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REVIEW

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The yin-yang of the interaction between myelomonocytic cells and NK cells

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Abstract

NK cells are innate lymphoid cells, which play a key role in the immune response to cancer and pathogens and participate in the shaping of adaptive immunity. NK cells engage in a complex bidirectional interaction with myelomonocytic cells. In particular, macrophages, dendritic cells and neutrophils promote differentiation and effector function of NK cells and, on the other hand, myelomonocytic cells express triggers of checkpoint blockade (eg PD-L1) and other immunosuppressive molecules, which negatively regulate NK cell function. In addition, NK cells express high levels of IL-1R8, which acts as a checkpoint for IL-18 driven differentiation and activation of NK cells. Evidence suggests that targeting the myeloid cell-NK cell crosstalk unleashes effective anti-tumour and anti-viral resistance.

1 | INTRODUCTION

Natural killer cells (NK) are innate lymphoid cells that play a key role in the immune responses against cancer and pathogens.[1,2] NK cell activation depends on a delicate balance between activating and inhibitory signals and the integration of these pathways may prevent NK self-reactivity and governs NK cell activation in the presence of cells in "distress".[3,4] NK cells, once activated, can be actively cytotoxic through the release of perforin and granzymes and can secrete cytokines, such as IFNγ, thus participating in the shaping of the adaptive immune responses.[4-8] NK cell effector functions also include antibody-dependent cell cytotoxicity (ADCC): NK cells recognize antibody-coated

target cells through the FcγRIIIA (CD16), which is coupled to CD3ζ and FcRγ transducing chains bearing the ITAM (immunoreceptor tyrosine-based activation motif) domains.[3,9] NK cells recognize damaged, stressed, infected or tumour cells, which upregulate or express de novo ligands interacting with activating NK cell receptors. Stress-induced ligands on host cells, such as human ULBP and MIC or mouse RAE1, H60 and MULT1 molecules can interact with the activating receptor NKG2D on NK cells.[10] Other ligands of activating receptors are viral encoded non-self ligands, which include cytomegalovirus-encoded m157, directly recognized by Ly49H in the mouse, and TLR ligands, even though the direct role of TLRs in NK cells remains an unsettled issue.[11-15] The natural cytotoxicity receptors (NCR), such as NKp46/NCR1, NKp44/NCR2 and NKp30/NCR3, which are linked to ITAM-bearing CD3ζ, FcRγ or DAP12, are other potent activating receptors, playing a major role in tumour/leukaemia cell lysis. NKp46 was reported to interact with influenza- and parainfluenza-derived hemagglutinins.[16] NCR also interact with soluble ligands with either agonist or antagonist activity. For example, PDGF-DD and Nidogen-1 bind to NKp44 inducing NK cell activation and inhibition, respectively.[17,18] Finally, a role for other activating receptors such as DNAM-1 belonging to the nectin family and 2B4 belonging to the SLAM family have been also described.[4]

NK cell inhibitory receptors prevent auto-reactivity while allowing recognition and killing of stressed target cells. NK cells express several MHC class I-specific inhibitory receptors that include the lectin-like Ly49 dimers in the mouse, the killer cell immunoglobulin-like receptors (KIRs) in humans and the CD94-NKG2A heterodimers in both species, all sharing the intra-cytoplasmic inhibitory ITIMs (immunoreceptor tyrosine-based inhibition motifs) domains.[19-21] Other NK cell inhibitory receptors act in a MHC class I independent manner.[21-23] NK cells can sense the lack of MHC class I occurring in virally infected or tumour cells and this process is called the "missing self" recognition.[24,25] Thus, healthy cells that express MHC class I molecules and low levels of stress-induced molecules are protected from NK cell killing, whereas cells "in distress" that upregulate stress-induced ligands and downregulate MHC class I molecules are recognized and killed.[23,26,27] The acquisition of NK cell tolerance to self depends on the expression of MHC class I specific-inhibitory receptors and on the "education" or "licensing" system. NK cell education occurs during NK cell development and leads to the prevention of auto-reactivity, ensuring the generation of self-tolerant killer cells.[28-30] As NK cell receptors do not undergo somatic recombination, their potential for auto-reactivity is due to the fact that the expression pattern of MHC class I receptors is largely random and is controlled by the education process. Some NK cells lack inhibitory receptors that recognize MHC class I, and/or express activating receptors that recognize self ligands, including MHC molecules.[20] During the education process, NK cells that lack self MHC-specific inhibitory receptors become hyporesponsive. For instance, in mice or humans that lack MHC class I molecules, NK cells fail to kill MHC class-I deficient autologous cells and display reduced responses to other stimulations.[31-33] NK cells that express receptors specific for MHC are properly functional, as they are responsive to activating signals, but still tolerant to self cells, because of the interaction between inhibitory receptors and their MHC ligands.[34,35] The intensity and quality of NK cell response reflect the number of self-MHC inhibitory receptors as well as of activating receptors expressed by NK cells and their ligands on target cells.

