REVIEW ARTICLE

Natural Killer (NK) Cells from Killers to Regulators: Distinct Features Between Peripheral Blood and Decidual NK Cells

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Natural killer (NK) cells are a key component of innate immunity, particularly crucial during the early phase of immune responses against certain viruses, parasites, and microbial pathogens. The role of NK cell during pregnancy has been vividly discussed over the past years and it is now becoming increasingly clear that NK cells control pregnancy maintenance at several levels. In normal pregnancy, it appears that they provide benefit by properly secreting cytokines, chemokines and angiogenic factors rather than functioning as cytotoxic effector cells. However, as they are endowed with all the cytolytic weapons, they promptly become capable of attacking fetal and maternal tissues during infection and inflammation.

NK cells: general features

Natural killer (NK) cells are a key component of innate immunity and play a crucial role in the early phase of immune responses against certain viruses, parasites, and microbial pathogens. They represent a highly specialized subpopulation of lymphocytes which mediate cellular cytotoxicity and produce chemokines and cytokines such as interferon-γ (IFN-γ) and tumor necrosis factor-alpha (TNF-α) upon target cell recognition or stimulation by pro-inflammatory cytokines. NK cells recognize normal cells and abnormal cells (such as virus-infected or tumor cells) by using a repertoire of cell surface receptors that control their activation, proliferation, and effector functions.[1,2]

Natural killer cells represent about 5–20% of circulating peripheral blood lymphocytes, and are also resident in several lymphoid and non-lymphoid organs, such as the spleen, tonsils, lymph nodes, liver, lungs, and intestine.[3] Recently, a thymic subset of NK cells that bear molecular markers and functional capabilities distinct from most peripheral NK cells and are exported from thymus into the secondary lymphoid organs, has been described, thus suggesting the existence of pathway of NK cell development in the thymus:[4] notably, NK cells are the predominant leukocytes found in the decidual tissues, and their number in the uterus increases drastically in the late secretory phase during the menstrual cycle and early pregnancy.[5,6]

Natural killer cells rapidly accumulate in the parenchymas of several organs during viral infections, tumor growth and invasion, or inflammation, where they actively take part in the elimination of injured target cells or in the activation and recruitment of other immune cells by secreting several cytokines and chemokines.[7,8] Moreover, NK cells in

the secondary lymphoid organs and in damaged tissues can establish an intimate dialogue with dendritic cells (DC), thus playing a crucial role in the regulation of both innate and adaptive immunity.[9]

Different sophisticated recognition strategies are used by NK cells involving both activating and inhibitory receptors.[2] These include direct recognition of pathogen-derived molecules mediated by activating receptors or Toll-like receptors (TLR); recognition of self proteins whose expression is up-regulated on 'stressed' or damaged cells and which is mediated by the interaction with activating receptors, namely NKG2D; recognition by the inhibitory receptors of specific MHC class I molecules whose levels are frequently down-modulated in transformed or virus-infected cells, and thus become more susceptible to NK cell-mediated lysis.

To monitor MHC class I expression, NK cells utilize a number of receptors that specifically recognize groups of self classical and non-classical MHC class I alleles.[2]

In humans, the inhibitory receptors capable of recognizing MHC class I molecules belong to two distinct groups: the killer cell immunoglobulin-like receptor (KIRs) family that comprises receptors for human leukocyte antigen (HLA)-A, -B, -C alleles, and the C-type lectin receptors, i.e. CD94/NKG2A that binds to the widely expressed non-classical HLA-class I molecule, HLA-E. Both receptor families include an activating counterpart with similar specificity, but with different ligand affinity. The functional role of the MHC I activating receptors and the identity of their ligands are still obscure. All these receptors are oligoclonally distributed on the different NK cell subsets, but most of NK cells express at least one self MHC class I inhibitory receptor that when engaged by the specific ligand blocks NK cell activation by inhibiting the propagation of the activating signal. Recent evidence demonstrates the existence of some NK cells which do not express receptors for self MHC class I, thus raising the question of how these cells are prevented from attacking their host. Several mechanisms that lead to self tolerance of NK cells have been proposed and it is presently a matter of large debate.[10,11] Therefore, NK cell functions are the result of concomitant engagement of various activating and inhibitory receptors by the particular set of ligands expressed by target cells and in most instances the inhibitory signals over-ride the triggering ones.[2]

However, the induction of ligands for the activating receptors on stressed or injured target cells, such as the MHC class I-related A and B proteins (MICA and MICB) or the members of a family of proteins named UL16-binding proteins (ULBPs) leads to engagement of NKG2D activating receptor, which transmits signals that are predominant over the inhibitory ones, and thus NK cells are activated to kill these target cells.[12] The NKG2D ligands are expressed on the surface of tumor cells of different histotypes, infected cells, and are induced also following DNA damage.[13] Recently, we provided evidence that NKG2D ligands are also expressed on T cells proliferating in response to antigen stimulation.[14]

As for inhibitory receptors, NK cells express different activating receptors, which are coupled to different early signaling intermediates.

