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CD56^{bright} natural killer (NK) cells: an important NK cell subset

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Summary

Human natural killer (NK) cells can be subdivided into different populations based on the relative expression of the surface markers CD16 and CD56. The two major subsets are CD56^{bright} CD16$^{dim/-}$ and CD56^{dim} CD16^{+}, respectively. In this review, we will focus on the CD56^{bright} NK cell subset. These cells are numerically in the minority in peripheral blood but constitute the majority of NK cells in secondary lymphoid tissues. They are abundant cytokine producers but are only weakly cytotoxic before activation. Recent data suggest that under certain conditions, they have immunoregulatory properties, and that they are probably immediate precursors of CD56^{dim} NK cells. CD56^{bright} NK cell percentages are expanded or reduced in a certain number of diseases, but the significance of these variations is not yet clear.

Keywords: CD56^{bright}; immunoregulation; natural killer cells

Introduction

Natural killer (NK) cells have been the focus of interest of immunologists for almost two decades. The increasing knowledge of NK cell biology acquired throughout this period has led to a paradigm shift – for a long time NK cells were considered merely as relatively primitive killers but they are now seen not only as *bona fide* actors in innate immunity but also as important cells that shape and influence adaptive immune responses and are more and more being endorsed with an immunoregulatory role. However, NK cells are not a homogeneous cell population and several subtypes exist in both human and mouse.

In human peripheral blood, five NK cell subpopulations can be defined on the basis of the relative expression of the markers CD16 (or FcγRIIIA, low-affinity receptor for the Fc portion of immunoglobulin G) and CD56 (adhesion molecule mediating homotypic adhesion)[1–3]: (1) CD56^{bright} CD16^{-} (50–70% of CD56^{bright}), (2) CD56^{bright} CD16^{dim} (30–50% of CD56^{bright}), (3) CD56^{dim} CD16^{-}, (4) CD56^{dim} CD16^{bright}, and (5) CD56^{-} CD16^{bright}. In healthy individuals, populations (3) and (5) are numerically in the minority. Whereas the role of CD56^{dim} CD16^{-} cells is largely unknown, CD56^{-} CD16^{bright} NK cells are functional. They are often dramatically expanded in human immunodeficiency virus infection but are hyporesponsive under these conditions.[2] The CD56^{dim} CD16^{bright} NK cells represent at least 90% of all peripheral blood NK cells and are therefore the major circulating subset.[1,3] A maximum of 10% are CD56^{bright} NK cells.[1,3] The various subsets can easily be distinguished by flow cytometry as depicted in Fig. 1.

In this review, we will focus on the CD56^{bright} NK cell population because important and interesting discoveries regarding this subset have been made in recent years. We will mostly review the literature but also present some data obtained in our laboratory. Mouse NK cells are excluded from the discussion because they do not express CD56. However, on the basis of the differential expression of the surface markers CD11b and CD27, three mouse NK cell subpopulations with different functional properties have been described.[4] Recently, it has been suggested that mouse NK cells expressing the chemokine receptor CXCR3 might represent the murine equivalent to human CD56^{bright} cells.[5]

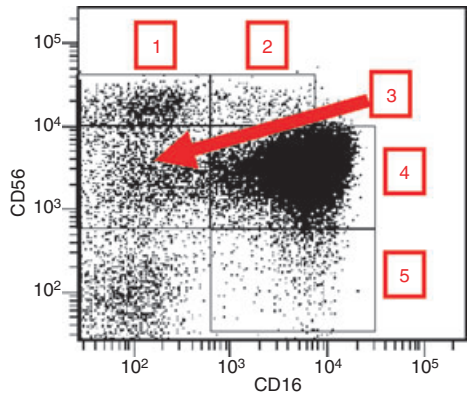

Figure 1. Natural killer (NK) cell subsets in human peripheral blood based on the relative expression of CD16 and CD56. Normal peripheral blood mononuclear cells (PBMC) were stained with anti-CD3, anti-CD14, anti-CD16, anti-CD19 and anti-CD56 antibodies conjugated to five different fluorochromes. A gate was set on CD3$^-$ CD19$^-$ cells (NK cells) and CD16 expression versus CD56 expression is shown. 1, CD56^{bright} CD16$^-$; 2, CD56^{bright} CD16^{dim}; 3, CD56^{dim} CD16$^-$; 4, CD56^{dim} CD16$^+$; 5, CD56$^-$ CD16$^+$.

