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Immunology Letters 145 (2012) 39–46

Contents lists available at SciVerse ScienceDirect

Immunology Letters

journal homepage: www.elsevier.com/locate/immlet

Review

Chemokines and NK cells: Regulators of development, trafficking and functions

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ARTICLE INFO

Article history:
Received 21 August 2011
Accepted 13 April 2012

Keywords:
NK cells
Chemokine receptors
Chemokines
Chemotaxis
Lymphocyte homing

ABSTRACT

NK cells are innate lymphocytes capable of killing malignant or infected cells and to produce a wide array of cytokines and chemokines following activation.

Chemokines, play critical roles in the regulation of NK cell tissue distribution in normal conditions as well as their rapid recruitment to the parenchyma of injured organs during inflammation, which is critical for NK cell ability to promote protective responses. In this regard, differences in chemokine receptor expression have been reported on specialized NK cell subsets with distinct effector functions and tissue distribution.

Besides their role in the regulation of NK cell trafficking, chemotactic molecules can also affect NK cell effector functions by regulating their priming and their ability to kill and secrete cytokines.

1. NK cell differentiation, tissue distribution and function

Natural killer (NK) cells represent a discrete subset of innate lymphocytes that act as first line of defense against several microbial infections, early cellular transformation and tumor growth. NK cell prompt response is mainly related to their ability to release cytolytic mediators such as perforin and granzymes or to express ligands able to trigger death receptors on target cells; moreover they can also secrete a wide array of cytokines and chemokines to recruit and to instruct other immune cell types [1,2]. The main site of NK cell differentiation is the bone marrow (BM) where they develop from a common lymphoid progenitor that generates also B and T lymphocytes. Notably, NK cell precursor has been found also outside the BM, thus suggesting that NK cell development can occur also in the peripheral tissue microenvironment [3,4].

During development, NK cells have to pass through several stages of differentiation in order to progressively acquire a mature phenotype consisting of both activating and inhibitory receptors as well as adhesion molecules and chemotactic receptors, and effector ability. Among growth factors critically involved in NK cell differentiation, a crucial role is played by IL-15 and its receptor. IL-15 needs to be trans-presented by cells expressing IL-15Ralpha chain and was found on the surface of several hematopoietic or non-hematopoietic cells such as dendritic cells or stromal cells both in the BM and in peripheral tissues where it promotes the generation of NK cells from their precursors and the differentiation of immature NK cells and represents a survival signal for mature NK cells [5,6]. In regard to human NK cell development, there are evidence that human $CD34^+$ hematopoietic stem cells and hematopoietic progenitors, including NK cell precursors [7], are present within the BM, and that co-culture of BM-derived $CD34^+$ cells with BM stromal cells promotes the differentiation of cytotoxic NK cells *in vitro* [8]; however, unlike the mouse, the identification of different stages of human NK cell differentiation within the BM is still lacking. By contrast, at least five distinct progressive stages of NK cell development have been described in the secondary lymphoid tissues such as lymph nodes (LNs) and tonsils, based on the expression of distinct set of markers and functional capability: stage 1, $CD34^+CD45RA^+CD117^-CD161^-CD94^-$; stage 2, $CD34^+CD45RA^+CD117^+CD161^{+/-}CD94^-$; stage 3, $CD34^-CD117^+CD161^+NKp46^-CD94^-$; stage 4, $CD34^-CD117^{+/-}NKp46^+CD94^+CD16^-CD56^{brigh}$; and stage 5, $CD34^-CD117^-NKp46^+CD94^{+/-}CD16^+CD56^{dim}$. From stage 1/pro-NK cells to stage 2/pre NK cells and stage 3/immature NK (iNK) cells, these cells become committed to the NK cell lineage; from stage 3 to 5, they undergo functional maturation in that iNK cells can produce GM-CSF and potentially type 2 cytokines, while stage 4/$CD56^{bright}$ NK cells preferentially release IFN-gamma, and stage 5/$CD56^{dim}$ NK cells are the principal cytotoxic population. Within stage 4 and 5, NK cells also acquire the killer inhibitory receptors (KIR) [4,9].

Similarly to human, mouse NK cell development involves distinct stages that can be identified by multi-parameter cell surface marker analysis and that comprise functionally distinct NK cell subsets. Precursor cells committed to the NK cell lineage (pNKs) express the common beta chain of the interleukin (IL)-2 and IL-15 receptors (CD122) and lack surface proteins associated with

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http://dx.doi.org/10.1016/j.imlet.2012.04.014

mature hematopoietic cells (referred to as Lineage negative or Lin$^-$), including most NK cell receptors with the exception of NKG2D and 2B4 (CD244) [3]. Generation of these cells does not require IL-15, but responsiveness to this cytokine is critical for later steps of the differentiation process [6]. As pNKs mature they progressively acquire a number of NK cell receptors, including NKR-P1C and NKp46. At this stage, the cells initiate expression of the major histocompatibility complex (MHC) class I-recognition receptors encoded by CD94 in combination with NKG2A/C/E, and the Ly49 genes, which encode a family of C-type lectin receptors. Subsequently, the cells up-regulate the alpha2/CD49b integrin (DX5) and acquire cytolytic and cytokine producing capacities. Within DX5$^+$ NK cells, two populations with different functional competence can be identified by the level of expression of the CD11b integrin chain (CD11b^{low} and CD11b^{high}). A better characterization of functionally distinct NK cell subsets is provided by the analysis of CD27, a costimulatory molecule belonging to the TNF receptor superfamily, that is downmodulated during CD11b^{high} NK cell differentiation. Thus, three distinct subpopulations that are developmentally related can be identified: CD11b^{low}/CD27^{high}, CD11b^{high}/CD27^{high}, that display the higher effector capacity and CD11b^{high}/CD27^{low}, that represents a subsequent stage of maturation [10] The latter population can also be identified by KLRG1 expression, a C-type lectin inhibitory receptor [11]. Recent observations suggest that CD27^{high} to CD27^{low} transition may occur in the spleen and is driven by splenic monocyte-presented IL-15.

Ablation of BM hematopoiesis irreversibly alters NK cell development. Nevertheless, NK cells from several extramedullary tissues display tissue specific phenotypes suggesting that maturation can be completed in organ different from BM including thymus, spleen, LNs and liver. In mice, the identification of immature NK cells in the liver that express the effector molecule TRAIL and the recent identification of thymus-derived GATA-3$^+$ CD127$^+$ NK cells are in agreement with the prediction of an organ-specific maturation of NK precursors [12]. Differently from BM-derived NK cells, thymic-derived NK cells preferentially home to LN, where they maintain CD127 and GATA-3 expression and display stronger cytokine production and less cytotoxic ability than their splenic counterpart. These functional characteristics are similar to the CD56^{hi}CD16$^-$ human NK cells subset, which was also found to be CD127$^+$ and to express Gata-3.

Mature NK cells predominantly circulate in the peripheral blood, but are also resident in several lymphoid and non-lymphoid organs, such as the spleen, tonsils, LNs, liver, lungs and intestine and uterus [13]. In all these organs, NK cells have been found in close proximity of vasculature, and in most instances in areas distinct from those of T or B cells. In the spleen, NK cells are primarily present in the red pulp where they co-localize with endothelial cells suggesting that splenic NK cells are mainly distributed within blood sinuses or vessels [14–16]. Also in mouse BM a fraction of NK cells, comprising mostly mature cells, was found to reside in sinusoids [17]. Using immunohistochemical analysis and dynamic intravital imaging of the LNs, it has been shown that NK cells reside in the medulla, in the perifollicular regions as well as in the paracortex where they co-localize with dendritic cells (DC). In a steady state condition, the density of LN NK cells is higher in the medulla than in T or B cell areas and they are mainly located within lymphatic sinuses [18].

