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REVIEW

The natural killer cell: a further innate mediator of gouty inflammation?

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Natural killer (NK) cells are vital effector cells of innate immunity because of their rapid cytotoxic and cytokine-producing responses to cell stress or infection. A distinguishing feature of NK cells is the ability to balance these signals with those of normal homeostasis through the expression of an array of inhibitory and activating receptors. Two functional subsets of NK cells exist: the more mature CD56^{dim} population is potently cytotoxic, whereas CD56^{bright} NK cells have low cytotoxicity but produce much greater amounts of cytokines, and express homing molecules for secondary lymphoid organs and sites of inflammation. NK cells have been identified as important modulatory cells in shaping adaptive immune responses by interacting with dendritic cells (DCs) and T cells. NK cells also interact with cells of the innate immune system such as monocytes and macrophages. This review outlines the biology of NK cells and the potential role of NK cells in modulating gouty inflammation.
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Human natural killer (NK) cells are large, granular and short-lived cells from the lymphocyte lineage.[1,2] They develop primarily in the bone marrow from haematopoietic progenitor cells after activation by Notch ligands[3–5] and are characterized by the expression of neural cell adhesion molecule-1 (CD56) and lack of CD3.[6] The level of CD56 expression also delineates two functionally distinct subsets of NK cells: the potently cytotoxic CD56^{dim} subset, and the poorly cytotoxic CD56^{bright} subgroup that secretes large amounts of cytokines.[6–8] Unlike T and B lymphocytes, which possess receptors for a single cognate antigen, NK cells express a repertoire of germline-encoded receptors that survey an array of molecular signals of self and the steady-state condition, as well as markers of cell stress, malignancy and infection.[9] This confers NK cells with the unique ability to sense and integrate a diverse range of signals of both homeostasis and disease. Owing to their rapid cytotoxic or cytokine-producing responses in the early stage of bacterial, viral and parasitic infection, NK cells are considered predominantly an innate immune cell.[10–14] In addition, a vital modulatory role for NK cells is emerging in which they interact with and modulate cells of both innate and adaptive immune responses.[14–21]

Acute gout is an orchestrated inflammatory response to monosodium urate (MSU) crystals that is mediated by cells and soluble factors of the innate immune system.[22–28] The involvement of NK cells in gouty inflammation has not yet been studied. Due to the important innate effector and modulatory functions of this cell, particularly the release of pro-inflammatory cytokines,[8,15] a role for NK cells in inflammatory conditions is proposed. This review summarizes the biology of human NK cells and data that suggest a potential involvement of human NK cells in mediating acute gouty arthritis.

Human and murine NK cells share cytotoxic and cytokine-producing functions, and to a large extent their phenotypes and signalling mechanisms are conserved.[29] A major distinction between NK cells from the two species is the lack of CD56 and presence of NK1.1 (which is not expressed in humans) on murine NK cells, which hinders direct comparison.[12,30] However, subsets of murine NK cells have been defined by CD27 and CD11b expression, which progresses from CD27^{high}CD11b^{low} to CD27^{low}CD11b^{high}.[31] The murine CD27^{high} group may correspond to human CD56^{bright} NK cells, with similarities in expression of chemokine receptors, inhibitory receptors and cytokines.[31] In this review, we focus on human NK cells.

NK CELL RECEPTORS AND SIGNAL INTEGRATION

During transient contact with NK cells, ligands that are expressed on the surface of target cells interact with a multitude of inhibitory and activating NK cell receptors.[32,33] Inhibitory receptors sense signals of normal homeostasis, such as major histocompatibility complex class I, and related molecules that are downregulated on stressed, infected or malignant cells,[34,35] whereas activating receptors bind to non-self ligands (for example, ectopically expressed viral proteins) or molecules that are upregulated on stressed or transformed cells.[36–38] The inhibitory receptors comprise two main groups: immunoglobulin superfamily receptors including killer-cell immunoglolubin-like receptors and leukocyte immunoglobulin-like receptors/transcripts,