Finally, the functional activation of NK cells is modulated through the crosstalk with other leucocytes. Thanks to the broad repertoire of pattern recognition molecules, phagocytes have the potential to recognize a variety of microbial moieties of bacterial, fungal, viral and parasite origin, as well as damage-associated molecular patterns. They can sense infections and tissue damage, thus activating innate immune responses and orienting adaptive immune responses. Innate immune activation leads to release of cytokines and other soluble mediators, and to induction of cell-to-cell contacts among leucocytes and other cell types, such as endothelial cells. NK cell responses are affected by the cytokine microenvironment and the interaction with other immune cells, such as dendritic cells (DCs), macrophages, neutrophils and T cells. IL-12, IL-18, IL-15 and type I IFN are strong activators of NK cell effector functions and IL-2 favours NK cell proliferation and activation (Figure 1). $CD4^+$ T cell-produced IL-2 in lymph nodes, and DC and macrophage-derived IL-18 and IL-15 activate NK cells, whereas T regulatory cell-derived TGFβ negatively regulates NK cell functions. It has been appreciated that, despite their original definition as natural killers, NK cells do require "priming" to gain a full activation state. IL-15 and IL-18 are well-described mediators of NK cell priming in both steady state and inflammatory conditions.[36-44]

NK cell maturation drives the acquisition of several chemotactic receptors and adhesion molecules, allowing NK cells to migrate from the bone marrow through the blood to spleen, liver, lung, lymph nodes, omentum and uterus during gestation.[45,46] Tissue-specific NK cells are functionally diverse and this is dependent on intrinsic factors, related to the distinct NK cell subsets found in different organs and extrinsic factors, in particular, mediators derived by other resident cells and leucocytes. This, in turn, influences NK cell interaction with other cell types.[46]

Here, we will focus on the interplay between phagocytes and NK cells, and on the impact of this crosstalk on