In humans, while the majority of blood NK cells are CD56^{dim}, the predominant NK cell population found in the LNs and tonsil secondary lymphoid tissues is CD56^{bright}. As above mentioned, CD56^{bright} and CD56^{dim} NK cell populations are quite different, in that they have a distinct inhibitory and activating receptor profile, display diversity in their adhesion molecules and chemokine receptor profile and thus they have different homing capability, and most importantly, they are endowed with unique functional ability being CD56^{bright} the major source of cytokines and the CD56^{dim} the major cytotoxic population.

Among non lymphoid organs, NK cells are selectively enriched both in liver where they are mainly situated in the lumen of the intrahepatic sinusoids and in uterus, where they are located around endometrial glands and vessels [19,20]. Recently, a human CD56$^+$CD3$^-$ cell population that is predominantly located in the mucosa surrounding the lymphoid follicles of tonsils and Peyer's Patches of the ileum and appendix have been described and referred as NK-22 cells based on its ability to release IL-22 [21]. The human NK-22 cells, express the NKp44 receptor and the chemokine receptor CCR6 and seem to have important roles in protective immunity.

In the mouse intestine, CD3$^-$NKp46$^+$ cells can be divided into two main subsets based on the expression of IL7Ralpha (CD127) and NK1.1 [22]. Importantly, these subsets appear to mediate different functions because IL7Ralpha$^-$NK1.1$^+$ cells are similar to conventional NK cells, producing perforin and IFN-gamma, whereas IL7Ralpha$^+$NK1.1$^-$ cells lack these effector functions. Instead, they express IL-22 and RORgamma and, in contrast to conventional NK cells, do not require IL-15 for differentiation. [22–24]. The origin and lineage of gut mucosa associated human NKp44$^+$ cells and murine NKp46$^+$ cells is still debated and it is still unclear if they are developmentally related to the NK cells and/or to the lymphoid tissue inducer (LTi) cells or if they represent a distinct innate immunity cell types [25,26].

Tissue resident NK cells can perform many functions including cytotoxicity or cytokine release mostly related to maintain tissue integrity, but in some cases, *i.e.* uterine NK cells, they can make a more specialized function by modulating vessel behavior, promoting vascular remodeling or influencing the recruitment and activation of other leukocytes to ensure a good outcome of pregnancy.

Although, in steady-state conditions, mature NK cells can be found in some lymphoid and non lymphoid organs, following an insult such as a viral infection, inflammation or tumor growth, specialized NK cell subsets can be rapidly recruited from blood and accumulate in the parenchyma of injured organs to perform their specific function and participate to the restoration of tissue integrity.

2. Chemokine receptor expression by NK cells: impact on NK cell function

A large body of evidence indicate that NK cells can express several receptors for CXC, CC, C and CX3C chemokines, with great heterogeneity in the chemokine receptor repertoire among different NK cell populations and between resting *versus* activated NK cells [27–29].

It has been previously reported that peripheral blood human NK cells express both CXCR1 and CXCR2 as CXCL8 (IL-8) receptor [30–32] and CX3CR1 as CX3CL1 (fractalkine) receptor [33]. These observations have been further extended by Campbell et al. who provided the first evidence that distinct (CD56^{pos}CD16^{neg} and CD56^{pos}CD16^{pos}) peripheral blood NK cell subsets have a unique repertoire of chemokine receptors [34]. CD16^{pos}, that are bona fide CD56^{low}, NK cells uniformly express high levels of CXCR1 and CX3CR1, low levels of CXCR2 and CXCR3 and no detectable levels of CXCR5. By contrast, CD16^{neg} (mostly CD56^{bright}) NK cells express high levels of CXCR3, CCR5 and CCR7, the latter molecule mainly involved in the homing of lymphocytes to secondary lymphoid organs and low levels of CX3CR1, and are negative for CXCR1, CXCR2 and CXCR5; moreover, both NK cell subsets express high levels of CXCR4, the receptor for CXCL12 (SDF-1alpha/beta). The differences in chemokine receptor expression correlate with differences

in the migratory behavior, being CD16^{pos} NK cells more responsive to CXCL8 and CX3CL1 and the CD16^{neg} cells to CCL19 and CCL21 as well as to CXCL10 and CXCL11. Both NK cell subsets strongly migrate in response to the ligand of CXCR4, CXCL12 [34,35]. Besides chemokine receptors, human and mouse NK cells were also shown to express receptors for chemotactic molecules that do not belong to the chemokine superfamily, and can regulate NK cell trafficking under steady state and inflammatory conditions. In this regard, NK cells were shown to migrate in response to the pro-inflammatory plasma protein chemerin, and CD56^{low}CD16^{pos}, but not CD56^{high}CD16^{neg} NK cells express its receptor, ChemR23. Sphingosine 1-phosphate (S1P) is a sphingo-phospholipid generated by the conversion of sphingomyelin into ceramide by sphingomyelinase, that influences lymphocyte trafficking as well as proliferation, adherence and morphogenesis [36]. Previous reports show that human NK cells express the mRNA for S1P1, while mouse NK cells express both S1P1 and S1P5 and migrate in response to S1P [37,38]. Interestingly, the selective expression of CXCR3 on CD56^{high} and of CX3CR1 on CD56^{low} NK cells is very similar to their expression pattern on the two main subsets of mouse mature NK cells defined as CD27^{high} and CD27^{low}. Indeed, as compared to CD27^{low} NK cells, CD27^{high} (both CD11b^{low} and CD11b^{high}) cells have higher expression of the chemokine receptor CXCR4, selectively express CXCR3 and have much lower expression of the chemoattractant receptor S1P5 and CX3CR1 [28,38]. Moreover, the recent identification of chemokine receptor expressing mouse NK cell subsets with distinct effector functions suggests that discrete subsets of NK cells can be defined according to their chemokine receptor expression profile [17,39,40].

The expression of chemokine receptors and the corresponding NK cell chemotactic response is also modulated upon cytokine stimulation. A significant decrease of CXCR3 expression and chemotaxis to CXCL10 was reported in human NK cells treated for 6 or 24 h with IL-2 and IL-12, used alone or in combination. IL-2 down-regulated CCR7 receptor expression on NK cells whereas induced the CCR4 and CX3CR1 molecules [41]. Stimulation for longer periods of time with IL-2 resulted in increased expression of CCR1, CCR2, CCR4, CCR5 and CCR8 [42], while expression of CXCR2 and ChemR23 decreased [43]. CXCR4 and CX3CR1 have been shown to be down-regulated through stimulation with other cytokines, including IL-15, whereas TGF-beta has been proven to be a potent inducer of CXCR4 on NK cell subset s [42,44]. In addition, treatment with IL-18 resulted in selective induction of CCR7 expression and enhanced response to CCL21 of the CD56^{low} NK cell subset [45].

