contact [8]. NK cells discriminate from myeloid immature dendritic cells, which typically underexpress MHC class I molecules, and mature dendritic cells, which upregulate MHC class I expression after antigen uptake [10]. The killing of immature dendritic cells by NK cells has been interpreted as a control of the quality of dendritic cells, allowing only mature dendritic cells to migrate to the lymph nodes [11].

NK cells develop primarily in the bone marrow in adults and are widely distributed in the body, but the largest population can be found in spleen, lung, liver, bone marrow, and peripheral blood. NK cells can migrate to various tissues [12]. Intestinal NK cells are phenotypically distinct from their counterparts in the blood and resemble "helper" NK cells, which have potentially important functions both in promoting antipathogen responses and in the maintenance of intestinal epithelium [13]. It has been suggested that NK cells in gut, like T cells, require priming for activation, a process that involves cytokines such as IFN-γ, IL-15, and IL-18 [13].

3. Pathogenic Role of NK Cells in IBD

3.1. Alteration of Lamina Propria NK Cells in IBD. NK cells are present within the gut-associated lymphoid tissue including intraepithelial lymphoid compartment, intestinal lamina propria, Peyer's patches, and mesenteric lymphoid nodes and display a proinflammatory cytokine profile (e.g., IFN-γ, TNF, IL-2, IL-17, and IL-22) in response to commensal enteric bacteria through the innate immune system and cytolytic activity, indicating that intestinal NK cells play an important role in mucosal innate immunity and tolerance [13–17]. These mucosal NK cells are distinct from conventional NK cells in the periphery, characterized by the expression of a transcription factor, RORC in human or RORγt in mice, CD127 (IL-7Rα) and NKp44 in humans or NKp46 in mice. CD56 serves as an important marker defining functionally distinct subsets of NK and NKT cells based on their ability in the periphery. In humans, $CD56^{bright}$ NK cells show potential for cytokine secretion, while $CD56^{dim}$ NK cells have elevated cytotoxicity associated with a mature differentiation state. Similar subsets of NK cells are also found in mice based on their expression of CD27. Mucosal $CD56^+$ NK cells express a mature phenotype and produce high amounts of IFN-γ and TNF. A relative reduction in $CD56^+$ NK cells may conversely have an impact on intestinal epithelial repair processes in the gastrointestinal tract [18, 19]. Recently, $NKp46^+CD56^+CD3^-$ NK cells have been found in gut lamina propria surrounding colonic crypts and do not express MHC class I-specific killer cell immunoglobulin receptor KIR2D. Phenotypic analysis reveals that lamina propria $NKp46^+CD3^-$ NK cells are $CD127^+$c-$kit^+CD122^{low}CD27^{low}Ly49^-$. Importantly, these subsets of NK cells express RORγt, produce high level of IL-22 but not IFN-γ and IL-17 after stimulation *in vitro*, and lack NK cell cytolytic function [20–22]. These data indicate that $NKp46^+CD3^-$ NK cells in gut mucosa are distinct from conventional NK cells characteristic of IFN-γ production and cytotoxicity and may be involved in intestinal epithelial homeostasis and prevention of intestinal inflammation.

The precise role of NK cells in the pathogenesis of IBD is still elusive. Increasing evidence has indicated that distinct functional subsets of intestinal mucosal NK cells with an alteration in activation and cytotoxic activity potentially contribute to the pathogenesis of IBD [19, 23, 24]. NK cells have been found to be increased in inflamed mucosa of IBD patients, and NK cell differentiation is also accelerated in the lamina propria, suggesting that NK cells are involved in the disease pathophysiology. $CD16^+$ NK cells are found to be increased in the lamina propria from both CD and UC patients compared with healthy controls, and azathioprine preferentially inhibits proliferation of $CD16^+$ NK cells and induces apoptosis in resting but not in preactivated NK cells [23], indicating that NK cells with cytolytic potential are enriched in the colonic lamina propria of IBD patients and that azathioprine is associated with a reduction in these cells and a normalization of NK cell population in gut mucosa. However, previous work has reported that the populations of $CD161^+$ NK cells are significantly decreased in the inflamed mucosa of UC, whereas the frequency of conventional $CD161^+$ cells is similar among IBD patient and healthy controls. These data indicate that colonic lamina propria $CD161^+$ NK cells are thought to play important roles as anti-inflammatory cells and that the decrease in the proportions of these cells in inflamed colon may be associated with colonic inflammation progresses in IBD [24].