The best studied activating receptor is the low-affinity Fc-receptor γ IIIA (CD16) that mediates the antibody-dependent cellular cytotoxicity.[1] Other activating receptors, namely NKp46, NKp44, and NKp30, are Ig-like molecules and belong to the natural cytotoxicity receptor family.[15] At present, controversial are the evidences available on the nature of NKp46 and NKp44 ligands.

Natural killer cells also express a number of receptors acting as activating or co-stimulatory molecules such as CD2, CD244 (2B4), NKp80, β1 and β2 integrins and DNAM-1 (CD226).[16] DNAM-1 is associated with the β2 integrin LFA-1 and binds to the poliovirus receptor (PVR, CD155) and to Nectin-2 (CD112), two members of the Nectin family regulating cell–cell interaction and leukocyte extravasation.[15,16] Finally, NK cells also can express receptors for microbial products belonging to TLR family, such as TLR-3, TLR-7, TLR-9.

All these receptors are not unique to the NK cells in that they are also expressed by cells of other hematopoietic lineages such as T cells or myeloid cells. In addition, their expression on NK cells is highly regulated during NK cell differentiation and activation, and some of them are expressed only on distinct NK cell subsets.

Based on the receptor repertoire and surface receptor levels, phenotypically distinct NK cell populations have been identified; it has been suggested that they represent specialized subsets mediating different functions and showing distinct migratory properties.[17] At least two major subsets of NK cells have been described in human peripheral blood: the

$CD56^{low}CD16^{high}$ subset that represents the majority (about 90%) of NK cells and the $CD56^{high}CD16^{low}$ subset that comprises about 10% of NK cells. The $CD56^{high}CD16^{low}$ NK cell subset is the primary source of the immunoregulatory cytokines produced by NK cells, whereas the $CD56^{low}CD16^{high}$ subset is the principal cytotoxic NK cell population.

It is still a matter of debate whether the different NK cell populations represent functionally distinct subsets of mature NK cells, or whether the $CD56^{high}$ NK cells are terminally differentiated cells indistinguishable from mature NK cells recently activated by cytokines.[17,18]

NK cell regulation of T-cell-mediated responses through the production of cytokines and chemokines

Natural killer cells contribute to maintain the homeostasis of the immune system and regulate adaptive immune responses through production of cytokines and chemokines. During microbial[19] and protozoal[20] infection, NK cells represent the early major source of IFN-γ that is critical for T helper 1 (Th1) polarization. In addition, it has recently been shown that mature DC and some adjuvants can promote the recruitment to the draining lymph nodes of NK cells that provide an early source of IFN-γ necessary for Th1 polarization.[21] Distinct subsets of human NK cells can produce type 1 (IFN-γ and TNF-α) and type 2 (IL-5, IL-13, IL-10) cytokines.[17,18,22] Beside IL-10, NK cells can also produce transforming growth factor-beta (TGF-β).[23]

Natural killer cells do not only affect the nature of T-cell-mediated immune responses by secreting different cytokines but also control the recruitment of specific T-cell subsets through the release of a variety of chemokines. During viral and bacterial infections, NK cells coordinately produce IFN-γ and a number of chemokines such as MIP-1α, MIP-1β, RANTES, and lymphotactin that are important to attract and activate other inflammatory cells.[24]

NK cell–DC cross talk

Increasing evidences show that NK cells and DC can be reciprocally activated during an immune response.[9] NK cells are directly involved in controlling DC maturation, a crucial step in the induction of adaptive immune responses. Several *'in vitro'* experiments have demonstrated that IL-2-activated human NK cells can induce DC maturation through IFN-γ production through a process dependent on cell-to-cell contact and TNF-α. Further, the interaction of immature DC with IL-2 activated NK cells can result in either maturation or cell death depending on the NK–DC ratio used in the co-culture system, suggesting that NK cells can contribute to eliminate immature DC from inflamed tissues. Studies aimed at identifying the receptors involved in the NK-cell-mediated cytotoxicity of both immature and mature DC indicate an important role of NKp30 and DNAM-1/nectin-2 receptor pair. The *'in vivo'* relevance of DC activation by NK cells has been described during MCMV infection, skin graft and tumor rejection.[25,26] In turn, mature DC also stimulate NK cell effector functions and proliferation, through cell-to-cell contact and production of several cytokines such as IL-12, IL-15, IL-18 and IFN-α/β.[27,28]

At present, the sites where the NK cell interaction with different DC populations might take place are still unknown.[29] Evidence indicate that following MCMV infection, it can occur in the liver.[25] On the other hand, recent reports have revealed that human NK cells are abundant in secondary lymphoid organs[30] providing another possible location in which DC–NK cell interactions might occur during an immune response.