Besides migration, other human and mouse NK cell functions can be affected by chemokines. Indeed, chemokines can activate an NK cell defense machinery that may directly counteract an infectious agent by performing cytotoxicity or by secreting pro-inflammatory cytokines that recruit and activate other effector cells [46]. Soluble and membrane-bound CX3CL1 (fractalkine) induce IFN-gamma production by NK cells and affect NK cell ability to kill tumor cells both *in vitro* and in [47,48]. Enhancement of NK cell degranulation has been also demonstrated in response to other chemokines belonging to the CC family and to CXCL10 [46,49]. In addition, CC chemokines-mediated redistribution of adhesion molecules on NK cell surface may also increase NK cell cytotoxicity by promoting effector-target cell interaction [50].

CX3CL1 has been found to be a pivotal molecule driving immune synapse formation during DC/NK cell interaction leading to efficient NK cell activation. Importantly, the absence of CX3CR1, or CX3CL1-blockade, abrogated the ability of NK cells to produce IFN-gamma when exposed to DC, underlying a key role of this chemokine during DC-mediated NK cell priming [51]. Thus, the CX3CR1/CX3CL1 axis regulates NK cell functions at different levels promoting their migration through endothelial vessels, their activation and their ability to kill or to secrete cytokines.

3. Chemokine receptors and NK cell development into bone marrow

Lymphocyte development in the bone marrow and thymus requires repeated changes of their migration properties, which facilitate the sequential localization of individual precursors into selected microenvironments important for their maturation.

A number of studies show the important role of CXCL12/CXCR4 axis in the regulation of the positioning, retention and homing of hematopoietic cells into the BM [52–55]. CXCL12/CXCR4 chemokine/receptor pair plays a crucial role also in B cell differentiation, mainly acting at the earliest stages both in fetus and adult mice [56]. CXCL12 deficiency has been associated with severely reduced number of early B cell precursors in fetal liver during embryogenesis. Also the adult BM of irradiated mice reconstituted with CXCR4-deficient fetal cells shows a marked reduction of B cell precursor, including pre-pro B cells that correlate with their enrichment in blood as compared to control mice [57]. Correspondingly, adventitial reticular cells that express high level of CXCL12 (CXCL12 abundant reticular (CAR) cells) were found to be in strict contact with pre-pro B cells [58]. Beside BM, CXCR4 play a role also during thymocyte differentiation being CXCR4 deficiency associated to a reduced number of thymocytes, likely due to the loss of mitogenic stimuli provided by CXCL12 [59].

The role of chemokines in NK cell development is less defined. It has been demonstrated that NK cells change their chemokine expression profile during development in BM. CXCR4 is highly expressed by pNK cells but its expression progressively decreases during development. The progressive decrease of CXCR4 parallels the increased expression of CXCR3, CCR1 and CX3CR1 on mature NK cells, being the expression of CX3CR1 mainly confined to the KLRG1^{+} subset that poorly expresses CXCR4 and does not express CXCR3 [17,60 and GB unpublished observation]. Interestingly, expression of CX3CR1 on KLRG1^{+} cells was shown to define a more differentiated NK cell subset that is developmentally related to KLRG1^{+}CX3CR1^{-} NK cells [17]. The role of CXCR4 receptor on NK cell retention in BM was analyzed by *in vivo* administration of CXCR4 antagonist AMD3100, that induced the reduction of immature and mature NK cells in the bone marrow and their increase in spleen and peripheral blood, indicating that CXCL12 regulates the retention of selected NK cell subsets at various stages of maturation in the BM during development [60]. This is also supported by the evidence that retention of NK cells residing in BM sinusoids, that likely represent cells that have completed their maturation in BM and are ready to exit into systemic blood circulation, is CXCR4-independent [17]. Recently, Noda et al. showed that NK cell development is severely impaired in adult CXCR4 conditionally deficient mice and this was correlated with reduced number of NK cell precursors, decreased proliferation rate of CXCR4 deficient DX5^{-} iNK cells and with the ability of CXCL12 to promote mature NK cell generation from lymphoid precursor and immature NK cells in the presence of IL-15 [61]. In addition, using chemokine receptor deficient mice it was evidenced that also CCR5 but not CCR1 can participate to NK cell differentiation and this was associated to regulation of developing NK cell proliferation under physiological conditions [62]. In regard to CXCR4, it was demonstrated that a fraction of CAR cells co-express IL-15 and IL-15Ralpha and thus CAR cells may trans-present IL-15 and provide CXCL12 to NK cells during development. The latter hypothesis is supported by immunofluorescence studies on BM tissue sections showing that NKp46^{+} NK cells can be found in close proximity to CAR cells *in vivo*. The observation that the residual fraction of NKp46^{+} NK cells that

develop into BM in CXCR4-deficient mice is still close to CXCL12-producing cells suggested that CXCR4 is not required for NK-CAR cell co-localization. However, a role of CXCR4 in NK cell localization in BM microenvironments during normal development cannot be excluded as CXCR4-deficiency led to a strong impairment of NK cell development and to marked reduction of maturing NK cell subsets. In addition, CXCL12 may also be presented by other BM cells, including osteoblasts.

Overall, CXCR4/CXCL12 interaction may play a dual role during NK cell development: it may directly promote NK cell differentiation by acting on NK cell precursors and more immature $DX5^{neg}$ NK cells. Indeed, although their CXCR4 expression is higher as compared to more mature NK cells, *ex vivo* migration and *in vivo* retention of these cells into BM is less influenced by CXCL12, while *in vivo* proliferation of more immature NK cell is more dependent on CXCR4 expression [60,61]. On the other hand, CXCR4/CXCL12 interaction is required to maintain immature and mature NK cells in BM parenchyma during maturation and thus indirectly can favor NK cell response to differentiation stimuli (Fig. 1).

4. *In vivo* regulation of NK cell functions by chemokines

NK cells express several chemotactic receptors that are involved in the control of NK cell migration across endothelium and in the correct tissue positioning of lymphocytes, but only recently we are beginning to appreciate the contribution of chemotactic factors on NK cell trafficking and tissue distribution under homeostatic and pathological conditions.

Although the differential expression of chemokine receptors and chemotactic responsiveness of the $CD27^{low}$ and $CD27^{high}$ subsets strongly suggests a correlation with their tissue distribution, at present few chemoattractant receptors have been demonstrated to play a role in NK cell subset distribution *in vivo* under normal conditions. A drastic decrease in NK cell numbers has been observed in the blood, spleen, and lungs of S1P5-deficient mice, associated with increased number of NK cells in the BM and LNs. This altered distribution has suggested that S1P5 provides an egress signal to NK cells, promoting their exit from BM and LNs [38]. In addition, the observation that CX3CR1-deficient mice display a selective reduction of $DX5^{+}CD3^{-}$ cell number in the lung, strongly suggests that this receptor is important for the accumulation of at least one subset of NK cells in this organ under steady state conditions [63]. Maintenance of a subset of NK cell in the liver depends on the chemokine receptor CXCR6. Indeed, the ligand for CXCR6, CXCL16, is constitutively presented by the liver sinusoidal endothelium and $CXCR6^{+}$ NK cells that represent a consistent fraction of liver NK cells, are drastically reduced in $CXCR6^{-/-}$ mice [40]. Also the expression of CXCR4 profoundly affects NK cell subset distribution likely by contributing to the maintenance of an NK cell pool within BM, as shown by the recruitment of BM iNK and mNK cells into circulation and spleen following *in vivo* delivery of the CXCR4 pharmacological antagonist AMD-3100 [60].