Although $NKp44^+$ or $NKp46^+$ IL-22-producing NK cells are present in intestinal mucosa, their role in the

pathogenesis of IBD is still unknown. Recent work has demonstrated that peripheral blood $CD56^+CD3^-$ NK cells strongly express NKp30, NKp46, CD122, NKG2D, and CD244, but not NKp44, CD127, and CD69 [25]. On the contrary, gut lamina propria $CD56^+CD3^-$ NK cells could express NKp30, NKp44, NKp46, CD122, CD127, NKG2D, CD244 and CD69. Interestingly, both $NKp44^+$ and $NKp46^+$ NK cells are found to be present in intestinal mucosa. $NKp44^-NKp46^+$ NK cells preferentially express high levels of CD122 but low levels of RORC and CD127 and produce IFN-γ after stimulation *in vitro*, whereas $NKp44^+NKp46^-$NK cells express high levels of RORC and CD127 and produce IL-22 [25]. These IFN-γ-producing $NKp46^+$ NK cells are found to be significantly increased in inflamed mucosa of CD patients, while IL-22-producing $NKp44^+$ NK cells are markedly decreased compared with those in UC patients and healthy controls. IL-23 could promote $NKp46^+$ NK cell activation to produce large amounts of IFN-γ. These data indicate that the balance between IFN-γ-producing $NKp46^+$ and IL-22-producing $NKp44^+$ NK cells is disrupted in inflamed mucosa of CD patients and that these $NKp46^+$ NK cells may be involved in the development of IBD.

3.2. NK KIR Genotypic Association with IBD. As part of the innate immune system, NK cells recognize human leukocyte antigen (HLA) class I molecules in target cells through their membrane receptors. The main receptors of NK cells are the killer immunoglobulin-like receptors (KIRs) [26]. The human KIR gene family comprises 15 genes and 2 pseudogenes, which are located within the IBD6 linkage region at chromosome 19q13.4. KIRs contain either two or three immunoglobulin-like domains with either long (2DL, 3DL) or short (2DS, 3DS) cytoplasmic tails. The presence of a long cytoplasmic tail (L) with immune tyrosine-based motifs (ITIM) permits the transduction of inhibitory signals and characterizes the inhibitory KIRs (2DL, 3DL), which inhibit NK- and cytotoxic T cell-mediated lysis of target cells expressed appropriate HLA class I ligands. In contrast, the presence of a short cytoplasmic tail (S) is associated with the activating or noninhibitory KIR (2DS, 3DS), which may promote cytolysis of target cells [26]. Therefore, a variety of inhibitory and activating KIRs which recognize and bind to their HLA class I ligands in target cells could regulate activation and inhibition of NK cell responses. Various KIR/HLA combinations may program the differentiation of NK cells during immune responses.

Recent genetic association studies have implicated that both KIR and their ligands display considerable genetic diversity in the development of several inflammatory conditions, including human IBD [26]. KIR and HLA C locus (HLA-Cw) variants that reduce NK cell inhibition have been shown to increase susceptibility to the development of IBD [27]. We have found that the KIR2DL1 and KIR2DL3 gene frequencies are significantly lower in UC patients compared with healthy controls (0.71 versus 0.896; 0.62 versus 0.821). The KIR2DL1 gene phenotype frequency is markedly decreased in CD patients more than healthy controls (0.731 versus 0.896). Interestingly, KIR2DL1–HLA-C2 combination is observed to be decreased in IBD patients compared with controls (0.38 versus 0.575 in UC; 0.404 versus 0.575 in CD) [27]. These data suggest that the decrease of combination KIR2DL1 and HLA-C2 may reduce the activating threshold of NK cells and CTL, enhance the cytolytic activity of lymphocytes, promote their multiplication, and finally lead to immune response to a subset of commensal enteric bacteria in IBD. Thus, KIR genotype and HLA ligand interaction may contribute to the genetic susceptibility of IBD.

3.3. Proinflammatory Cytokines in the Induction of NK Cell Activation in IBD. Previous work has proven that both stromal cells and cytokine/growth factors play a critical role in the development of NK cell development. Some proinflammatory cytokines (e.g., IL-2, IL-15, IL-21, and IL-23) have been observed to be involved in the immune responses of NK cells under inflammatory conditions such as IBD.