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and those of the C-type lectin domain family (Table 1). Activating NK cell receptors include molecules that are structurally related to inhibitory receptors, such as killer-cell immunoglolubin-like receptors and C-type lectin-domain receptors, as well as many unrelated receptors, such as the natural cytotoxicity family (Table 2). With the exception of CD16, an activating receptor that binds to the Fc component of immunoglobulin G, enabling cytotoxicity towards antibody-coated target cells, the synergetic effects of multiple coactivating receptors are required to induce NK cell activation.[39]

The opposing effects of proximal activating and inhibitory NK cell receptors are integrated by the net phosphorylation of intracellular signalling molecules resulting from the activity of kinases or phosphatases recruited by the receptors.[9] Activating receptors recruit kinases through motifs in their own cytoplasmic tails or through accessory molecules bearing immunoreceptor tyrosine-based motifs or other kinase-recruiting motifs.[40–43] All inhibitory receptors associate with accessory molecules that contain immunoreceptor tyrosine-based inhibition motifs, enabling the recruitment of Src homology-2 domain-containing inositol-5-phosphatase 1 and Src homology-2 domain-containing tyrosine phosphatases 1 and 2.[44–47]

Several questions regarding the activation and signalling of NK cells remain unanswered. The mechanisms by which NK cell activation diverges to generate different effector functions are unclear.[48] Furthermore, NK cells can be activated by cytokines[49] and Toll-like receptor ligands.[50] However, it is not known whether these receptors share the same signalling pathways as receptors for membrane-bound ligands.

PHENOTYPES OF NK CELL SUBSETS

Two major phenotypic and functional subsets of NK cells are distinguished by CD56 expression levels.[6] $CD56^{dim}$ NK cells are the more cytotoxic population, whereas the $CD56^{bright}$ subset has limited cytotoxicity but secretes large amounts of cytokines and chemokines.[6–8] When resting, these populations differ in their expression of 473 transcripts, with 176 expressed exclusively by the $CD56^{dim}$ subset and 130 expressed only by $CD56^{bright}$ NK cells.[51] Consistent with the known functional differences between the subsets, $CD56^{bright}$ cells express lower levels of a number of activating receptors, including killer-cell immunoglolubin-like receptors, the natural cytotoxicity receptors and CD16, but constitutively express the inhibitory heterodimer CD94/NKG2A[8,52,53] (Table 3). In contrast, cytokine receptors tend to be more highly expressed on the $CD56^{bright}$ subset, including those for interleukin (IL)-1, IL-2, IL-15 and IL-18.[52,54] Furthermore, the high-affinity IL-2 receptor (CD25) is expressed constitutively on $CD56^{bright}$ NK cells, but is absent from the $CD56^{dim}$ subset.[55] $CD56^{bright}$ NK cells also express c-kit, a receptor tyrosine kinase that enhances IL-2-induced proliferation.[55,56] NK cell subsets also possess

Table 1 Activating natural killer (NK) cell receptors[32,33]

Activating receptors	*Ligands*
2B4 (CD244)	CD48
BY55 (CD160)	HLA-C
CD2	LFA-3 (CD58)
CD7	SECTM1, Galectin
CD11c/18	ICAM-1, iC3b
CD16 (FcgRIIIA)	IgG
CD44	Hyaluronan
CD59	C8, C9
CRACC (CD319)	CRACC (CD319)
DNAM-1 (CD226)	PVR (CD155), CD112
KIR2DL4 (CD158d)	HLA-G (soluble)
KIR2DS1-2	HLA-C (low affinity)
KIR2DS3-6	Unknown
KIR3DS1	Unknown
LFA-1 (αLβ2, CD11a/18)	ICAM-1-5
MAC-1 (αMβ2, CD11b/18)	ICAM-1, iC3b, fibrinogen
NKG2C (CD94/159c)	HLA-E
NKG2D (CD314)	ULBPs, MICA, MICB
NKp30 (CD337)	BAT-3
NKG2E	HLA-E
NKp44	Viral hemaglutinin
NKp46 (CD335)	Viral hemaglutinin
NTBA	NTBA
VLA-4 (α4β1, CD49d/29)	VCAM-1, fibronectin
VLA-5 (α5β1, CD49e/29)	Fibronectin