While the contribution of chemokines in the regulation of NK cell tissue distribution during homeostasis has been poorly addressed so far, a number of studies indicate that selected chemokines play a critical role in the orchestration of NK cell trafficking during inflammation. It has been reported that during murine cytomegalovirus infection, NK cells migrate through a CCL3-dependent mechanism to sites of liver infection where they contribute to antiviral defense [64]. This evidence was further supported by the demonstration that CCL3-deficient mice show decreased resistance to cytomegalovirus infection that is associated with a dramatic reduction of NK cell accumulation and IFN-gamma production in the liver. The recruitment of NK cells to the liver during infection required the receptor for CCL3, CCR5, and the receptor for CCL2, CCR2 [64,65]. IFN-gamma-dependent recruitment of NK cells to liver has also been described in a model of Concanavalin A-induced hepatitis. In this case, NK cell entry in the liver was reduced in the absence of CCR1 and involved NK cells that used CXCR3 to exit the spleen [66]. CXCR6 was also shown to play a relevant role for the maintenance into liver of a population of $CXCR6^{+}$ NK cells that retained antigen-specific memory after antigen challenge [40].

A role for CCL3 in recruitment of NK cells has also been demonstrated by intrapulmonary transient transgenic expression of this chemokine that resulted in increased *Klebsiella pneumoniae* lung clearance associated with NK cell activation and accumulation in this organ [67]. In addition, a specific defect of NK cell recruitment to pulmonary granulomas was observed in CCR1-deficient mice [68]. Another chemokine, CCL2 was shown to regulate accumulation of NK cells in the lungs of mice with invasive aspergillosis [69]. In addition, using an *in vivo* model of NK cell-mediated lung tumor cell clearance in CX3CR1-deficient mice or after treatment with blocking antibodies against CX3CL1 or CX3CR1, it has been demonstrated that decreased clearance of tumor cells following perturbation of CX3CL1/CX3CR1 interaction is attributable to defective NK cell recruitment to the lung [63,70]. Using CXCR3-knockout mice, recruitment of NK cells in the lungs has been also shown to participate to the pulmonary host defence against *Bordetella bronchiseptica* [71].

In the central nervous system (CNS), CXCL10 has been reported to promote innate defence mechanisms following coronavirus infection by recruiting and activating NK cells, while CCR5 deficiency results in impaired NK cell ability to limit herpes virus spread to brain [72,73]. $CX3CR1^{GFP/GFP}$ mice showed a selective deficiency of NK cell recruitment in the CNS during experimental autoimmune encephalomyelitis that was accompanied by severe disease. A recent report indicates that the loss of the regulatory influence of NK cells on Th17 differentiation accounts for the severe EAE phenotype in $CX3CR1^{GFP/GFP}$ mice [74]. In accordance, alterations of $CX3CR1^{+}$ NK cell numbers are observed in patients with multiple sclerosis.

The involvement of CXCL10 and CX3CL1 in supporting anti-tumor NK cell response *in vivo* has been also described. CXCL10 was shown to promote a strong anti-leukemic NK cell-mediated response *via* enhanced induction of cytotoxicity and expression of the T cell co-stimulatory molecule B7-H1 [75]. In addition, a link between IFN-gamma induction of CXCR3 ligand expression during the anti-tumor immune response and $CD27^{high}$ NK cell recruitment within the tumor mass was found to be critical for host survival [76]. In addition, CX3CL1-transfected tumor cells exhibit a reduced growth capability that is mediated by an increased recruitment and activation of NK cells [70].

The selective role of chemokine/chemokine receptor interaction in NK cell migration *in vivo* suggests that different NK cell subsets may be independently recruited in distinct inflammatory settings, as the two major subsets of mature NK cells, $CD27^{high}$ and $CD27^{low}$, can be characterized by the mutually exclusive expression of CXCR3 and CX3CR1. By using selective depletion and adoptive transfer experiments, Martin-Fontecha et al. have reported that DC-induced recruitment of NK cells into LN occurs in a CXCR3- but not CCR7-dependent manner. The entry of NK cells within the T cell area of secondary lymphoid organs has several implications allowing their correct priming by DC as well as an efficient T cell polarization [77,78]. The role of CXCR3 as well as CCL5 receptors has also been emphasized within the spleen in the recruitment of red pulp-localized NK cells to the white pulp during TLR ligand stimulation *in vivo* [16]. Interestingly, the entry of NK cells into the splenic red pulp is Pertussis Toxin (PTX)-insensitive, thus suggesting that NK cell localization into this organ is regulated by a chemokine-independent or a PTX-insensitive chemokine receptor.

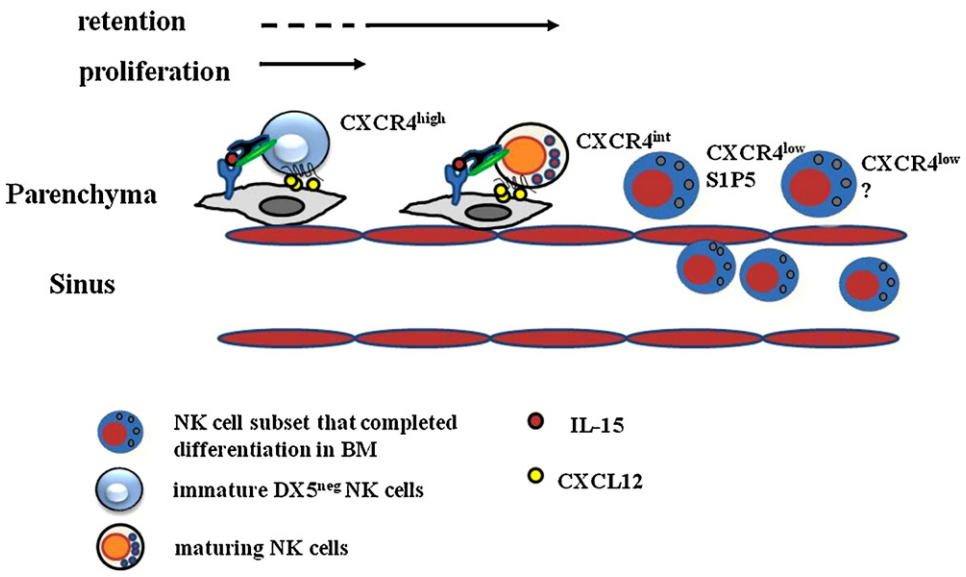

Fig. 1. Hypothetical model of CXCR4 role on NK cell development during NK cell interaction with stromal cells. During development, high expression levels of CXCR4 on immature NK cells may potentiate their response to IL-15, directly favoring their proliferation and differentiation, while CXCR4/CXCL12-mediated retention may influence stromal cell-promoted differentiation in later differentiation stages. Down-modulation of CXCR4 coincides with NK cell subset exclusion from BM-parenchyma and enrichment in sinusoids and is likely to allow responsiveness to other chemoattractant including S1P and CCL3, allowing egress from BM.

These data collected in a number of mouse models strongly support the *in vivo* relevance of a number of chemokine receptor-ligand interactions, including CX3CR1-CX3CL1, CXCR3-CXCL10/CXCL11, CCR5-CCL3/CCL4, CCR5-CCL5, that have been shown to mediate human NK cell chemotactic response *in vitro*.