Expression of co-stimulatory ligands on activated NK cells: positive regulation of T-cell-mediated responses

Much evidence shows that NK cells can shape T-cell-mediated adaptive immune responses by indirect mechanisms involving the secretion of cytokines or chemokines, and DC maturation/activation. However, more recent studies suggest the possibility that activated NK cells also communicate with T cells by direct cognate cell-to-cell interaction. *'In vitro'* activated human NK cells express several ligands for T-cell co-stimulatory molecules, such as CD86, CD80, CD70, and OX40L.[31,32] Co-stimulatory molecules are observed not only *'in vitro'* but more importantly *'in vivo'* on human NK cells from inflamed tonsils or cytomegalovirus-infected uterine decidua.[32] These co-stimulatory molecules are functional relevant as activated NK cells can co-stimulate TCR-induced proliferation and cytokine production of autologous $CD4^+$ T cells in a manner dependent on OX40–OX40L[31] and CD28–B7 interactions.[31,32] Several studies

indicate that direct interaction between NK and T cells can also involve other co-stimulatory receptor pairs including CD244 (2B4)-CD48.[33] A functional interaction between NK and T cells promoting T-cell immune responses has been described also *'in vivo'*. NK cells have been found to promote the development of anti-tumor $CD4^+$ T-cell memory-mediated immune response without the requirement of conventional type-1 cytokines, and to contribute to the alloresponse against solid organs through functional interactions with T cells.[34–36]

Similar to the NK cell–DC interaction, it is still undefined where NK and T cells might meet. It is conceivable that their interaction might occur in both the peripheral tissues and secondary lymphoid organs. As regards, NK and T cells they have been concomitantly found in the cardiac allograft vasculopathy lesions [36] and in the liver during MCMV infection.[25]

Thus, during the course of an immune response NK cells are activated by inflammatory cytokines and/or by recognition of abnormal or damaged cells (virus-infected cells, tumor cells or allogeneic cells). NK cell activation results in the induction of different ligands for T-cell co-stimulatory molecules and promotion of T-cell responses. NK cells may provide additional signals that could promote T-cell priming, survival and/or effector functions (Fig. 1a).

NK cell-mediated down-regulation of T-cell responses

Different reports suggest that NK cells have the ability to regulate T-cell responses negatively.[37] Moreover, studies in animal models have suggested a regulatory role of NK cells in the initiation and progress of autoimmune disorders such as the experimental autoimmune encephalomyelitis (EAE).[38–40] The inhibitory role of NK cells in rodent EAE has been strengthened by the finding that NK cells inhibit T-cell proliferation and cytokine production in response to myelin basic protein by a cell-to-cell contact dependent mechanism.[40] Similarly, in an *'in vivo'* mouse model of colitis, NK cells were found to inhibit $CD4^+$ effector T cells by a mechanism dependent on perforin, suggesting that NK cells can directly lyse T cells or some other intermediate immune cells such as DC.[41] In accordance with the protective role of NK cells against autoimmune