Table 2 Inhibitory NK cell receptors[32,33]

Inhibitory receptors	*Ligands*
CEACAM1	CEACAM1
IRp60 (CD300a)	Unknown
KIR2DL1 (CD158a)	HLA-C group 2
KIR2DL2/3 (CD158b)	HLA-C group 1
KIR2DL5	Unknown
KIR3DL1	HLA-B alleles and Bw4
KIR3DL2	HLA-A alleles
KLRG1/MAFA	E/N/P-cadherin
NKG2A (CD94/CD159a)	HLA-E
NKR-P1A (CD161)	LLT1
LAIR1	Collagen
LIR-1/IL-T2 (CD85j)	Multiple HLA class I
Siglec-7 (CD328)	Sialic acid
Siglec-9 (CD329)	Sialic acid

Table 3 Phenotype of NK cell subsets[8,54]

Subset markers	*$CD56^{bright}$*	*$CD56^{dim}$*
CCR7	++	–
CD2	++	+
CD16	+/–	++
CD44	++	+
CD49e	++	+
CD56	++	+
CD62L	++	+/–
CD94/NKG2A	++	+/–
CD117 (c-kit)	++	–
CXCR1	–	++
CX3CR1	–	++
CXCR3	++	+/–
IL1R1	++	+
IL18R	++	+
IL2R-αβγ	+	–
IL2R-βγ	++	+
ILT2	–	+
KIR	–	+
NKp46	++	+
LFA-1	+	++

++, Strong expression; +, weak expression; +/–, variable expression; –, lacking expression.

distinct homing characteristics, and their phenotypes differ with respect to adhesion molecules and chemokine receptors.[57] In particular, the expression of CD62L, CCR7 and CXCR3 on CD56^{bright} NK cells enables their entry to lymph nodes.[57–59]

Evidence has recently emerged showing that CD56^{bright} NK cells represent an immature population that differentiates to the CD56^{dim} phenotype. First, CD56^{bright} NK cells have longer telomeres.[60,61] Second, the CD56^{bright} population has a greater proliferative potential, which is reflected in their expression of the high-affinity IL-2 receptor and c-kit.[55,56] Third, at 10 days after transfer of NK cells into NOD–SCID mice, almost all CD56^{bright} cells acquire the CD56^{dim}CD16+ phenotype, whereas the CD56^{dim} cells do not change their expression of CD56 or CD16.[61]

DISTRIBUTION OF NK CELL SUBSETS

NK cell distribution in steady-state conditions

Natural killer cells represent a minor population of lymphocytes in the peripheral blood and secondary lymphoid organs in which they represent 10–15% of lymphocytes and 5% of all mononuclear cells, respectively.[62] NK cells are also present in non-lymphoid tissues, including the liver, bone marrow and the uterus during pregnancy.[63]

CD56^{dim} NK cells are the dominant subgroup in peripheral blood, comprising 90% of NK cells.[6] In contrast, 75–95% of NK cells in secondary lymphoid organs apart from the spleen belong to the CD56^{bright} subset.[52,53] Owing to the large reservoir of lymphocytes in secondary lymphoid tissues, CD56^{bright} NK cells are probably at least as numerous as the CD56^{dim} subset overall.[54,64] The high proportion of CD56^{bright} cells in most secondary lymphoid organs is because of the expression of the chemokine receptors CCR7 and CXCR3, and the adhesion molecule CD62L, which interacts with high endothelial venules.[58] Within the secondary lymphoid tissues, CD56^{bright} NK cells home to the parafollicular regions, in which T cells and dendritic cells (DCs) are also found.[52] Expression of the sphingosine-1-phosphate 5 receptor increases with maturation in both mice and human NK cells.[65] This is proposed to account for the preferential migration of the more mature subsets to the peripheral blood, in which sphingosine-1-phosphate is present at higher concentrations than in the tissues.[65]