Similarly to mouse, also in humans, inflammatory responses can induce drastic changes in the NK cell chemokine receptor expression pattern and in the expression of their ligands in inflamed or injured tissues, thus altering NK cell subset recruitment and redistribution. Indeed, expression of CCL1, CCL5 and CXCL10 and of chemerin was associated with recruitment of NK cells in skin biopsies of patients with psoriasis. In addition, a strong correlation between ChemR23 expression and co-localization of $CD56^{low}$NK cells with DC was observed in human biopsies of oral lichen planus in areas where chemerin is present [43]. Differently, in skin lesions, $CD56^{high}CD16^{-}$ NK cells are preferentially recruited and display a $CCR6^{+}CXCR3^{+}CCR5^{+}ChemR23^{+}$ receptor profile.

5. Regulation of the functional interaction between NK cell and other immune cells by chemokines

Besides the role of NK cell-mediated cytotoxicity in the direct lysis of tumor or infected cells, NK cell cytolitic and cytokine secretion potential can affect innate and adaptive immune response by controlling the function of other immune cells in several conditions (Fig. 2). On the other hand, the achievement of the full effector capacity by NK cells requires various factors, including DC or macrophage-presented IL-15, IL-12 or IL-18 thus emphasizing the importance of a functional crosstalk between NK cells and immune cells. In this regard, a potent cross-talk can occur between NK cells and DCs: on one hand NK cells release high levels of cytokines including IFN-gamma and TNF-alpha which promote DC maturation, and in turn DC secrete cytokines such as IL-12, IL-18, IFN-alpha and IL-15 that induce NK cell activation and proliferation. When present at high numbers, NK cells can also kill immature DCs.

Secretion of chemokines is key to the co-localization of NK cells with other hematopoietic cells in areas of inflammation. In this regard, during inflammation activated DCs can secrete several chemokines such as CCL4, CCL5, CX3CL1, CXCL8, and CXCL10 [79].

In vivo, interaction between NK cells and DC has been suggested to occur in the spleen during viral or bacterial infection [80]. Following infection with *Listeria monocytogenes*, CCR2-mediated signals promote emigration of monocytes from bone marrow into the blood stream and eventually to infected tissues where monocytes differentiate into TNF and iNOS producing DCs (Tip-DCs). In this regard Auffray et al. showed that recruitment of monocytes to the spleen during *Lm* infection involves another chemokine receptor, namely CX3CR1 [81]. During infection, DC cells where shown to promote a marked $CD11b^{+}$ and NK cells reorganization in clusters positioned in the T cell areas of the spleen, with the $CD11b^{+}$ cells organized centrally and the NK cells localized peripherally [82]. NK cells were the predominant producers of IFN-gamma, inducing differentiation of $CD11b^{+}$ monocytes into Tip-DC. Among a number of chemokine receptors analyzed, mice deficient in CCR5, the receptor for CCL3-5, had a consistent but partial defect in NK cell clustering while myeloid cell localization were little affected by the lack of this receptor. NK cell interaction with monocytes in spleen may occur also during steady state. Indeed, Soderquest et al. recently evidenced that splenic monocytes drive transition of $CD11b^{high}CD27^{high}$ NK cell into $CD11b^{high}CD27^{low}$ in a IL-15-dependent manner [83]. Beside spleen, several chemokines participates in the recruitment of immune cells into LNs that represent critical sites for NK cell interaction with other immune cells such as DCs and for their ability to modulate DC-dependent Th1 cell polarization during inflammation promoted by adjuvants or LPS-activated DCs [77,78]. NK cell entry was shown to be CXCR3-dependent and this correlated with a rapid and transient expression of CXCL9 in the luminal side of reactive nodes. Subsequent interaction with DC occurs to promote NK cell priming and may be driven by DC-produced chemokines including another CXCR3 ligand, CXCL10. Intravital imaging studies suggested that NK cell priming during inflammation does not require the formation of stable contact between NK cells and DCs during time and paralleled a broader distribution of NK cells that were more located in the deep T cell zone as compared to steady state [84].

In the course of inflammation, NK cells are found in close proximity to DC also in non-lymphoid tissues likely resulting in reciprocal activation. In oral lichen planus, a pathological condition known to be characterized by elevated DC tissue accumulation,

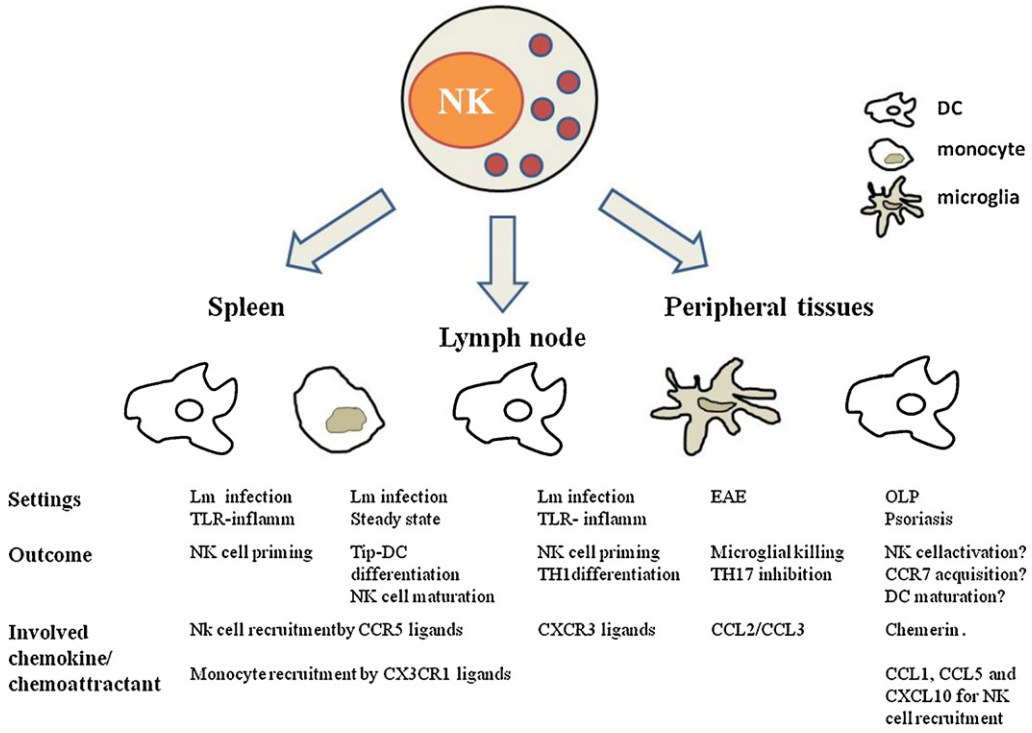

Fig. 2. Chemokines regulate NK cell cross-talk with other immune cells in lymphoid and non lymphoid tissues. NK cells functional interaction with DC, monocytes or tissue resident machrophages can be facilitated by tissue expression of chemokines that promote simultaneous recruitment of cells from circulation facilitating their communication *in vivo*. In addition, several *in vitro* studies have evidenced the role of chemokines produced by NK cells and other immune cells, including CCR5, CXCR3 and XCL1 ligands for reciprocal attraction.

expression of the receptor for chemerin ChemR23, was evidenced on $CD3^{-}CD56^{+}$ NK cells and on $CD123^{+}$/$BDCA^{+}$ and DC-$SIGN^{+}$ DC that were close to each other in proximity of chemerin-expressing endothelial cells lining blood vessels [43].