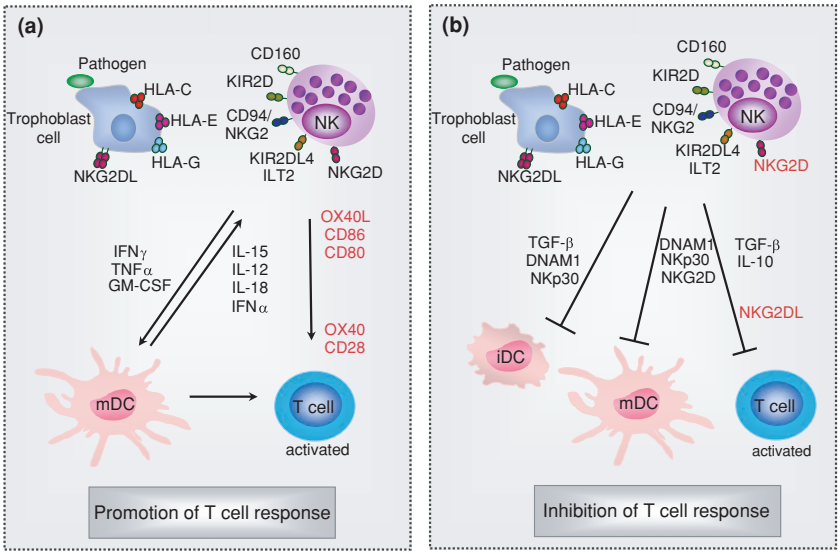

Fig. 1 Natural killer (NK) cell-mediated regulation of T-cell responses. A number of inhibitory and activating receptors are involved in uterine NK cell recognition of trophoblast cells during normal or pathological pregnancy. (a) Activated NK cells can promote T-cell response by inducing maturation of dendritic cells (DCs) through the secretion of several cytokines (granulocyte-macrophage colony-stimulating factor, tumor necrosis factor and IFN-γ). In turn, mature DCs produce different cytokines (IFN-α/β, interleukin IL-12, IL-18, IL-15) capable of enhancing NK cell proliferation and functions. In addition, activated NK cells expressing the ligands for several co-stimulatory receptors can directly co-stimulate antigen-induced T-cell proliferation and effector functions. (b) Activated NK cells can down-modulate T-cell responses by secretion of transforming growth factor-β and IL-10 which can block DC maturation and/or directly inhibit T-cell proliferation and effector functions. Activated NK cells kill immature DCs and mature DCs as well as activated T cells involving different NK cell-activating receptors (NKG2D, NKp30, DNAM-1).

diseases shown in the murine studies, decreased NK cell activity and numbers are found in the peripheral blood of patients with multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and type I diabetes.[38]

Natural killer cells can attenuate T-cell adaptive immune response by several mechanisms including killing of DC and/or activated T cells[14,42,43] and secretion of inhibitory cytokines.[22,23]

With regard to the NK cell-mediated killing of T cells, it has been shown that IL-2 activated mouse NK cells recognize and lyse syngeneic T-cell blasts in a perforin-dependent manner through the NK activating receptor NKG2D.[43] Expression of NKG2D ligands such as MICA, ULBP-1,ULBP-2 and ULBP-3 on T cells has been reported also in humans. MICA is induced on the surface of T cells following anti-CD3 stimulation [44,45] and the presence of ULBP-1,2-3 transcripts on $CD3^+$ activated $CD8^+$ T cells cultured with IL-7 and IL-15 has been reported.[45] Interestingly, our recent studies indicate that activation of human T cells by alloantigen or superantigen is sufficient to induce surface expression of MICA, ULBP-1,2 and 3 on $CD4^+$ and $CD8^+$ T lymphocytes and these cells become susceptible to autologous NK lysis via NKG2D/NKG2DLs interaction and granule exocytosis.[14]

Thus, NK cells can contribute to the suppression of the induction of T-cell responses and to the maintenance of T-lymphocyte homeostasis by direct elimination of antigen presenting cells and activated T cells, and/or by release of inhibitory cytokines such as TGF-β and IL-10 which inhibit DC maturation or T-cell activation and functions (Fig. 1b).

Uterine NK cells

Natural killer cells are the predominant lymphocyte population present in the uterus.[5,6] Their number increases drastically in the late secretory phase during the menstrual cycle and early pregnancy of human, and at implantation site in rodents. They accumulate as single cells or aggregates around endometrial glands and vessels playing a crucial role for the normal development of placenta and/or its vasculature.[46]

Phenotypic and functional analysis of first trimester human decidual CD56high $CD16^-$ NK cells indicate that uterine NK (uNK) cells are a unique population distinct from the blood counterpart, and recent findings have demonstrated that they exhibit a unique transcriptional profile.[47] With regard to the molecules that can be potentially involved in the control of NK cell accumulation, they exhibit a distinct repertoire of adhesion molecules and chemokine receptors when compared with the peripheral blood counterpart.[48] In particular, they express high levels of αEβ7, α1β1, αXβ2, αDβ2, whereas do not express α6β1 laminin receptor. In addition, uterine NK cells also display the β5 integrin subunit and selectively express high levels of tetraspanic 5, CD151, and CD9 tetraspanins that are constitutively associated with integrins and modulate integrin function.