CD56^{bright} NK cells in peripheral blood

Historically, the first description of different NK cell subsets was given by Nagler *et al.*[6] in 1989, and their data have been abundantly confirmed by other groups. Usually CD56^{bright} NK cells were compared with CD56^{dim} CD16^{bright} NK cells in terms of phenotype and functions, and later also regarding their differential homing capacities.

Phenotype

The inhibitory receptors killer cell immunoglobulin-like receptors (KIR) and immunoglobulin-like transcript 2 (ILT2) are absent from CD56^{bright} NK cells but are found on various (according to the receptors and the individuals) proportions of CD56^{dim} cells.[1,7] CD94/NKG2A, another major inhibitory receptor, is likewise expressed on a fraction of CD56^{dim} cells in contrast to its expression at a higher density on all CD56^{bright} NK cells.[1] CD94 is a chaperone molecule that can also associate with NKG2C which is an activating receptor. Both isoforms (CD94/NKG2A and CD94/NKG2C) recognize the non-classical human leucocyte antigen (HLA) class I molecule HLA-E, which presents peptides derived from signal sequences of classical HLA class I molecules.[1,3,8] Regarding the activating receptor NKp46, its density is usually highest on the CD56^{bright} population.[9] Only CD56^{bright} cells express the haematopoietic stem cell marker CD117 (c-kit) and the high-affinity receptor for interleukin-2 (IL-2) and proliferate in response to picomolar concentrations of this cytokine.[1] They also proliferate efficiently in response to IL-21.[10] Other cytokine receptors, such as IL-1 receptor I (IL1RI) and IL18R are likewise expressed at a higher level by this subset (Table 1).[1]

Table 1. Phenotypic comparison between CD56^{bright} and CD56^{dim} natural killer cells

	CD56^{bright}	CD56^{dim}
CD56	++	+
CD16	±	++
Inhibitory receptors		
KIR	−	+
ILT2	−	+
CD94/NKG2A	++	±
Activating receptors		
NKp46	++	+
CD117(c-kit)	++	−
Cytokine receptors		
IL2R$\alpha\beta\gamma$	+	−
IL2R$\beta\gamma$	++	+
IL1RI	++	+
IL18R	++	+
Chemokine receptors		
CCR7	++	−
CXCR3	++	±
CXCR1	−	++
CX3CR1	−	++
Adhesion molecules		
CD2	++	±
CD11c	++	±
CD44	++	+
CD49e	++	+
CD54	++	±
CD62L	++	±
CD11a	+	++
Other molecules		
CD57	−	+
CD160	−	++
CD55	++	+
CD59	++	+
HLA-DR	+	−

++, strong expression (bright); +, weak expression (dim); ±, expression only on a subpopulation; −, no expression.

The chemokine receptor repertoire is completely different between the two populations. CD56^{bright} cells are the only ones to express CCR7 and they bear CXCR3 at a much stronger density than CD56^{dim} NK cells.[1,11] In contrast, the latter cells express CXCR1 and CX_3CR1 exclusively.[1,11] Regarding the adhesion molecules, CD56^{bright} NK cells display a stronger expression of CD2, CD11c, CD44, CD49e, CD54 and CD62L, whereas CD56^{dim} NK cells express more CD11a (Table 1).[1] The consequence of these different repertoires of chemokine receptors and adhesion molecules are divergent migratory properties: the CD56^{bright} subset preferentially migrates to secondary lymphoid organs whereas the CD56^{dim} cells migrate to acute inflammatory sites.[1,11]

In contrast to CD56^{dim} cells, the CD56^{bright} subset lacks expression of CD57[12] and CD160,[13] but displays the complement regulatory proteins CD55 and CD59 at a higher level.[14] Also, the CD56^{bright} subset is HLA-DR^{+} (Table 1).[12]

The phenotypic differences between both subsets have been confirmed and extended by gene chip arrays and protein arrays.[15,16] Wendt *et al.*[16] have shown that resting NK cell populations differ in 473 transcripts, 176 being exclusively expressed in CD56^{dim} cells and 130 exclusively in CD56^{bright} cells.