Expansion of CD56^{bright} NK cells in sites of inflammation

Expanded CD56^{bright} NK cell populations have been observed in various inflamed sites, including the joints[15,66] airways and pleural space[15,67] peritoneal space[15] and in psoriatic skin.[68] Preferential recruitment of the CD56^{bright} subset of NK cells into sites of inflammation may account for these observations. All chemokine receptors except CCR4 are found at greater levels on the CD56^{bright} subset.[57] In particular, CCR5 has been identified as a crucial chemokine receptor for migration of NK cells to inflamed tissues,[69] and is more highly expressed on CD56^{bright} than CD56^{dim} NK cells from the synovial fluid of inflamed joints.[66]

The expansion of CD56^{bright} NK cells in inflamed sites may also occur because of preferential survival. Several studies have shown enhanced survival of the CD56^{bright} subset when compared with CD56^{dim} NK cells upon exposure to reactive oxygen and nitrogen species, which are generated by activated neutrophils and macrophages during inflammation.[70,71] In agreement with these findings, CD56^{bright} cells are less susceptible to apoptosis than CD56^{dim} NK cells when exposed to pleural fluid from tuberculosis patients.[72] Selective depletion of CD56^{dim} NK cells may contribute to the expanded ratios of CD56^{bright} NK cells observed in inflamed tissues; however, as the total number of NK cells is not decreased in these sites,[66] other processes are likely to be involved. Enhanced proliferation of CD56^{bright} NK cells is a further potential mechanism of their accumulation in inflamed sites. NK cell proliferation is induced by IL-2,[52] IL-15[73] and IL-21.[74] Because of the expression of the high-affinity IL-2 receptor and c-kit on CD56^{bright} NK cells, these cells are more sensitive to stimulation with IL-2 than CD56^{dim} NK cells.[52,56] The proliferative response to IL-2 is further enhanced in the CD56^{bright} subset, but not in CD56^{dim} NK cells, in the presence of IL-21.[75]

NK CELL FUNCTIONS

The vital role of NK cell cytotoxicity in controlling intracellular pathogens is well known, and is shown by severe or fatal viral infections in the few reported cases of selective NK cell deficiency.[76–78] There is also a large body of evidence showing that NK cells kill malignant cells.[79] Two mechanisms of NK cell cytotoxicity exist: the deposition of lytic granules into target cells and the expression of death receptor ligands, such as tumour necrosis factor (TNF), TNF-related apoptosis-inducing ligand and Fas ligand.[80–82] NK cell granules contain granzymes, serine proteases that induce apoptosis by caspase-dependent and independent mechanisms, and perforin, a pore-forming protein that disrupts the target cell membrane. Granzymes can be transported into target cells in the absence of perforin through receptor-mediated endocytosis; for example, by the mannose-6-phosphate receptor on target cells.[83,84] When resting, CD56^{dim} NK cells show greater cytotoxicity than the CD56^{bright} population.[6,7] Lytic granules produced by CD56^{dim} NK cells contain 10 times more perforin and granzyme A than those of CD56^{bright} cells.[7] Unlike the CD56^{bright} population, CD56^{dim} NK cells also express CD16, which enables antibody-mediated cytotoxicity.[7] However, the cytotoxic capability of the two subsets is equalized after stimulation with IL-2 or IL-12.[85]