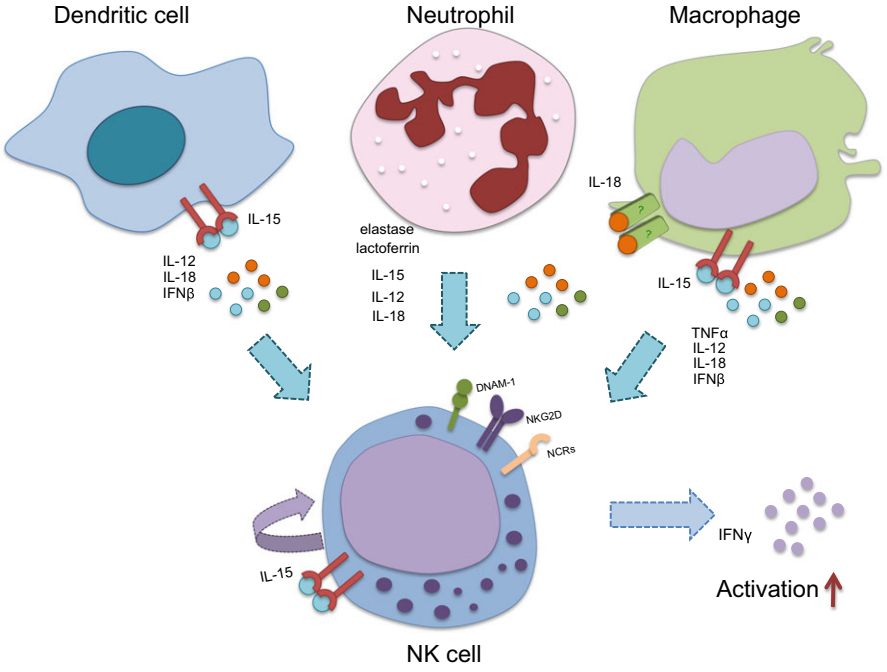

FIGURE 1 NK cell activation mediated by dendritic cells, neutrophils and macrophages. Both soluble factors and cell-to-cell contact are involved in the induction or boosting of NK cell effector functions. DCs, neutrophils and macrophages produce IL-12, IL-18, IFNβ, TNFα and IL-15 which induce NK cell activation. IFNβ is responsible for the production of IL-15, which can occur not only in DCs but also in NK cells themselves

NK cell and phagocyte responses in both physiological and pathological conditions.

2 | THE INTERACTION BETWEEN NK CELLS AND MACROPHAGES

Macrophages are able to prime NK cells through soluble factors and cell-to-cell contact and, in turn, NK cells can produce several inflammatory mediators, thus shaping the tissue microenvironment and influencing macrophage functional skewing [47] (Figure 1). In response to in vitro stimulation with cytokines and bacterial products, macrophages undergo M1 (classical) or M2 (alternative) activation, which represent the two extremes of a continuous spectrum of functional activation. Functional skewing of mononuclear phagocytes occurs in vivo either under physiological conditions, such as ontogenesis and pregnancy or in pathological processes, such as allergic and chronic inflammation, tissue repair, infection and cancer. Mirroring the Th1/Th2 paradigm, classical activation, generating M1 macrophages occurs in the presence of Toll-like receptor (TLR) ligands and Th1 cytokines, such as IFNγ, one of effector molecules released by NK cells. On the contrary, alternative M2 activation is dependent on Th2 cytokines, such as IL-4 and IL-13. Although phagocytosis is a key mechanism shared by both classically and alternatively activated macrophages, functional activation of macrophages leads to cytotoxicity and killing of the pathogen in M1 macrophages, whereas it favours M2-like macrophage-dependent tissue repair, healing, regeneration and angiogenesis.[48-50]

Macrophages and NK cells can interact in a contact-dependent manner through the generation of a sort of immune synapse. Indeed, clustering of receptors and adhesion molecules, such as ICAM-1 and LFA-1, expressed respectively by human macrophages and NK cells, as well as accumulation of F-actin, was observed at the site of contact in in vitro co-culture.[51] Regarding soluble mediators, through in vitro studies with mouse cells, in the early 1990s, it was demonstrated that macrophage-produced TNFα and IL-12 induced the secretion of IFNγ by NK cells,[52] whereas macrophage TGFβ production inhibited lung NK cell activation.[53] Then, IL-12, IL-18, IL-15 and IL-23 emerged as the key cytokines responsible for NK cell activation and their prominent role was originally demonstrated using macrophages infected in vitro with different pathogens.[44,47] Indeed, several studies showed that macrophages stimulated with TLR agonists,[54-56] infected with parasites (*Plasmodium falciparum* and *Leishmania*),[57,58] viruses (influenza A virus, Sendai virus, human cytomegalovirus)[59] or bacteria (*Salmonella*, *Mycobacterium tuberculosis*, *Enterococcus faecalis*, *Staphylococcus aureus*, *Lactobacillus*, *Streptococcus pneumoniae* and *Bacillus anthracis*)[60-65] induced NK cell activation, leading to CD69 expression, IFNγ production and degranulation. The interaction between NK cell 2B4 and macrophage CD48 was reported to be critical for the induction of NK cell proliferation and IFNγ production, but not of NK cell cytotoxicity.[66] Moreover, it was observed that upon priming with IL-2 and IL-15 produced by accessory cells, IL-12 and IL-18, both secreted by *Salmonella*-infected macrophages, induced a full NK cell activation in vitro.[60] Interestingly, they observed that