Functions

The cytotoxic activity of CD56^{dim} NK cells is significantly higher than that of CD56^{bright} cells (the CD56^{bright} CD16^{-} population being the less cytotoxic)[1,6] and they contain much more perforin, granzymes and cytolytic granules.[7] They also form more conjugates with K562 target cells.[7] The high expression level of CD16 makes them efficient mediators of antibody-dependent cellular cytotoxicity, whereas CD56^{bright} CD16^{dim} NK cells perform antibody-dependent cellular cytotoxicity only weakly and CD56^{bright} CD16^{-} NK cells of course not at all.[1,6] Upon stimulation with cytokines such as IL-2 or IL-12, the cytotoxic activity of all NK cell subsets dramatically increases.[1,6]

Regarding cytokine production, the situation is inverted. Indeed, CD56^{bright} NK cells are the most efficient cytokine producers.[1] The major cytokines released are interferon-γ (IFN-γ) (NK cells are one of the most important sources of this cytokine), tumour necrosis factor-α, granulocyte–macrophage colony-stimulating factor, IL-10 and IL-13, depending on the precise conditions of stimulation (for example, the combination of IL-12 and IL-18 is the best to induce a strong production of IFN-γ, which is 20–30 times higher in CD56^{bright} than in CD56^{dim} NK cells).[17]

CD56^{bright} NK cells in secondary lymphoid organs

In the spleen, 7–50% of mononuclear cells are NK cells, mostly with a CD56^{dim} CD16^{+} phenotype.[18] They probably correspond to the same population in peripheral blood that is simply circulating through the red pulp.[18]

Among mononuclear cells in lymph nodes (LN), 1–5% are NK cells[18,19] whose subset distribution is a mirror image of the one found in peripheral blood. Indeed, 75 to > 95% are of the CD56^{bright} type.[18,19] These cells are localized in parafollicular T-cell zones of the LN.[19] Considering that LN contain 40% of all lymphocytes in the body (in contrast to 2% in peripheral blood), it appears that despite their low LN percentages, the biggest reservoir of NK cells is in the LN and not in blood and that there are many more CD56^{bright} than CD56^{dim} NK cells.[20] The vast majority of tonsil NK cells[18] are also CD56^{bright}.

Phenotype

Lymph node CD56^{bright} NK cells display a slightly different phenotype than their blood counterparts. They lack not only CD16 and KIR, but also CD8, CD62L, CCR7, the activating receptor NKp30 and HLA-DR. CD94/NKG2A and NKp46 are present only on a fraction of these cells.[18,20]

Tonsil CD56^{bright} NK cells share the phenotype of LN NK cells. However, in inflamed tonsils, they become activated and NKp44^{+} CD69^{+} HLA-DR^{+}.[18,20] Before the discovery of this subtype, NKp44 expression had only been observed *in vitro* on NK cells activated with IL-2.[21]

As LN NK cells are in contact with T cells[19] the effect of T-cell-derived IL-2 on these NK cells has been investigated. This cytokine upregulates or induces, respectively, the expression of CD16, KIR, NKp46 and NKp30 as well as of perforin, ending up with a phenotype close to that of peripheral blood CD56^{dim} CD16^{+} cells.[18]

Functions

The phenotype of *ex vivo* isolated NK cells from secondary lymphoid organs suggests the absence of cytotoxic activity, and this is indeed the case.[18] However, culture in IL-2 not only changes the phenotype (see above), but also induces an efficient cytotoxic activity.[18] In addition, NK cells from inflamed tonsils produce IFN-γ and 35% of them proliferate upon culture in IL-2.[18,20]