Natural killer cells also contribute to the innate immune response by cytokine production. They are a major source of interferon-γ (IFN-γ), which has a panopoly of effects including anti-viral and anti-bacterial actions, promotion of Th1 responses, suppression of proliferation of infected or transformed cells, stimulation of major histocompatibility complex class I expression and DC maturation.[86–92] Another important pro-inflammatory cytokine released by NK cells is TNF-α.[8,93,94] Depending on context, NK cells can also express the anti-inflammatory cytokines, transforming growth factor-β (TGF-β)[8,95] and IL-10,[8,96] and the haematopoietic factors, granulocyte-macrophage colony-stimulating factor and IL-3,[8,97] and promote T helper 2 responses by producing IL-5 and IL-13.[98] In addition to cytokines, NK cells produce several chemokines, including macrophage inflammatory protein-1α and -β and RANTES.[99–101] Stimulation with different cytokines can induce specific responses by NK cells. For example, the combination of IL-12 and IL-18 induces IFN-γ expression by NK cells,[49] whereas IL-12 and IL-15 together induce IL-10.[8] The CD56^{bright} population of NK cells produce cytokines more vigorously than CD56^{dim} cells after stimulation.[8]

Both the cytotoxic and cytokine-producing functions of NK cells were previously thought to occur without prior sensitization. However, recent work has shown that NK cell responses to bacterial and viral pathogens require priming by DCs, involving the cross-presentation of membrane-bound IL-15 in secondary lymphoid organs.[102] IL-18 may also contribute to *in vivo* NK cell priming.[103] It has been suggested that normal exposure to commensal microbes may be sufficient to induce a population of primed NK cells,[104] which is consistent with the finding that only a small proportion of isolated NK cells respond to activation signals.[39] A further unexpected adaptive feature of NK cells is the capability to develop immunological memory.

Two investigators have recently published data showing enhanced responses to antigen re-exposure by a long-lived subset of NK cells.[105,106]

INTERACTION OF NK CELLS WITH OTHER IMMUNE CELLS

Natural killer cells can promote or limit immune responses by releasing cytokines, providing co-stimulatory molecules or by selective cytotoxicity of other immune cells. Interactions between NK cells and numerous cell types have been documented. The most significant cross-talk seems to involve DCs, other lymphocytes and monocytes/macrophages, which are discussed individually below.

NK cell interactions with dendritic cells (DCs)

Interactions between NK cells and DCs have recently been the focus of considerable research. The CD56^{bright} subset is of particular importance because of its proximity to DCs in secondary lymphoid tissues.[52] DCs secrete IL-15, which is required for NK cell development, priming, function and survival.[49,102,107–109] DC-derived IL-2, IL-12 and IL-18 also activate NK cell function and proliferation.[16,110–112] The effects of NK cells on DCs may be either pro- or anti-inflammatory. NK cells activate DCs and induce maturation, leading to polarization to a T helper 1 response.[18] NK cells can also kill immature DCs, which have lower major histocompatibility complex class I expression.[19,113,114] This 'immune editing' can strengthen the immune response by reducing the development of tolerogenic DCs.[115] A tolerogenic phenotype can also be induced in DCs by a subset of immune-suppressive CD56^{+} CD16^{+} CD69^{+} NK cells.[116] These NK cells are not cytotoxic, express IL-10, IL-21 and TGF-β and can be derived from NK precursor cells by exposure to the transmembrane form of IL-15.[116]

NK cell interactions with other lymphocytes

T-cell-derived IL-2 is a potent inducer of NK cell proliferation and activity, particularly in the CD56^{bright} subset.[52] NK cell function is suppressed by TGF-β production by regulatory T cells.[117,118] In turn, NK cells provide co-stimulation for T and B cells by the surface expression of molecules, including CD40L, OX40, CD86 and CD70.[119,120] NK cells also promote B-cell activation and class switching,[121] and prime CD8 T cells by producing IFN-γ that can exert an effect directly on T cells or indirectly by promoting DC maturation.[16,86] NK cells may also negatively regulate other lymphocytes, for example, by reversibly suppressing T-cell clonal expansion by inducing cell-cycle arrest,[122] or by lysing active T cells.[123,124]