IL-12Rβ2 co-localized with actin at the immune synapse, suggesting the importance of cell-to-cell contact, as reported for IL-15 in DCs and IL-18 in DCs and macrophages [38-40,67] (see below). Another group showed that macrophages infected with *Salmonella* produced high levels of IL-23, IL-18 and IL-1β and these cytokines stimulated NK cells to produce IFNγ and GM-CSF. IFNγ and GM-CSF, in turn, could stimulate the production of IL-23 and IL-12p70 by monocytes and macrophages, confirming the importance of the NK cell-macrophage interplay during *Salmonella* infection.[68] Lopez-Botet et al[59] analysed the effect of functional polarization of macrophages in the activation of NK cells, in response to cytomegalovirus infection. NK cells were highly cytotoxic against both proinflammatory (M1-like) and antiinflammatory (M2-like) infected macrophages, generated in the presence of GM-CSF and M-CSF, respectively. In contrast, IFNγ production was only induced by M1 infected macrophages. Cytotoxicity was triggered by NKp46, DNAM-1 and 2B4 activation, whereas IFNγ production was partially dependent on IL-12 produced by macrophages.[59] Finally, NK cells were demonstrated to be activated by LPS-tolerant macrophages. Indeed, NK cells co-cultured with LPS-stimulated macrophages expressed high levels of NKG2D, which, in turn, promoted the recognition and the lysis of overactivated macrophages through various NKG2D ligands, such as UL16-binding proteins (ULBP1, ULBP2 and ULBP3) and MHC class I-related chain A (MICA).[51] NK cells have been shown to have cytotoxic activity against allogeneic and autologous human microglial cells. This cytotoxicity was mediated by perforin and dependent on NKG2D and NKp46 engagement and counterbalanced by MHC class I binding inhibitory NK cell receptors. In contrast with macrophages that are resistant to autologous NK cell cytotoxicity unless they are activated by TLR ligands,[51] microglial activation by LPS was associated with upregulation of MHC class I molecules and resistance to NK cell-mediated killing.[69]

Mattiola et al[41] dissected the crosstalk between human NK cells and autologous in vitro -derived macrophages, unveiling a complex network of interactions. It was shown that resting NK cells were primed to produce IFNγ and expressed higher levels of CD107a and CD69 upon co-culture with classically activated M1 macrophages or treatment with M1-conditioned media.[41] IL-1β and IFNβ production by M1 macrophages was responsible for the induction of NKp44 and NKG2D in NK cells and interestingly, IFNβ induced IL-15 cis-presentation in NK cells, consequently enhancing IFNγ production. The triggering of NK cell activating receptors NKp30, NKG2D and 2B4 by M1 macrophages was also involved in cell-to-cell contact-dependent NK cell activation. Finally, it was observed that M1-primed NK cells could, in turn, promote type 1 macrophage skewing, even reverting alternative M2 polarization.[41]

Bellora et al[38,56] showed that in vitro resting M0 and alternatively activated M2 macrophages reprogrammed towards a classical M1 phenotype through LPS treatment were able to induce NK cell activation, in terms of cytotoxicity, IFNγ production, CD69 expression, IL-2 responsiveness and migration through acquisition of CCR7 expression (Figure 2). IFNγ production was demonstrated to be induced by DNAM-1 and 2B4 pathways in a contact-dependent manner and, interestingly by IL-18 expressed as a membrane-bound form on macrophages.[38,56] In turn, activated human NK cells were able to kill autologous macrophages in vitro through NKp46 and DNAM-1.[38] In particular, M1 macrophages were more resistant to lysis compared to M0 and M2 macrophages and this was due to inhibition of NK cells mediated by higher expression of HLA class I molecules in M1-polarizing conditions.[56]

Macrophage-NK cell crosstalk is also an important component of the immune response against cancer. NK cells have a key role in the inhibition of tumour progression, through cytotoxic activity and IFNγ production, whereas macrophages recruited in tumours can exert both pro-tumoural and anti-tumoural activity, depending on their polarization state.[49,70] In this regard, Bellora et al[71] analysed the interaction between tumour-associated macrophages (TAMs) from ascites of ovarian cancer patients and NK cells. Untreated TAMs induced low upregulation of CD69 and CD25 in NK cells, whereas LPS-treated TAMs regained the capacity to fully activate NK cells, in terms of CD69, CCR7, CD25 expression and IFNγ production. Indeed, LPS-treated TAMs activated NK cell-dependent lysis of a NK cell-resistant ovarian cancer cell line (OVCAR-3), possibly through IL-12/IL-18-induced IFNγ production.[71]

These studies underline that in type 1-oriented immune responses, NK cells amplify both innate and adaptive responses, as a result of their interaction with classically activated M1-polarized macrophages.