CD56^{bright} NK cells in the uterus

The endometrium contains a high number of NK cells that are almost exclusively CD56^{bright} CD16^{-}.[22] The density of expression of CD56 is even higher on these cells than on peripheral blood CD56^{bright} NK cells.[23] Accounting for 20% of lymphocytes in the proliferative endometrium, they increase to 50% in the secretory phase and to 70–80% in early pregnancy decidua.[22] A high percentage of these cells is proliferating, which suggests that local expansion could explain the dramatic increase in numbers. They play a role in implantation, angiogenesis and maintenance of pregnancy.[22,23]

Koopman *et al.*[23] have compared uterine NK cells with the two major peripheral blood NK cell subsets by using gene microarrays. The profiles reveal that the uterine NK cells are different from the peripheral blood NK cells, and that they are more different from them than the two major peripheral blood NK cells are different from each other. They particularly over-express some tetraspanins and integrins, the activating receptors NKG2C and NKG2E, KIR, galectin-1 and granzyme A. CD9 and the immunosuppressive molecule PP14 (glycodelin A) are exclusive to uterine NK cells. Although they contain cytotoxic granules and express KIR, they are only weakly cytolytic *ex vivo*.[23]

Interactions of CD56^{bright} NK cells with other cells of the immune system

Bidirectional interactions between NK cells and dendritic cells (DC) have been extensively investigated and reviewed. Regarding in particular CD56^{bright} CD16^{-} NK cells, Vitale *et al.*[24] have shown that these cells preferentially proliferate in coculture with immature DC and lipopolysaccharide and abundantly produce IFN-γ. *In vivo*, CD56^{bright} NK cells interact in LN with incoming DC from the periphery.[20]

In sites of peripheral inflammation, CD56^{bright} NK cells represent 40–60% of all NK cells and display an activated phenotype (CD69^{+}).[25] Upon stimulation by monokines (IL-12, IL-15, IL-18), they produce IFN-γ and increase significantly the percentage of tumour necrosis factor-α-producing monocytes. In this type of bidirectional interaction, a direct physical contact between NK cells and monocytes is required for a maximal effect.[25]

It is possible that CD56^{bright} NK cells also interact with T and B lymphocytes in a manner that is different from that of CD56^{dim} NK cells, but this has, to the best of our knowledge, not been investigated in detail.

Relationship of CD56^{bright} and CD56^{dim} NK cells

According to Caligiuri,[3] NK cell precursors leave the bone marrow, transit through peripheral blood and join the LN, where they differentiate into CD56^{bright} NK cells under the influence of cytokines produced by stromal cells and DC.

A question that has been debated for a long time is the precise nature of the relationship between the two major NK cell subsets, CD56^{bright} and CD56^{dim}. Are the CD56^{bright} NK cells precursors of CD56^{dim} cells, or are they both finally differentiated cell types with no direct relation and arising from two different haematopoietic precursor cells?

In favour of the former hypothesis, it has been proposed that the phenotypic and functional properties of both subsets rather define CD56^{bright} NK cells as immature precursors and CD56^{dim} NK cells as finally differentiated cells. Maturation would be characterized by the downregulation of CD56, the acquisition of CD16 and of KIR, and CD56^{bright} CD16^{dim} cells would be an intermediate stage between the most immature (CD56^{bright} CD16^{-}) and the most mature (CD56^{dim} CD16^{+}) cell types.[6,26]

However, as CD56^{bright} NK cells produce greater amounts of cytokines than CD56^{dim} NK cells, and possess a completely different repertoire of adhesion molecules and chemokine receptors leading to different migration properties,[1,11] the concept of two different terminally differentiated cell populations is likewise conceivable.