NK cell interactions with monocytes and macrophages

Emerging data also support a complex interaction between NK cells and monocytes/macrophages (Figure 1). There is potential for this interaction *in vivo*, as these cells come into contact in the red pulp and marginal zone of the spleen and in peripheral tissues.[125] NK cell responses to various stimuli are enhanced by interactions with monocytes or macrophages. These include NK cell responses to bacterial pathogens,[17,20,21,126–129] parasites,[14,130–132] tumour cells,[133] and endogenous danger signals.[134] The stimulation of NK cell survival and function by monocyte and macrophage-derived cytokines, such as IL-12, IL-15 and IL-18, is well established.[14,17,49,52,99,135] In addition to cytokine release, monocytes and macrophages can modulate NK cell activity through various contact-dependent mechanisms,[15] including expression of ligands for the activating NK cell receptors NKGD2[20,21,126,129] and NKp80,[133] or interactions mediated by co-stimulatory molecules.[128,132] Conversely, under some experimental conditions, monocytes can inhibit NK cell activation[136] and suppress NK cell proliferation.[137]

Interactions between monocytes/macrophages and NK cells are reciprocal, and can result in activation or suppression of monocyte/macrophage activity. Activated NK cells promote the maturation of monocytes by secreting IFN-γ and TNF-α, and can profoundly alter monocyte differentiation.[138] Several studies have shown mutual activation of NK cells and monocytes. The co-culture of NK cells from inflamed joints with peripheral blood monocytes induces increased expression of TNF-α by monocytes and IFN-γ by CD56^{bright} NK cells in a contact-dependent manner.[15] Furthermore, engagement of NKp80 by activation-induced C-type lectin on monocytes increases the production of TNF-α by both cell types and enhances IFN-γ expression by NK cells.[133]

Depending on the experimental conditions, NK cells can also inhibit monocyte/macrophage responses. Cytotoxicity by NK cells has been implicated in this interaction. Lipopolysaccharide-treated macrophages are killed because of upregulation of stress-induced ligands for the NKGD2 receptor.[20] In contrast, killing of monocytes activated by IL-4 and IL-13 is mediated by engagement of natural cytoxicity receptors on NK cells.[137] Lack of NK cell cytotoxicity towards monocytes in perforin-deficient mice leads to accumulation of monocytes with excess TNF-α production.[139] It is possible that the production of anti-inflammatory cytokines, such as IL-10 and TGF-β, by NK cells could also regulate monocytes and macrophages; however, this has not yet been analysed.

THE NK CELL AS AN INNATE MEDIATOR OF ACUTE GOUTY INFLAMMATION?

Acute gout is a self-limited inflammatory response to MSU crystals in the joints and periarticular tissue. Cells of innate immunity, monocytes/macrophages, mast cells and neutrophils, are critical to the pathogenesis of acute gouty inflammation. These cells

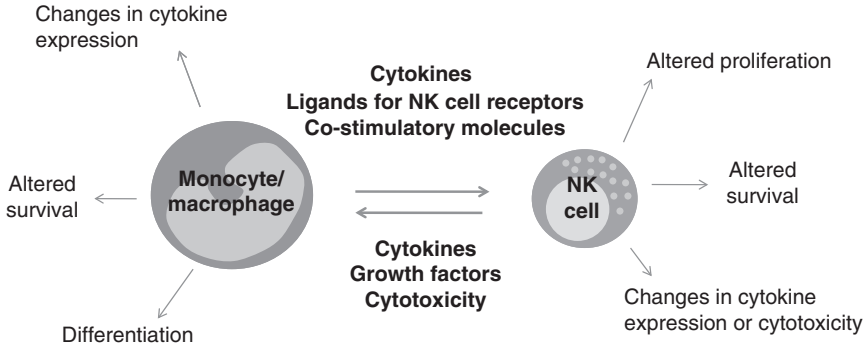

Figure 1 Interactions between natural killer (NK) cells and monocytes.

produce soluble mediators that further amplify the inflammatory response.[22–28,140,141]

