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REVIEW

Stromal-cell regulation of natural killer cell differentiation

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Abstract Natural killer (NK) cells are bone-marrow-derived lymphocytes that play a crucial role in host defense against some viral and bacterial infections, as well as against tumors. Their phenotypic and functional maturation requires intimate interactions between the bone marrow stroma and committed precursors. In parallel to the identification of several phenotypic and functional stages of NK cell development, recent studies have shed new light on the role of stromal cells in driving functional maturation of NK cells. In this review, we provide an overview of the role of bone marrow microenvironment in NK cell differentiation.

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Keywords Natural killer cells · Transcription factors · Stromal-cell regulation

Introduction

Natural killer (NK) cells were originally described as a distinct subset of lymphoid cells capable of lysing certain tumor cells without prior sensitization [1]. Over the years, they have been found to play an important role in combating infections, in graft rejection, and in pregnancy [2–6]. Upon activation, they directly lyse target cells,

through exocytosis of perforin- and granzyme-containing granules, CD95 ligand (FasL), or tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) pathways [7–9], and they produce cytokines, such as interferon (IFN)-γ, TNF-α, and granulocyte–macrophage colony stimulating factor (GM-CSF) [10–16]. NK cell target recognition depends on the expression of a set of inhibitory and activating receptors that recognize ligands on target cells, and their activation is subjected to the balance of signaling through these inhibitory vs activating receptors (reviewed in [17–19]).

In the mouse, there are two families of major histocompatibility complex (MHC) class I specific inhibitory receptors, Ly49 and CD94-NKG2A, both of which are expressed on overlapping subsets of mature NK cells [17]. These inhibitory receptors, by preventing NK cell activation and killing of normal self cells that express high levels of autologous class I MHC molecules, provided the molecular basis for the "missing self" hypothesis [20], although non-MHC-binding inhibitory receptors have more recently broadened the definition of self [21–24]. As for mouse-activating receptors, such as NKRP1A and NKRP1C (NK1.1), DX5, CD69, Ly49D and H, and NKp46 and NKG2D [19, 25, 26], they recognize ligands on target cells, which are induced upon infection, transformation, or stress (reviewed in [27, 28]). Adhesion molecules also participate in interaction between NK cells and their target cells, such as mouse or human CD2 (LFA-2), CD11a (LFA-1), CD11b (Mac-1), CD43 (sialoadhesin), and CD44, or human Lag3 and CD56 (N-CAM), which are expressed by NK cell subsets [29–31].

Early experiments have shown that NK cells in the adult mouse are derived from bone marrow hematopoietic precursors and that their full maturation into cytolytic cells requires an intact bone marrow microenvironment [32–34]. Unlike other lymphocytes, they are present in severe combined immunodeficiency (SCID) or recombination activating gene (RAG)-1 or RAG-2-deficient mice, suggesting that their differentiation does not require events essential for antigen receptor rearrangement [35–38].

Recent progress has been made by identifying molecules, such as cytokines, receptors, and transcription factors contributing to NK development [29, 39], as well as receptors expressed by immature and mature NK cells [17, 19, 40, 41]. In line with the identification of self-MHC class I specific receptors, several studies have attempted to define the active mechanisms that control self-tolerance of NK cells and/or drive their functional maturation [42–45].

This review will address some recent findings in the field of NK cell development, with particular emphasis on the role of bone marrow stromal cells in the acquisition of inhibitory and activating NK cell receptors and NK cell effector functions.

Identification of NK progenitors

In the embryo

Early studies have established the existence of a restricted NK/T cell progenitor in the fetal thymus, which expresses FcγRIII and gives rise to either TCRαβ$^+$T cells or NK cells after intrathymic or intravenous transfer [46]. Subsequent studies have shown that this population is heterogeneous, with some of the cells expressing the NK markers NK1.1 and DX5 but not CD117 (c-Kit), while others express NK1.1 and CD117 but not DX5 [47, 48]. Based on in vitro culture systems and functional activities using both types of precursor cells, it was concluded that the CD117$^+$ population represents bipotent T/NK precursor cells, while the CD117$^-$ DX5$^+$ cells are mature NK cells.