Three recent papers[27–29] have finally shown, quite convincingly, that CD56^{bright} NK cells are very likely precursor cells of the CD56^{dim} subset. Indeed, CD56^{dim} NK cells display shorter telomeres than CD56^{bright} NK cells from peripheral blood and LN, which implies that the latter are less mature than the former. In addition, purified CD56^{bright} CD16^{-} NK cells cultured in the presence of synovial or skin fibroblasts can differentiate into CD56^{dim} cells that have the characteristic phenotypic and functional features of peripheral blood CD56^{dim} NK cells.[27] A role for an interaction between CD56 and the fibroblast growth factor receptor-1 for this differentiation process has been demonstrated.[27] As an argument for the differentiation of CD56^{bright} NK cells into CD56^{dim} NK cells in LN *in vivo*, Romagnani *et al.*[28] show that efferent lymph and highly reactive LN contain a substantial proportion of CD56^{dim} KIR^{+} NK cells.

In contrast, Keskin *et al.*[30] demonstrate that upon culture in the presence of transforming growth factor-β, CD16^{+} NK cells convert into CD56^{superbright} CD16^{-} CD9^{+} CD103^{+} KIR^{+} NK cells. However, this phenotype corresponds to decidual NK cells and not to peripheral blood CD56^{bright} NK cells, these populations being very different from each other.[23] It could nevertheless be interesting to investigate if the transition from CD56^{dim} CD16^{+} cells into CD56^{bright} CD16^{-} NK cells is possible *in vitro*, although this would go against the current paradigm.

CD56^{bright} NK cell expansions and reductions in human pathology

In this field, several recent observations have been published. Some authors only investigate CD56^{bright} CD16^{-} NK cells, whereas others also include CD56^{bright} CD16^{dim} NK cells in their studies. We suggest that this point should be harmonized between different groups interested in the topic, and to follow the leader in the field, Michael A. Caligiuri[1], who always considers both subpopulations together as CD56^{bright} NK cells. Indeed, there is no obvious reason to ignore the CD56^{bright} CD16^{dim} subset.

Expansion of CD56^{bright} NK cells

In healthy donors, not more than 10% of all peripheral blood NK cells are usually CD56^{bright}. However, expansions above this low percentage have been described during reconstitution of the immune system after bone marrow transplantation, where the first lymphocytes to appear in blood are CD56^{bright} NK cells.[31] This population also increases in patients who are treated daily with a low dose of IL-2.[31]

Interestingly, there are increasing numbers of papers describing expansions of CD56^{bright} NK cells in different diseases, and the list is probably far from being finished.

Our group[32] has shown that in two cases of transporter associated with antigen processing (TAP) deficiency,

which is characterized biologically by a very low amount of surface expression of HLA class I molecules, and clinically by chronic respiratory infections, bronchiectasis and deep skin ulcers, CD56^{bright} NK cells represent 37% and 54%, respectively, of all peripheral blood NK cells. This was recently confirmed, although to a lesser extent, in a new case of TAP deficiency.[33] Interestingly, asymptomatic TAP-deficient patients have normal percentages of CD56^{bright} NK cells.[32] In the first study, we compared the TAP-deficient patients with a small series of individuals with vasculitis or with respiratory diseases of other origins. The percentage of CD56^{bright} NK cells was higher than 10% (12·60–25·52%) in approximately one-third of them.[32] These data suggest that the expansion of CD56^{bright} NK cells is in no way a hallmark of TAP deficiency, but can occur in several diseases of other origins.

In favour of this interpretation, Cac and Ballas[34] present the observation of a woman with recalcitrant and treatment-resistant periungual warts. Flow cytometry revealed that 13·30% of her lymphocytes (and not of her NK cells, which makes the expansion quite dramatic) were CD56^{bright} and only 0·83% of the lymphocytes were CD56^{dim}. Not surprisingly, the patient had a severe reduction in NK cell-mediated cytotoxicity. The warts almost disappeared and NK cell cytotoxicity was restored upon treatment with IFN-α, whereas the proportion of CD56^{bright} NK cells decreased. It is well known that IFN-α stimulates the cytotoxicity of NK cells, but maybe it also favours the maturation of NK cells towards the CD56^{dim} stage. This process was probably blocked before the introduction of IFN-α, but for completely unknown reasons.

An inverse situation is described by Saraste *et al.*[35]who treated a group of 11 multiple sclerosis patients with IFN-β and observed an expansion of CD56^{bright} NK cells with a concomitant decrease of CD56^{dim} cells after 12 months of treatment (14·7 ± 2·5% of all NK cells were CD56^{bright}).