3 | SUPPRESSION OF NK CELL FUNCTION BY MACROPHAGES

It has long been known that myelomonocytic cells can suppress NK cell activity either as a result of tissue driven differentiation, as shown originally for lung alveolar macrophages,[72] or of skewed activation.[73] In particular, TAMs are endowed with an armamentarium of immunosuppressive molecules, including triggers of checkpoint blockade.[49] Pesce[74] identified a subset of NK cells expressing PD-1, which triggers functional inhibition. Recent evidence indicated that in Hodgkin's lymphoma macrophage-expressed PD-L1 is a major driver of NK cell suppression.[73] Macrophage-mediated suppression of NK

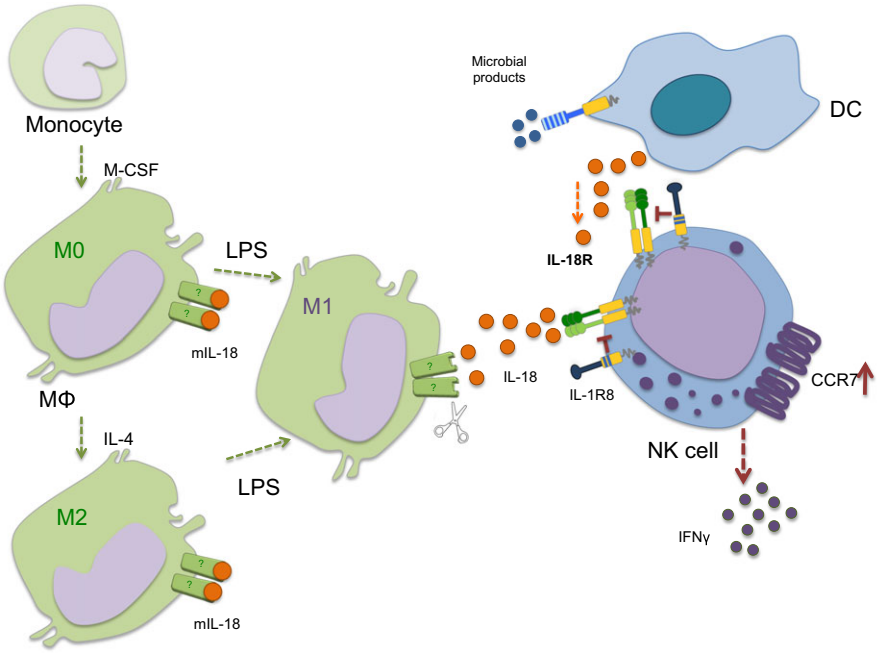

FIGURE 2 IL-18 as a central player in NK cell activation. IL-18 is a crucial proinflammatory cytokine promoting NK cell activation. M0 and M2 macrophages express a membrane-bound form of IL-18 (mIL-18), which is released upon treatment with LPS. IL-18 release by macrophages favours NK cell activation. DCs express IL-18 upon microbial product exposure and a cell-to-cell proximity is required to trigger a full NK cell activation

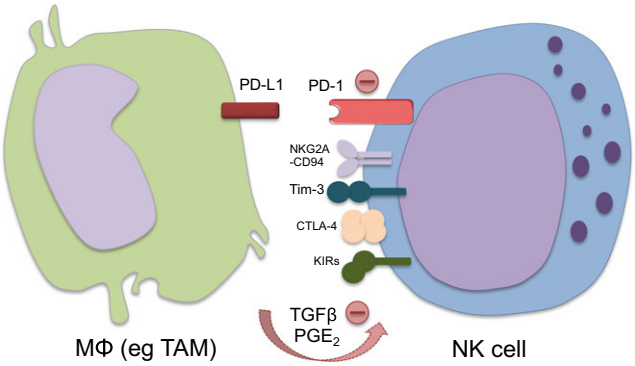

FIGURE 3 Suppression of NK cell function by macrophages. Among inhibitory pathways in NK cells, those regulated by macrophages have been emphasized: NK cell suppression mediated by TAM-derived PGE_2, TGFβ and the engagement of PD-1 by macrophage-expressed PD-L1. MΦ, macrophage; TAM, tumour-associated macrophage

cells can also be mediated by other complementary pathways such as TGFβ and prostaglandins (Figure 3).