3.3.1. IL-2. IL-2 is a lymphocytotrophic cytokine that is involved in the growth and differentiation of T and B cells and enhances the cytolytic activities of NK cells. It induces the proliferation of $CD4^+$ and $CD8^+$ T cells by upregulating and maintaining the expression of the IL-2 receptor (IL-2R) α-subunit, which forms, together with the β-subunit and γ-subunit, the high-affinity IL-2R. IL-2 is also required for maturation and development of NK cells [28]. It has been documented that *in vitro* expanded NK cells have increased natural cytotoxicity receptors, TRAIL and NKG2D expression, and superior tumor cytotoxicity compared with short-term IL-2-activated NK cells. There is controversial about the amount of IL-2 in the mucosa of IBD patients. Some studies have shown that mRNA levels of IL-2 are increased in inflamed mucosa of active CD, while in other studies, both mRNA and protein levels of IL-2 are reduced in both CD and UC [29, 30]. IL-2 homeostasis may lead to preferential depletion of regulatory T-cell subsets, which cause exacerbation of inflammation in the gut [31]. In contrast, it has been conceived that eruption of IBD is associated with disturbed homeostasis and dominance of effector cells including colitogenic T-cell clones [32]. Therefore, the disruption of IL-2 signaling may evolve as a deleterious mechanism in the context of autoimmunity, rather than an immunosuppressive strategy [31]. Therefore, IL-2 secreted by intestinal mucosal T cells in IBD may contribute to NK homeostasis and the development of IBD.

3.3.2. IL-15. IL-15 is mainly derived from nonlymphoid cells and shares many similarities to IL-2. It has been also found to be produced by intestinal macrophages and other cell types in response to luminal bacterial stimulation and plays an important role in growth and differentiation of immune cells within the intestinal mucosa, including T and B lymphocytes, NK cells, macrophages, and monocytes [33]. IL-15 exerts most of these effects by binding to a heterotrimeric complex composed of the IL-2Rβ chain, the IL-2R γc chain, and the IL-15Rα chain. IL-15 induces T-cell proliferation and cytokine production, stimulates locomotion and chemotaxis

of normal T cells, and protects them from apoptosis. Importantly, IL-15 enhances NK cell cytotoxicity and antibody-dependent cell-mediated cytotoxicity and upregulates NK cell survival and production of NK cell-derived cytokines such as IFN-γ, GM-CSF, and TNF [28, 33]. Consistent with this, IL-15-deficient mice display a marked reduction of $CD8^+$ T cells, as well as certain intraepithelial lymphocytes. Incidentally, these mice also lack NK cells, suggesting that IL-15 may also be involved in expansion and survival of NK cells [34]. In rodent models of intracellular bacterial infections, evidence has demonstrated that IL-15 could attract NK cells to infected sites and limit bacterial colonization [35]. In the intestine IL-15 is observed to stimulate NK, NKT, and TCR$\gamma\delta$ T-cell activation [36]. However, after IL-15 treatment, both intraepithelial lymphocytes and NK cells have a greater killing potential against target cells [37]. Given that IL-15 is markedly increased in inflamed mucosa of IBD [38], IL-15 is also thought to be involved in the induction of NK cell activation and immune responses in IBD.

3.3.3. IL-21. IL-21 is a member of the IL-2 family of cytokines, expressed mainly by $CD4^+$ T cells, including Th1, Th2, and Th17 cells, and recently implicated in Th17 cell differentiation. IL-21R is structurally related to IL-2R and IL-15R and expressed in T, NK, B, and dendritic cells. IL-21 has been found to stimulate T-cell proliferation and differentiation, enhance clonal expansion of antigen-activated naïve $CD4^+$ and $CD8^+$ T cells, and induce the gene encoding IFN-γ, IL-18R, IL-2Rα, IL-12Rβ2, and the Th1-associated transcription factor T-bet in activated memory T cells [39, 40]. IL-21 also synergized with IL-15 and IL-18 in stimulating IFN-γ gene expression in these same cultures. Wurster et al. [41] reported that exposing naïve $CD4^+$ T cells to IL-21 under conditions that skew differentiation towards the Th1 phenotype actually inhibited IFN-γ production although it had little effect on other Th1 cytokines such as TNF or IL-2. IL-21 is also associated with the Th2-mediated immune response and plays a role in inhibiting the differentiation of naive Th cells into IFN-γ-producing Th1 cells. Moreover, IL-21 is found to promote human NK cell maturation and activation in synergy with IL-15, Ftl-3 ligand, and stem cell factor and enhance IFN-γ production and cytotoxicity [42].