In another series of 22 multiple sclerosis patients[36] a combined treatment with IFN-β and daclizumab was administered. Daclizumab is a humanized monoclonal antibody directed against the IL-2 receptor α chain (CD25) that was very efficient in stabilizing multiple sclerosis in clinical trials. Also in this case, an expansion of CD56^{bright} NK cells, which correlated with a reduction in brain inflammation, was observed during treatment. The mechanism of action most likely corresponds to an upregulation of CD122 (β chain of the IL-2 receptor) with a better response to endogenous IL-2 as a consequence. *In vitro*, NK cells from the patients inhibited T-cell proliferation in a contact-dependent manner and are therefore considered as regulatory NK cells by the authors.

A study using daclizumab in five patients with active uveitis[37]confirmed its therapeutic efficiency on the one hand and the selective expansion of CD56^{bright} NK cells over time (it ranged from fourfold to 20-fold) on the other hand. The CD56^{bright} NK cells produced high amounts of the immunosuppressive cytokine IL-10, and this molecule might be at the origin of the beneficial effect by downregulating the autoimmune response. It is tempting to speculate that CD56^{bright}-mediated secretion of IL-10 explains the therapeutic effects in the three studies presented. Likewise, an efficient immune response against human papillomavirus-induced periungual warts in the case described by Cac and Ballas[34] might have been precluded because of the IL-10 production by the abundant CD56^{bright} NK cells. In this context, the concept of regulatory NK cells ('NKreg') is clearly emerging in the literature[22,38] and deserves further investigation to check, for example, if the entire CD56^{bright} population or only a subset have immunoregulatory properties.

In a case report of a human herpes virus type 6-associated acute necrotizing encephalopathy in a young child, Kubo *et al.*[39] likewise noticed a dramatic expansion of CD56^{bright} NK cells during the convalescent phase. Here, the authors speculate, without any demonstration, that the CD56^{bright} NK cells produce high levels of inflammatory cytokines (indeed found in the serum of the patient) and that a high percentage of these cells is a risk factor for the development of encephalitis during infection with human herpes virus type 6.

A patient with X-linked severe combined immunodeficiency with Omenn syndrome-like manifestations[40] had increased circulating NK cells (59·50% of lymphocytes), half of them (28·50%) being CD56^{bright} CD16^{-}. The skin, displaying marked thickening and severe erythema, was infiltrated predominantly by CD56^{bright} CD16^{-} NK cells expressing high levels of messenger RNA for not only inflammatory cytokines but also for IL-10.

In a cohort of female patients chronically infected with hepatitis C virus (HCV)[41] compared with HCV resolvers and normal uninfected controls, total NK cell percentages among lymphocytes were reduced in the first group whereas the proportion of CD56^{bright} cells among total NK cells was increased. These cells produced more IFN-γ than CD56^{bright} NK cells from the other two groups, and overall NK cell cytotoxicity was not impaired.

Exactly the same picture, i.e. reduction of NK cell numbers but increased percentage of CD56^{bright} NK cells, was found among individuals with a positive tuberculin skin test (TST^{+}) compared with patients with overt tuberculosis and normal controls.[42]

The significance of the observations from these two studies is currently unclear. In the case of HCV infection, the authors[41] speculate that CD56^{bright} NK cells might contribute to T-cell polarization and liver damage, and that their expansion might be the result of a decreased rate of differentiation towards CD56^{dim} cells. The TST^{+} subjects might be protected from active tuberculosis by

the CD56^{bright} NK cells secreting high amounts of IFN-γ.[42]

Schepis *et al.*[43] describe an increased proportion of CD56^{bright} NK cells in systemic lupus erythematosus regardless of disease activity. However, the authors do not consider nor do they investigate CD56^{bright} CD16^{dim} cells, their gating strategy does not exclude CD56^{dim} CD16^{-} cells, and finally, as most patients have one or more treatments at the time of blood drawing, the potential role of these treatments in the CD56^{bright} NK cell expansion is not considered. Nevertheless, systemic lupus erythematosus might be added to the growing list of diseases characterized by an increased proportion of CD56^{bright} NK cells, although this topic deserves further investigation.