The lineage and origin of uterine NK cells are presently unknown. They may arise by *in utero* proliferation and differentiation of NK cell progenitors. Proliferation of uNK in late-secretory endometrium and decidua has been demonstrated, and is under the control of the sex steroid hormones estrogen and progesterone. Proliferation and differentiation of uterine NK cells can also be induced by IL-15, which is detectable in the decidual microenvironment.[49,50] Recently it has been reported that TGF-β released by decidual stromal promotes the conversion of peripheral blood $CD16^+$ NK cells in $CD16^-$ NK cells suggesting that TGF-β can play a major role in the control of uterine NK cell differentiation.[51]

Alternatively, uNK cells may be recruited from $CD56^+$ cells in the blood. With regard to chemokine receptors, first trimester human decidual NK cells express higher levels of CCR1, CCR3, CXCR3, CXCR2, and lower levels of CCR7, CXCR4, CX3CR1 when compared with $CD56^{high}CD16^{low}$ peripheral blood NK cells (A. Gismondi et al., unpublished observations).[52–55] This receptor profile is consistent with evidence showing the ability of uterine NK cells to migrate in response to CXCL9, CXCL10, CXCL12 and CCL3[52–54] that have shown to be produced by the trophoblast, the endometrial cells or by the decidual vessels.[56]

Altogether, the phenotypic differences between uNK cells and those in the blood suggest that CD56 NK cells homing from the blood, independently from their stage of maturation, must undergo tissue-specific differentiation in the uterine microenvironment.

The function(s) exerted by uNK cells that are critical for a successful pregnancy have not been yet fully defined.

Uterine NK cells are poorly cytotoxic when compared with the peripheral blood counterpart, although they express a number of activating

receptors including NKG2D, CD244, NKp30, NKp44, NKp46, and are endowed with an intact cytolytic machinery, namely perforin, and granzymes[57]. The failure of uNK cells to kill trophoblast cells has been attributed to their surface expression of inhibitory receptors such as CD94/NKG2A, ILT-2 and KIRs recognizing the respective HLA-G, HLA-E and HLA-C ligands on the extravillous trophoblast. Moreover, the resistance of trophoblast cells to uNK cell lysis has been also ascribed to the expression of an inhibitor of Fas-mediated apoptosis by first trimester trophoblast. More recently, however, it has been described that uNK cells exhibit a defective secretory pathway as they fail to polarize the microtubule-organizing center and the cytolytic granules toward the synapse.[58]

Although uNK cells are poor killers, they are capable of secreting a wide array of cytokines and chemokines without stimulation, suggesting that they have undergone activation in the decidua.

Through the release of cytokines and chemokines, uNK cells can control extravillous trophoblast invasion, as well the recruitment and functions of other immune cells such as DC and T lymphocytes.[48,59] Recent reports demonstrate an intimate contact between NK cells and DC-SIGN+ immature DC in the human decidua of first trimester pregnancy, strongly suggesting the existence in this tissue of an interplay between these two dominant leukocytes.[60] A possible scenario of NK-DC cross-talk has been suggested in which NK cells through the release of GM-CSF and IL-10, contribute to the maintenance of a DC tolerogenic phenotype.

The close encirclement of spiral arteries by uNK cells together with their ability to produce angiogenic factors such as VEGF, PGF, and angiopoietin 2 suggest that they can play a major role by influencing mucosal vascularization and placental development.[59,61,62]

Recent evidence indicates that particular combinations of maternal KIR (KIRAA) and fetal MHC class I (HLA-C2 group of alleles) can be associated with an increased risk of pre-eclampsia, thus suggesting that interaction between maternal KIR present on decidual NK cells and paternal derived HLA-C alleles expressed by extravillous cytotrophoblast has important functional consequences in term of regulation of placental development and vascular remodelling.[63] From this report, it was also predicted that the risk of pre-eclampsia would be higher among couples consisting of Japanese women in whom the incidence of KIRAA genotype is 60% and a Caucasian father as the frequency of HLA-C2 group is 32% in this population, rather than a Japanese father being 9% the HLA-C2 group frequency in this population. However, a report on the incidence of pre-emclampsia among couples consisting of Japanese women and Caucasian men using a relative small number of samples did not support this prediction,[64] suggesting that a large cohort of couples should be studied to test this hypothesis.

Conclusions

The importance of NK cells in the control of pregnancy at several levels is becoming increasingly clear. In normal pregnancy, it appears that they provide benefit by properly secreting cytokines, chemokines and angiogenic factors rather than functioning as cytotoxic effector cells. However, as they are endowed with all the cytolytic weapons, they promptly become capable of attacking fetal and maternal tissues during infection and inflammation.

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