Recently, a single-cell analysis of early lung adenocarcinoma lesions revealed a poor infiltration of NK cells in tumour lesions compared to normal lung and a nonfunctional state of the infiltrating NK cells, in terms of IFNγ, granzyme B and CD57 expression. T cell activation was compromised and T regulatory cells were enriched. Interestingly, the impaired NK and T cell anti-tumour immunity was associated with a suppressive phenotype of myeloid cells, indicated by the enrichment of $PPAR\gamma^{high}$ macrophages and depletion of $CD16^+$ monocytes and $CD141^+$ dendritic cells.[75]

Although most of these data have been generated in vitro, macrophage functional polarization states does occur in vivo,[50,75] suggesting the importance of myeloid cell plasticity and dynamic changes in physiological and pathological conditions, in particular in cancer, and affecting other cell types such as NK cells.

4 | THE INTERACTION OF NK CELLS AND DENDRITIC CELLS

NK cells were originally defined as spontaneous cytotoxic innate lymphocytes, able to quickly kill target cells, without the need of any prior sensitization, differently from T cells, whose killing mechanism is antigen specific and MHC-restricted. In spite of this, the concept of NK cell priming has emerged and the interplay between NK cells and DCs was identified as a crucial mechanism involved in NK cell priming.[1,76-78]

In particular, it was shown that functional interactions between DCs and NK cells occur. DCs are required for $Ly49H^+$ NK cell accumulation in mouse cytomegalovirus infection and for proper NK cell response in Herpes simplex virus-1 infection.[79-82]

It was reported by the Diefenbach's group that DCs were required for NK cell response to pathogens in vivo and NK cell priming occurred upon IL-15 trans-presentation by DCs.[67] DCs constitutively expressed the IL-15/IL-15Rα complex, which was required for NK cell homeostasis and could be induced by type I IFNs in inflammatory conditions, favouring NK cell priming. Interestingly, it was then observed that IFNβ-induced IL-15/IL-15Rα expression

occurred not only in DCs, but also in NK cells themselves, allowing IL-15 cis-presentation and NK cell activation[39] (Figure 1). Remarkably, NK cell activation was impaired when both trans- and cis-presented IL-15 was lacking, whereas NK cell survival and homeostasis relied on a NK cell extrinsic, IL-15-dependent mechanism.[39,83,84] LPS- or *E. coli*-triggered DCs produced IL-2, IL-18 and IFNβ that were crucial not only to prime but indeed to induce a full activation state of NK cells, which were unable to directly sense LPS. Close contacts between DCs and NK cell in the lymph nodes were essential for the localized delivery of DC-derived IL-18 to NK cells[40] (see below). DC-derived IL-2, IL-18 and IFNβ were also fundamental to elicit NK cell cytotoxic responses, both in vivo in bacterial and viral infections and in vitro.[39,85,86]

In certain inflammatory or infectious conditions, NK cells can be involved in the regulation of the adaptive response, through the killing of immature DCs, which would lead to an improper T cell activation. Immature DCs express lower levels of MHC-I molecules compared to mature DCs, being therefore more susceptible to NK cell-mediated recognition. Defective interactions between NK cells and DCs, and impaired NK cell-mediated lysis of autologous immature DCs have been observed in HIV-1-infected viremic patients.[87] The defective lysis was due to reduced expression of NKp30 and TNF-related apoptosis-inducing ligand (TRAIL) in NK cells, particularly in a $CD56^{-}CD16^{+}$ subset.[88] Moreover, mature DCs from viremic patients had reduced capacity to secrete IL-10 and IL-12 and to prime NK cell proliferation and activation.[88]