Although they unfortunately do not discriminate between CD56^{bright} and CD56^{dim} NK cells, three papers[44–46] describe a dramatic expansion of NKG2C^{+} NK cells in human infections caused by human immunodeficiency virus type 1 and cytomegalovirus. As a subset of CD56^{bright} NK cells expresses NKG2C,[47] this discrimination would be very interesting and important to make in future investigations.

Whereas the studies presented so far all deal with peripheral blood NK cells, others describe the presence of CD56^{bright} NK cells in different tissues during disease states. CD56^{bright} CD16^{-} KIR^{-} NK cells are found, among other cell types, within acute psoriatric plaques and abundantly produce IFN-γ upon stimulation.[48] In rheumatoid arthritis, the proportions of different peripheral blood NK cell subsets are the same as in healthy donors, but the synovial fluid of the patients almost exclusively contains CD56^{bright} KIR^{-} NK cells.[49] Likewise in sarcoidosis,[50] no difference is observed between patients and normal controls in peripheral blood, whereas the former have more CD56^{bright} NK cells in their bronchoalveolar lavage fluid.

Reduction of CD56^{bright} NK cells

Interestingly, several recent observations show that in some diseases, the percentage of CD56^{bright} NK cells is reduced. In patients with coronary heart disease,[51] overall NK cell numbers are diminished as is the cytotoxic activity, and in addition, there is a tendency towards lower percentages of CD56^{bright} NK cells in the patients compared with normal controls. The rationale of this study was the fact that infections are considered to be a risk factor for coronary heart disease and that NK cells participate in immune responses against viruses and bacteria.

By analysing a small series of patients with allergic rhinitis and/or asthma, Scordamaglia *et al.*[52] found a significantly reduced percentage of CD56^{bright} NK cells compared with non-allergic individuals. The consequences are a weak IFN-γ production and impaired interactions with DC, so that in allergic diseases, NK cells might be unable to sufficiently shape adaptive immunity in the T helper type 1 direction. All these data will have to be confirmed by larger series but they provide interesting indications.

In juvenile rheumatoid arthritis with systemic onset, not only is the NK cell cytotoxic activity strongly reduced, but in some patients, the total absence of CD56^{bright} NK cells has been described.[53] The same phenomenon had previously been found in patients with macrophage activation syndrome and haemophagocytic lymphohistiocytosis. The authors suggest, without demonstrating it, that the CD56^{bright} NK cells have all been recruited to the sites of inflammation. It would be very interesting to check if in these patients, CD56^{bright} NK cells are found in the LN or in the synovium for example. If not, one would have to ask the question how CD56^{dim} NK cells can arise in the absence of CD56^{bright} precursors.

Conclusion

CD56^{bright} NK cells are currently extensively investigated and are no longer considered as just a minor subpopulation among total NK cells. As a result of their production of different cytokines, they might be important in early immune responses and in the shaping of the adaptive response (IFN-γ) as well as playing a role of regulatory NK cells (IL-10). This last point clearly deserves further studies.

Another interesting and emerging concept is the observation of increases or reductions, respectively, in the percentages of CD56^{bright} NK cells in various diseases. Why are these cells expanded in several clinical conditions? What are the mechanisms leading to the expansion? One might suppose that CD56^{dim} NK cells have a high turnover under these conditions and have to be replaced, and consequently their precursor cells (CD56^{bright}) are released in high numbers from the bone marrow and/or the LN. On the other hand, CD56^{bright} NK cells and their cytokine production might be important on their own in certain diseases and they would therefore selectively expand. Are these expansions a consequence of or a predisposing factor of the disease? Are they beneficial or deleterious for the host? The same questions of course also arise regarding the reductions or the absence of CD56^{bright} NK cells.

Rapid progress in this field can be expected, and soon we will know much more about the true relevance of the CD56^{bright} NK cell population in human health and disease.

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