IL-21 is involved in both cell-mediated and humoral responses and plays an important role in the pathogenesis of several autoimmune diseases, including IBD [39, 40]. Increased expression of IL-21 and IL-21R has been observed in the inflamed mucosa of IBD patients [43, 44]. We found that IL21R-positive cells are mainly expressed in $CD4^+$, $CD8^+$ T, B, and NK cells from peripheral blood and lamina propria of IBD patients [44]. IL-21 could expand already polarized IL-17A-producing cells in inflamed mucosa, promote a local inflammatory response in gut mucosa, and trigger intestinal mucosal T-cell activation and proinflammatory cytokine secretion [44]. Importantly, IL-21 could promote IBD NK cell activation to produce high levels of proinflammatory cytokines (e.g., IFN-γ and TNF) and enhance cytotoxicity against target cells. Our findings have confirmed that IL-21 is involved in the pathogenesis of IBD via the induction of NK cell activation and its cytolytic activity against target cells (e.g., intestinal epithelial cells). These data indicate that target immune therapy directed against IL-21R signaling may be warranted in some experimental colitis models, and that blockade of the IL-21R signaling pathway may have a therapeutic potential in IBD [45].

3.3.4. IL-23. IL-23 and IL-12 are members of a small family of proinflammatory heterodimer cytokines, sharing a common p40 subunit covalently linked either to a p35 subunit to form IL-12 or to a p19 subunit to form IL-23 [46]. IL-23R is predominantly expressed in T, NK, NKT cells, and, to a smaller extent, in monocytes, macrophages, and dendritic cells. After binding to the IL-23R, IL-23 preferentially induces memory T-cell activation. Evidence has demonstrated that IL-23 exhibits some similar biological activities to IL-12. However, in comparison with IL-12 with profound induction of Th1 immune response, as well as promotion of cytolytic, antimicrobial, and antitumor responses, IL-23 is found to play a critical role in the maintenance of immune response by controlling T-cell memory function and by influencing the proliferation and survival of IL-17-producing Th17 cells [47].

IL-23 has been reported to be increased expression in the sera and inflamed colon of IBD patients [48, 49]. Genome-wide association studies indicate that IL-23R is involved in the differentiation of Th17 cells, and is associated with susceptibility to CD and partly also to UC [50]. Our recent work has shown that the frequencies of IL-23R expression in $CD4^+$, $CD8^+$ T cells and NK cells are significantly increased in peripheral blood and lamina propria mononuclear cells from IBD patients compared with healthy controls [49]. Importantly, we found that IL-23 strongly induces IBD NK cell activation, showing increased secretion of proinflammatory cytokines (e.g., IFN-γ and TNF) and cytolytic activities. These findings indicate that IL-23 produced by intestinal mucosal macrophages/dendritic cells in inflamed mucosa of IBD could promote peripheral blood NK cell effector response. Recent work has demonstrated two distinct subsets of intestinal mucosal $NKp46^+$ NK cells according to the expression of RORγt. The RORγt^- subset functions as typical NK cells dependently on IL-15 but not on RORγt and displays NK cell activities (e.g., cytotoxicity and IFN-γ secretion), whereas the RORγt^+ subpopulation develops independently of IL-15 but required RORγt [21, 22]. Most interestingly, these $CD3^-NKp46^+$ cells located in the intestinal mucosa express RORγt and IL-22 but not IL-17A in response to IL-23 stimulation, and these cells lack normal NK cell function such as expression of perforin and IFN-γ, indicating that these NK cells play an important role in mucosal homeostasis and protectable immune response, particularly under microbial challenge [20]. These data suggest that intestinal mucosal NK cells may also be associated with proinflammatory response under inflammatory conditions and play an important role in mucosal homeostasis and defense against luminal microbial challenge although the precise role of IL-23 in the inductions

intestinal mucosal NK cell effect response need to be further investigated.

4. Conclusions

NK cells play an important role in linking innate and adaptive immunity. Evidence has proven that NK cells have a disease-promoting or -controlling role in autoimmune diseases, depending on the disease and the NK cell subset analyzed. Thus, ongoing studies should focus on intestinal mucosal NK cells and their interactions with other immune cells in inflamed mucosa of IBD, and these will provide powerful insights into potential role of NK cells in the pathogenesis of IBD.

Abbreviations

CD: Crohn's disease
HLA: Human leukocyte antigen
IBD: Inflammatory bowel disease
KIR: Killer immunoglobulin-like receptor
NK: Natural killer cells
UC: Ulcerative colitis.

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