5 | NK CELLS AND NEUTROPHILS

The interplay between neutrophils and NK cells has recently emerged as a crucial mechanism regulating innate and adaptive responses (Figure 1). In different contexts, neutrophils were reported to be able to both activate and suppress NK cells.[89] Several groups demonstrated that neutrophil-derived ROS and arginase I could compromise the effector functions of NK cells, in particular of the $CD56^{low}$ NK cell subset.[90-95] In contrast, lactoferrin, elastase and other neutrophil granule-contained proteins were able to induce NK cell activation and cytotoxicity.[96,97]

in vivo models of bacterial infections revealed that neutrophil production of proinflammatory cytokines, such as IL-12, IL-15 and possibly IL-18, is crucial to polarize the immune response and favours NK cell-mediated IFNγ production.[98,99] In agreement, in vitro experiments showed that human TLR-stimulated neutrophils were involved in NK cell activation in an inflammasome-dependent manner.[99] In turn, neutrophil-stimulated NK cells were able to activate DCs, which then promoted T cell IFNγ production and proliferation, unveiling a complex interplay between innate and adaptive immune cells.[99] Moreover, it was recently observed that neutrophils are part of a network of interactions with 6-sulfo $LacNAc^{+}$ dendritic cells (slanDCs) and NK cells, in which neutrophils induced IL-12 production by slanDCs via CD18/ICAM-1, which in turn promoted NK cell activation.[100] The authors also showed direct NK cell-neutrophil interaction, which occurred through ICAM-3 and CD18, respectively, and led to IFNγ production by NK cells.[100] In line with this, in mice lacking neutrophils and in patients with autoimmune or severe congenital neutropenia NK cells displayed an immature and hyporesponsive phenotype.[101]

In a murine model of osteoarthritis, an early accumulation of NK cells and neutrophils was observed in the synovium and was associated with a worse disease progression. In this context, neutrophils expressing CXCL10 were responsible for CXCR3-mediated NK cell activation and recruitment in the inflamed joint.[102]

On the other hand, in vitro experiments revealed that human stimulated NK cells were able to prolong neutrophil survival inhibiting apoptosis, favour neutrophil activation, in terms of ROS production and phagocytic activity, and mediate the upregulation of activation markers.[103,104] NK cell-produced IFNγ, GM-CSF and TNFα were responsible for the enhanced neutrophil survival and activation, as shown by increased expression of activation markers (CD11b, CD69 and CD64 upregulation, and CD62L shedding).[103,104] In agreement, NK cells were shown to produce neutrophil chemo-attractants, such as CXCL8, CCL3, CCL4 and CCL5.[105,106] In contrast with these studies, it was reported that NK cells induced neutrophil apoptosis through NKp46 and Fas pathway.[107] Whether human NK cells have the ability to regulate neutrophils in pathologies characterized by a relevant infiltration of both cell types remains to be elucidated. NK cell-mediated regulation of neutrophil function in the mouse has been mostly characterized in NK cell-depleted mice. However, controversial results have been reported, possibly because of the use of different models of disease and NK cell depletion, and because of the contribution of other cell types, as carefully reviewed by Cassatella.[89] In the context of cancer, it was recently reported in a sarcoma transplantable model that NK cells regulated neutrophil functions via IFNγ. Upon NK cell depletion, neutrophils produced increased levels of VEGF-A, therefore promoting angiogenesis and tumour progression.[108]

6 | Il-18 AS A CENTRAL PLAYER IN NK CELL-PHAGOCYTE CROSSTALK

IL-18 was first described as "interferon γ (IFNγ)-inducing factor." IL-18 is a member of the IL-1 family, produced as an immature form and requiring caspase-1-mediated

cleavage to gain bioactivity.[109] IL-18 is a key cytokine implicated in innate and adaptive type 1 responses and plays a crucial role in the interplay between macrophages/DCs and NK cells.[109]