Also during psoriasis NK cells and DC were found in close proximity, but although chemerin and CCL5 and CXCL10 expression were associated with NK cell accumulation in diseased skin, this did not correlate with their interaction with DCs.

In vitro experiments evidenced other chemokine candidates for DC–NK cell interaction by showing that DCs triggered with bacterial fragments is able to attract $CCR5^{+}$ NK cells by producing CCL5. Contact with activated DC promotes IL-12/IL-18-mediated NK-cell activation, resulting in the production of IFN-gamma and CCR7 expression by a subpopulation of $CD56^{dim}CD16^{+}$ NK cells [79]. During an immune response, also NK cells produce chemokines in response to adhesive, cytokine or activating receptor stimuli, including IL-8, CCL2-5 and XCL-1. NK cell-derived chemokines can promote the recruitment of various leukocytes in inflamed tissues eventually leading to reciprocal activation.

Besides DC, other immune cells may be influenced by NK cell in peripheral tissues. Co-localization studies revealed that NK cells resided in close proximity to CNS microglial cells during experimental autoimmune encephalomyelitis and this correlated with microglial cell killing, thus resulting in NK cell-mediated suppression of Th17 differentiation. Furthermore, CNS NK cells readily produce CCL3 while microglia produced CCL2 likely resulting in reciprocal chemoattraction [74]. Recent evidences describe a cross-talk also between NK cells and neutrophils. Human NK cells may influence the survival and activation of neutrophils under co-culture conditions *via* the release of IFN-gamma or granulocyte macrophage colony-stimulating factor (GM-CSF) plus IFN-gamma, while neutrophil production of ROS reduces survival and activation of NK cells. It has been also suggested that the ROS preferentially affect the $CD56^{low}$ NK cell subset thus indirectly favoring $CD56^{high}$ NK cell-mediated responses. Thus, beside their ability to regulate neutrophil recruitment, chemokines production by NK cells could also affect NK cell–neutrophil encounter in inflamed tissues contributing to the pathogenesis of inflammatory diseases [85].

6. Conclusions

In the steady state, NK cells are present at a high frequency in the circulation, ready to extravasate to tissues under inflammatory conditions. The recent findings reviewed herein, highlight that NK cells respond to several chemoattractants regulating the maintenance of resting NK cells in the circulation or site of maturation, or the recruitment of activated NK cells into the sites of diseases and inflammation. In these locations, NK cells can play an important role as active participants in directing DC maturation and T cell response polarization and/or as cytotoxic effector cells. Involvement of chemokines in the regulation of DC-mediated NK cell priming and effector functions has also been documented and should be taken into account when analyzing the role of chemokines in NK cell-dependent immune responses

Acknowledgments

This work was supported by grants from Italian Association for Cancer Research (AIRC), MIUR-FIRB Futuro In Ricerca, “Sapienza” University, MIUR-L.297 FAR, and the Center of Excellence (BEMM).

References

[1] Trinchieri G. Biology of natural killer cells. Adv Immunol 1989;47:187–376.
[2] Lanier LL. NK cell recognition. Annu Rev Immunol 2005;23:225–74.
[3] Di Santo JP. Natural killer cell developmental pathways: a question of balance. Annu Rev Immunol 2006;24:257–86.
[4] Freud AG, Caligiuri MA. Human natural killer cell development. Immunol Rev 2006;214:56–72.