Monocytes and macrophages are critical in sensing MSU crystals and initiating acute gouty inflammation.[22,23] Recent *in vivo* evidence suggests that resident macrophages trigger the early response to MSU, which is followed by the infiltration of circulating monocytes to the inflamed site.[142] After activation by MSU crystals, monocytes/macrophages release pro-inflammatory mediators such as IL-6, IL-8, TNF-α and IL-1β.[141,143,144] In particular, monocyte/macrophage production of IL-1β has a pivotal role in mediating gouty inflammation.[23,145] Activation of the NALP3 inflammasome by phagocytosed MSU crystals results in the maturation and secretion of latent IL-1β through a caspase-1-dependent mechanism.[145] The critical role of monocyte/macrophage-derived IL-1β in MSU-induced inflammation has been confirmed in both *in vivo* studies[23,145] and small clinical trials of gouty inflammation.[146,147]

In addition to monocytes/macrophages, mast cells contribute to the initiation of gouty inflammation. Ablation of mast cells in a murine model of MSU crystal-induced peritonitis significantly reduces neutrophil recruitment,[24] and a transient peak in mast cell number precedes neutrophil influx in the rat air-pouch model of MSU-induced inflammation.[148]

After initiation of the acute gout attack, a large number of neutrophils are recruited into the joint. Neutrophils are rare in healthy synovial fluid and their influx into the affected joint is a hallmark of acute gout. In the inflamed joint, MSU crystals trigger the degranulation of neutrophils after phagocytosis,[148–150] receptor-mediated activation[151] or by direct lysis of the cell membrane,[152] which mediates the symptoms of acute gout by releasing potent mediators of pain, tissue damage, and further inflammation including prostaglandin E2, reactive oxygen species, nitric oxide, leukotriene B4, S100A8, S100A9, IL-1 and IL-8.[26–28,153–155]

It is currently unknown whether the NK cell, another cellular mediator of innate immunity, also has a role in the inflammatory response to MSU crystals. However, several lines of evidence suggest that the involvement of NK cells is plausible. First, as outlined above, NK cells interact with monocytes/macrophages, the primary cell type involved in the initiation phase of gout. Second, NK cells in the joints of patients with inflammatory arthritis (including gout) show an expansion of the CD56^{bright} population, which can produce large amounts of both pro- and anti-inflammatory cytokines.[8,15,66] Therefore, CD56^{bright} NK cells could potentially have a role in either enhancing or resolving gouty inflammation by interacting with other innate immune cells. The documented contact-dependent reciprocal activation of monocytes and CD56^{bright} NK cells[15] indicate a positive feedback loop that could contribute to the amplification of the inflammatory response in acute gout. Alternately, NK cells could, in principle, be involved in the spontaneous resolution phase of gout, which is also mediated by cells of the innate immune system.[156] Specifically, inflammation is dampened by the clearance of neutrophils by monocytes/macrophages and release of TGF-β by differentiated macrophages.[156] NK cells are capable of expressing anti-inflammatory cytokines, such as IL-10 and TGF-β, and have also been shown to limit pro-inflammatory monocyte activity by killing highly active cells.[20,139] The potential anti-inflammatory effect of the expanded CD56^{bright} NK cell populations observed in inflammatory arthritis has not yet been analysed.

CONCLUSION

NK cells, particularly the CD56^{bright} subset, are capable of shaping innate immune responses because of their ability to migrate to sites of inflammation and produce large quantities of cytokines and chemokines. Interactions between NK cells and other innate immune cells such as monocytes and macrophages *in vitro* induce diverse outcomes, including activation, maturation, differentiation and death. Acute gout represents an inflammatory condition in which immune modulation by NK cells could potentially occur, as it is primarily orchestrated by cells of the innate immune response. Affected joints from patients with inflammatory arthritis have an enriched population of CD56^{bright} NK cells, and NK cells isolated from these joints interact with monocytes in a pattern of reciprocal activation. Monocytes and macrophages are critical in initiating and propagating the inflammatory response to MSU crystals. Further analysis into how NK cells might regulate monocyte/macrophage function is warranted and has the potential to identify a new modulatory role for NK cells in acute gouty inflammation.

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