In this regard, in vitro M-CSF-derived resting M0 and alternatively activated M2 macrophages express a membrane-bound form of IL-18, which can be released as a soluble form (sIL-18) upon stimulation with LPS. The release of sIL-18 was shown to be dependent on a protease-mediated shedding of the membrane-bound protein.[38] Macrophage-derived IL-18 promoted NK cell activation and CCR7 expression and therefore migration towards lymph nodes (Figure 2). Interestingly, endotoxin tolerant macrophages, which are generated with chronic exposure to TLR ligands, lacked the expression of mIL-18 and did not release relevant amounts of sIL-18, being therefore unable to activate NK cells.[38]

Recently, it was elegantly shown in a tumour model that lymph node-resident NK cells are activated by DCs within the lymph node, upon LPS exposure.[40] DC-activated NK cells are the ones that preferentially egress the lymph node, then reach the tumour site and exert anti-tumour effector functions. Interestingly, two-photon microscopy analysis revealed that prolonged interactions occurred between NK cells and DCs in the peripheral T cell area of the lymph node, in response to LPS treatment. IL-18 was previously shown to be produced by activated DCs and be secreted at the immune synapse generated between DCs and NK cells. The authors demonstrated that LPS-activated DCs, in turn, activate NK cells through IL-18, which requires cell-to-cell proximity and the formation of a proper and stable interaction to exert its function [40] (Figure 2).

In line with this findings, we reported that NK cells deficient of IL-1R8, a negative regulator of the IL-1 receptor and TLR family members,[110] display enhanced maturation and effector functions, in terms of IFNγ production and cytotoxicity in tumour and viral infection models.[111] The increased NK cell differentiation and activation observed in the absence of IL-1R8 was dependent on the IL-18 pathway, both in basal levels and in tumour models. Co-culture experiments of NK cells and CpG- or LPS-primed bone marrow-derived DCs revealed that NK cell activation was mainly dependent on IL-18 in both IL-1R8-competent and deficient conditions (Figure 2). Moreover, IL-1R8-deficient NK cell phenotype after co-culture was abolished upon IL-18 neutralization. Importantly, IL-1R8-deficient NK cells were protective in a model of sarcoma-derived lung metastases and colorectal cancer-derived liver metastases and the phenotype was abolished upon neutralization or genetic deletion of IL-18.[111] Moreover, IL-1R8-deficiency unleashed NK cell-mediated resistance against MCMV.[111]

Collectively, these evidences highlight the crucial contribution of IL-18 in the regulation of NK cell activation in the interplay with macrophages and DCs.

7 | CONCLUSIONS

NK cells are innate lymphoid cells with cytotoxic potential against cancer or virally infected cells. Engagement of various activating and inhibitory receptors on the NK cell with ligands present on the target cell surface, initiates balanced signalling pathways leading to NK cell function or tolerance. In addition, NK cells engage bidirectional interactions with other leucocytes, including macrophages, DCs and neutrophils, which affect both cell types. Macrophage-NK cell crosstalk is an important component of the immune response against microbes and cancer. In particular, in type 1-oriented immune responses, NK cells amplify both innate and adaptive responses, as a result of their interaction with M1-polarized macrophages. Furthermore, the interaction with DCs and trans-presented cytokines represents a crucial mechanism leading to NK cell priming and full activation. Similarly, the interaction between NK cells and neutrophils through soluble mediators and adhesion molecules, influences NK cell maturation and responsiveness, as well as neutrophil survival. In addition to IL-12 and IL-15, IL-18 is emerging as a key myeloid cell-derived factor involved in the activation of NK cells. IL-18 activity is tightly regulated by IL-1R8, a negative regulator of the IL-1 receptor family, acting as a novel checkpoint of the anti-viral and anti-tumour functions of NK cells, both against primary liver tumours and metastasis.

Given the diversity and complexity of myeloid cell functional polarization, NK-myeloid cell crosstalk can result in diverse functional outcomes in a site- and context-specific manner. The development of high-throughput technologies allowing a detailed and unbiased characterization of cell types and functional states and dissecting macrophage complexity beyond the M1 and M2 paradigm will be crucial to deeply understand the yin-yang of NK and myeloid cells interactions.

In a translational perspective, these bidirectional interactions with phagocytes, myeloid-derived factors, and their regulation must be taken into account to fully exploit the potential of NK cells to restrain primary cancer and metastasis.

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