[5] Kennedy MK, Glaccum M, Brown SN, Butz EA, Viney JL, Embers M, et al. Reversible defects in natural killer and memory CD8T cell lineages in interleukin 15-deficient mice. J Exp Med 2000;191:771–80.
[6] Vosshenrich CA, Samson-Villeger SI, Di Santo JP. Distinguishing features of developing natural killer cells. Curr Opin Immunol 2005;17:151–8.
[7] Srour EF, Brandt JE, Briddell RA, Leemhuis T, van Besien K, Hoffman R. Human CD34+ HLA-DR- bone marrow cells contain progenitor cells capable of self-renewal, multilineage differentiation, and long-term in vitro hematopoiesis. Blood Cells 1991;17:287–95.
[8] Miller JS, Verfaillie C, McGlave P. The generation of human natural killer cells from CD34+/DR− primitive progenitors in long-term bone marrow culture. Blood 1992;80:2182–7.
[9] Caligiuri MA. Human natural killer cells. Blood 2008;112:461–9.
[10] Chiossone L, Chaix J, Fuseri N, Roth C, Vivier E, Walzer T. Maturation of mouse NK cells is a 4-stage developmental program. Blood 2009;113:5488–96.
[11] Huntington ND, Tabarias H, Fairfax K, Brady J, Hayakawa Y, Degli-Esposti MA, et al. NK cell maturation and peripheral axis is associated with KLRG1 up-regulation. J Immunol 2007;178:4764–70.
[12] Vosshenrich CA, García-Ojeda ME, Samson-Villéger SI, Pasqualetto V, Enault L, Richard-Le Goff O, et al. A thymic pathway of mouse natural killer cell development characterized by expression of GATA-3 and CD127. Nat Immunol 2006;7:1217–24.
[13] Santoni A, Zingoni A, Cerboni C, Gismondi A. Natural killer (NK) cells from killers to regulators: distinct features between peripheral blood and decidual NK cells. Am J Reprod Immunol 2007;58:280–8.
[14] Salazar-Mather TP, Ishikawa R, Biron CA. NK cell trafficking and cytokine expression in splenic compartments after IFN induction and viral infection. J Immunol 1996;157:3054–64.
[15] Dokun AO, Chu DT, Yang L, Bendelac AS, Yokoyama WM. Analysis of in situ NK cell responses during viral infection. J Immunol 2001;167:5286–93.
[16] Gregoire C, Cognet C, Chasson L, Coupet CA, Dalod M, Reboldi A, et al. Intrasplenic trafficking of natural killer cells is redirected by chemokines upon inflammation. Eur J Immunol 2008;38:2076–84.
[17] Sciumè G, De Angelis G, Benigni G, Ponzetta A, Morrone S, Santoni A, et al. CX3CR1 expression defines 2 KLRG1+ mouse NK-cell subsets with distinct functional properties and positioning in the bone marrow. Blood 2011;117:4467–75.
[18] Bajénoff M, Breart B, Huang AY, Qi H, Cazareth J, Braud VM, et al. Natural killer cell behavior in lymph nodes revealed by static and real-time imaging. J Exp Med 2006;203:619–31.
[19] Whitelaw PF, Croy BA. Granulated lymphocytes of pregnancy. Placenta 1996;17:533–43.
[20] Doherty DG, O'Farrelly C. Innate and adaptive lymphoid cells in the human liver. Immunol Rev 2000;174:5–20.
[21] Cella M, Fuchs A, Vermi W, Facchetti F, Otero K, Lennerz JK, et al. A human natural killer cell subset provides an innate source of IL-22 for mucosal immunity. Nature 2009;457:722–5.
[22] Satoh-Takayama N, Vosshenrich CA, Lesjean-Pottier S, Sawa S, Lochner M, Rattis F, et al. Microbial flora drives interleukin 22 production in intestinal NKp46+ cells that provide innate mucosal immune defense. Immunity 2008;29:958–70.
[23] Luci C, Reynders A, Ivanov II, Cognet C, Chiche L, Chasson L, et al. Influence of the transcription factor RORgamma on the development of NKp46+ cell populations in gut and skin. Nat Immunol 2009;10:75–82.
[24] Sanos SL, Bui VL, Mortha A, Oberle K, Heners C, Johner C, et al. RORgamma and commensal microflora are required for the differentiation of mucosal interleukin 22-producing NKp46+ cells. Nat Immunol 2009;10:83–91.
[25] Spits H, Di Santo JP. The expanding family of innate lymphoid cells: regulators and effectors of immunity and tissue remodeling. Nat Immunol 2011;12:21–7.
[26] Colonna M. Interleukin-22-producing natural killer cells and lymphoid tissue inducer-like cells in mucosal immunity. Immunity 2009;31:15–23.
[27] Gregoire C, Chasson L, Luci C, Tomasello E, Geissmann F, Vivier E, et al. The trafficking of natural killer cells. Immunol Rev 2007;220:169–82.
[28] Hayakawa Y, Huntington ND, Nutt SL, Smyth MJ. Functional subsets of mouse natural killer cells. Immunol Rev 2006;214:47–55.
[29] Robertson MJ. Role of chemokines in the biology of natural killer cells. J Leukoc Biol 2002;71:173–83.
[30] Chuntharapai A, Lee J, Hebert CA, Kim K. Monoclonal antibodies detect different distribution patterns of IL-8 receptor A and IL-8 receptor B on human peripheral blood leukocytes. J Immunol 1994;153:5682–8.
[31] Morohashi H, Miyawaki T, Nomura H, Kuno K, Murakami S, Matsushima K, et al. Expression of both types of human interleukin-8 receptors on mature neutrophils, monocytes, and natural killer cells. J Leukoc Biol 1995;57:180–7.
[32] Casilli F, Bianchini A, Gloaguen I, Biordi L, Alesse E, Festuccia C. Inhibition of interleukin-8 (CXCL8/IL-8) responses by repertaxin, a new inhibitor of the chemokine receptors CXCR1 and CXCR2. Biochem Pharmacol 2005;69:385–94.
[33] Yoneda O, Imai T, Goda S, Inoue H, Yamauchi A, Okazaki T, et al. Fractalkine-mediated endothelial cell injury by NK cells. J Immunol 2000;164:4055–62.
[34] Campbell JJ, Qin S, Unutmaz D, Soler D, Murphy KE, Hodge MR, et al. Unique subpopulations of CD56+ NK and NK-T peripheral blood lymphocytes identified by chemokine receptor expression repertoire. J Immunol 2001;166:6477–82.
[35] Taub DD, Sayers TJ, Carter CR, Ortaldo JR. Alpha and beta chemokines induce NK cell migration and enhance NK-mediated cytolysis. J Immunol 1995;155:3877–88.
[36] Matloubian M, Lo CG, Cinamon G, Lesneski MJ, Xu Y, Brinkmann V, et al. Lymphocyte egress from thymus and peripheral lymphoid organs is dependent on S1P receptor 1. Nature 2004;427:355–60.
[37] Maghazachi AA. G protein-coupled receptors in natural killer cells. J Leukoc Biol 2003;74:16–24.
[38] Walzer T, Chiossone L, Chaix J, Calver A, Carozzo C, Garrigue-Antar L, et al. Natural killer cell trafficking in vivo requires a dedicated sphingosine 1-phosphate receptor. Nat Immunol 2007;8:1337–44.
[39] Marquardt N, Wilk E, Pokoyski C, Schmidt RE, Jacobs R. Murine CXCR3+ CD27bright NK cells resemble the human CD56bright NK-cell population. Eur J Immunol 2010;40:1428–39.
[40] Paust S, Gill HS, Wang BZ, Flynn MP, Moseman EA, Senman B, et al. Critical role for the chemokine receptor CXCR6 in NK cell-mediated antigen-specific memory of haptens and viruses. Nat Immunol 2010;11:1127–35.
[41] Hodge DL, Schill WB, Wang JM, Blanca I, Reynolds DA, Ortaldo JR, et al. IL-2 and IL-12 alter NK cell responsiveness to IFN-gamma-inducible protein 10 by down-regulating CXCR3 expression. J Immunol 2002;168:6090–8.
[42] Inngjerdingen M, Damaj B, Maghazachi AA. Expression and regulation of chemokine receptors in human natural killer cells. Blood 2001;97:367–75.
[43] Parolini S, Santoro A, Marcenaro E, Luini W, Massardi L, Facchetti F, et al. The role of chemerin in the colocalization of NK and dendritic cell subsets into inflamed tissues. Blood 2007;109:3625–32.
[44] Barlic J, Sechler JM, Murphy PM. IL-15 and IL-2 oppositely regulate expression of the chemokine receptor CX3CR1. Blood 2003;102:3494–503.
[45] Mailliard RB, Alber SM, Shen H, Watkins SC, Kirkwood JM, Herberman RB, et al. IL-18-induced CD83+ CCR7+ NK helper cells. J Exp Med 2005;202:941–53.
[46] Taub DD, Ortaldo JR, Turcovski-Corrales SM, Key ML, Longo DL, Murphy WJ. Beta chemokines costimulate lymphocyte cytolysis, proliferation, and lymphokine production. J Leukoc Biol 1996;59:81–9.
[47] Guo J, Chen T, Wang B, Zhang M, An H, Guo Z, et al. Chemoattraction, adhesion and activation of natural killer cells are involved in the antitumor immune response induced by fractalkine/CX3CL1. Immunol Lett 2003;89:1–7.
[48] Yoneda O, Imai T, Nishimura M, Miyaji M, Mimori T, Okazaki T, et al. Membrane-bound form of fractalkine induces IFN-gamma production by NK cells. Eur J Immunol 2003;33:53–8.
[49] Maghazachi AA, Al-Aoukaty A, Schall TJ. CC chemokines induce the generation of killer cells from CD56+ cells. Eur J Immunol 1996;26:315–9.
[50] Nieto M, Navarro F, Perez-Villar JJ, del Pozo MA, Gonzalez-Amaro R, Mellado M, et al. Roles of chemokines and receptor polarization in NK-target cell interactions. J Immunol 1998;161:3330–9.
[51] Pallandre JR, Krzewski K, Bedel R, Ryffel B, Caignard A, Rohrlich PS. Dendritic cell and natural killer cell cross-talk: a pivotal role of CX3CL1 in NK cytoskeleton organization and activation. Blood 2008.
[52] Ma Q, Jones D, Borghesani PR, Segal RA, Nagasawa T, Kishimoto T, et al. Impaired B-lymphopoiesis, myelopoiesis, and derailed cerebellar neuron migration in CXCR4- and SDF-1-deficient mice. Proc Natl Acad Sci USA 1998;95:9448–53.
[53] Dar A, Kollet O, Lapidot T. Mutual, reciprocal SDF-1/CXCR4 interactions between hematopoietic and bone marrow stromal cells regulate human stem cell migration and development in NOD/SCID chimeric mice. Exp Hematol 2006;34:967–75.
[54] Broxmeyer HE, Orschell CM, Clapp DW, Hangoc G, Cooper S, Plett PA, et al. Rapid mobilization of murine and human hematopoietic stem and progenitor cells with AMD-3100, a CXCR4 antagonist. J Exp Med 2005;201:1307–18.
[55] Broxmeyer HE. Chemokines in hematopoiesis. Curr Opin Hematol 2008;15:49–58.
[56] Egawa T, Kawabata K, Kawamoto H, Amada K, Okamoto R, Fujii N, et al. The earliest stages of B cell development require a chemokine stromal cell-derived factor/pre-B cell growth-stimulating factor. Immunity 2001;15:323–34.
[57] Foudi A, Jarrier P, Zhang Y, Wittner M, Geay JF, Lecluse Y, et al. Reduced retention of radioprotective hematopoietic cells within the bone marrow microenvironment in CXCR4−/− chimeric mice. Blood 2006;107:2243–51.
[58] Tokoyoda K, Egawa T, Sugiyama T, Choi BI, Nagasawa T. Cellular niches controlling B lymphocyte behavior within bone marrow during development. Immunity 2004;20:707–18.
[59] Plotkin J, Prockop SE, Lepique A, Petrie HT. Critical role for CXCR4 signaling in progenitor localization and T cell differentiation in the postnatal thymus. J Immunol 2003;171:4521–7.
[60] Bernardini G, Sciumè G, Bosisio D, Morrone S, Sozzani S, Santoni A. CCL3 and CXCL12 regulate trafficking of mouse bone marrow NK cell subsets. Blood 2008;111:3626–34.
[61] Noda M, Omatsu Y, Sugiyama T, Oishi S, Fujii N, Nagasawa T. CXCL12-CXCR4 chemokine signaling is essential for NK-cell development in adult mice. Blood 2011;117:451–8.
[62] Weiss ID, Shoham H, Wald O, Wald H, Beider K, Abraham M, et al. Ccr5 deficiency regulates the proliferation and trafficking of natural killer cells under physiological conditions. Cytokine 2011;54:249–57.
[63] Yu YR, Fong AM, Combadiere C, Gao JL, Murphy PM, Patel DD. Defective antitumor responses in CX3CR1-deficient mice. Int J Cancer 2007;121:316–22.
[64] Salazar-Mather TP, Orange JS, Biron CA. Early murine cytomegalovirus (MCMV) infection induces liver natural killer (NK) cell inflammation and protection through macrophage inflammatory protein 1alpha (MIP-1alpha)-dependent pathways. J Exp Med 1998;187:1–14.
[65] Hokeness KL, Kuziel WA, Biron CA, Salazar-Mather TP. Monocyte chemoattractant protein-1 and CCR2 interactions are required for IFN-alpha/beta-induced inflammatory responses and antiviral defense in liver. J Immunol 2005;174:1549–56.

[66] Wald O, Weiss ID, Wald H, Shoham H, Bar-Shavit Y, Beider K, et al. IFN-gamma acts on T cells to induce NK cell mobilization and accumulation in target organs. J Immunol 2006;176:4716–29.
[67] Zeng X, Moore TA, Newstead MW, Hernandez-Alcoceba R, Tsai WC, Standiford TJ. Intrapulmonary expression of macrophage inflammatory protein 1alpha (CCL3) induces neutrophil and NK cell accumulation and stimulates innate immunity in murine bacterial pneumonia. Infect Immun 2003;71: 1306–15.
[68] Shang X, Qiu B, Frait KA, Hu JS, Sonstein J, Curtis JL, et al. Chemokine receptor 1 knockout abrogates natural killer cell recruitment and impairs type-1 cytokines in lymphoid tissue during pulmonary granuloma formation. Am J Pathol 2000;157:2055–63.
[69] Morrison BE, Park SJ, Mooney JM, Mehrad B. Chemokine-mediated recruitment of NK cells is a critical host defense mechanism in invasive aspergillosis. J Clin Invest 2003;112:1862–70.
[70] Robinson LA, Nataraj C, Thomas DW, Cosby JM, Griffiths R, Bautch V, et al. The chemokine CX3CL1 regulates NK cell activity in vivo. Cell Immunol 2003;225:122–30.
[71] Widney DP, Hu Y, Foreman-Wykert AK, Bui KC, Nguyen TT, Lu B, et al. CXCR3 and its ligands participate in the host response to *Bordetella bronchiseptica* infection of the mouse respiratory tract but are not required for clearance of bacteria from the lung. Infect Immun 2005;73:485–93.
[72] Trifilo MJ, Montalto-Morrison C, Stiles LN, Hurst KR, Hardison JL, Manning JE, et al. CXC chemokine ligand 10 controls viral infection in the central nervous system: evidence for a role in innate immune response through recruitment and activation of natural killer cells. J Virol 2004;78: 585–94.
[73] Thapa M, Kuziel WA, Carr DJ. Susceptibility of CCR5-deficient mice to genital herpes simplex virus type 2 is linked to NK cell mobilization. J Virol 2007;81:3704–13.
[74] Hao J, Liu R, Piao W, Zhou Q, Vollmer TL, Campagnolo DI, et al. Central nervous system (CNS)-resident natural killer cells suppress Th17 responses and CNS autoimmune pathology. J Exp Med 2010;207:1907–21.
[75] Saudemont A, Jouy N, Hetuin D, Quesnel B. NK cells that are activated by CXCL10 can kill dormant tumor cells that resist CTL-mediated lysis and can express B7-H1 that stimulates T cells. Blood 2005;105:2428–35.
[76] Wendel M, Galani IE, Suri-Payer E, Cerwenka A. Natural killer cell accumulation in tumors is dependent on IFN-gamma and CXCR3 ligands. Cancer Res 2008;68:8437–45.
[77] Martin-Fontecha A, Thomsen LL, Brett S, Gerard C, Lipp M, Lanzavecchia A, et al. Induced recruitment of NK cells to lymph nodes provides IFN-gamma for T(H)1 priming. Nat Immunol 2004;5:1260–5.
[78] Lucas M, Schachterle W, Oberle K, Aichele P, Diefenbach A. Dendritic cells prime natural killer cells by trans-presenting interleukin 15. Immunity 2007;26:503–17.
[79] Van Elssen CH, Vanderlocht J, Frings PW, Senden-Gijsbers BL, Schnijderberg MC, van Gelder M. *Klebsiella pneumoniae*-triggered DC recruit human NK cells in a CCR5-dependent manner leading to increased CCL19-responsiveness and activation of NK cells. Eur J Immunol 2010;40:3138–49.
[80] Andrews DM, Scalzo AA, Yokoyama WM, Smyth MJ, Degli-Esposti MA. Functional interactions between dendritic cells and NK cells during viral infection. Nat Immunol 2003 Feb;4(2):175–81.
[81] Auffray C, Fogg DK, Narni-Mancinelli E, Senechal B, Trouillet C, Saederup N, et al. CX3CR1+ CD115+ CD135+ common macrophage/DC precursors and the role of CX3CR1 in their response to inflammation. J Exp Med 2009;206:595–606.
[82] Kang SJ, Liang HE, Reizis B, Locksley RM. Regulation of hierarchical clustering and activation of innate immune cells by dendritic cells. Immunity 2008;29:819–33.
[83] Soderquest K, Powell N, Luci C, van Rooijen N, Hidalgo A, Geissmann F, et al. Monocytes control natural killer cell differentiation to effector phenotypes. Blood 2011;117:4511–8.
[84] Beuneu H, Deguine J, Breart B, Mandelboim O, Di Santo JP, Bousso P. Dynamic behavior of NK cells during activation in lymph nodes. Blood 2009;114:3227–34.
[85] Costantini C, Cassatella MA. The defensive alliance between neutrophils and NK cells as a novel arm of innate immunity. J Leukoc Biol 2011;89:221–33.