Analysis of fetal blood revealed the existence of a prethymic NK1.1$^+$ CD90$^+$ CD117$^+$ NK/T-cell-restricted progenitor cell, which is capable of differentiating into NK cells or T cells but not into B cells or myeloid cells [49]. More recent studies have clearly established the existence of a clonal lineage-restricted T and NK cell progenitor both in the fetal liver and the fetal thymus [50, 51]. Using in vitro culture of early thymocyte precursors and OP9 stromal cells engineered to produce notch ligand delta 1, the existence of such bipotent T/NK precursors have been confirmed within the DN1 (CD44$^+$ CD25$^-$) and DN2 (CD44$^+$ CD25$^+$) early thymocytes [52, 53]. While these studies clearly show that single fetal DN2 thymocytes, differentiating into T-restricted precursors in the presence of notch ligands, still possess an NK lineage potential, the signals delivered by the thymic stroma driving these early thymocytes towards the NK lineage are still unknown. Among potential candidates, membrane lymphotoxin, which is indispensable for Vα 14 NKT cell differentiation, but not for the development of conventional T-cells, could be involved in NK cell differentiation in the thymus [54].

In the adult

NK cell development outside the bone marrow

In adult mice, while the bone marrow microenvironment is known to be critical for NK cell development, other sites were shown to also contribute to the emergence of peripheral mature NK cell pool [55–58]. NK cells originating in the thymus have been notably identified as a distinct population differing from bone-marrow-derived NK cells by the expression of GATA-3 and CD127 [interleukin-7 receptor alpha (IL-7Rα)] [57]. Whether these cells differentiate in the thymus from early or late bone-marrow-derived committed NK precursors is still unknown. The bone marrow could be involved in the initial steps of NK

cell differentiation, whereas their final maturation would be achieved in other sites [29, 58]. The existence of immature NK cells in the lymph node, spleen, and liver would be consistent with this possibility [9, 59], although mature NK cells are also found in the bone marrow [41, 60]. Notably, the fact that GATA-3^{+} NK cells are present in the thymus and bone marrow, and that IL-7 is produced by stromal cells in both of these sites, strongly suggests the existence of additional signals required for the selective homing and development of CD127^{+} NK cells in the thymus.

The same holds true for the liver, which should deliver in the adult specific signals for the homing or development of a unique Mac-1^{lo} DX5^{lo} NK cell subset that expresses cell surface TRAIL and can use this effector pathway [9]. On the contrary, the lymph nodes, which do not represent a site for NK cell development under steady-state conditions, can recruit CD62L^{+} CCR7^{+} NK cells under antigenic stimulation, providing an initial source of IFN-γ production necessary for TH1 polarization [61].

In human, the recent identification of NK precursors, which are CD34^{dim} CD45RA^{+} integrin $\alpha_4\beta_7^{hi}$ and are highly enriched in the lymph nodes, strongly suggests that bone-marrow-derived human NK precursors migrate from the bone marrow to the lymph node, where endogenous cytokines drive their differentiation into CD56^{bright} NK cells in vivo [55]. Altogether, these observations have led to models in which immature (and perhaps mature) NK cells originating from the bone marrow can migrate through the peripheral blood and colonize other sites where they receive specific signals to further proliferate and differentiate into specialized functional NK cell subsets.

NK cell development in the bone marrow

NK cells are mostly bone-marrow-derived, and they are dependent upon an intact bone marrow microenvironment for final maturation into lytic cells. Indeed, treatment of mice with ^{89}Sr, a bone marrow seeking isotope, results in selective destruction of the bone marrow cavity and loss of NK killing activity in the spleen, while the numbers and functions of B cells, T cells, and macrophages remain largely unchanged [32, 33]. This was further confirmed in estrogen-treated mice and in congenitally osteopetrotic (mi/mi) mice, which have NK1.1^{+} target binding, non-lytic, and non-IFN-inducible cells present in their spleens [62]. Interestingly, when NK progenitors from normal bone marrow were transplanted into estrogen-treated mice, lytic NK cells failed to develop while splenocytes from treated-animals gave rise to normal NK cells upon transplantation into irradiated normal animals [63, 64]. Collectively, these results indicated that there are two phases in NK cell differentiation. In the first one, early precursors differentiate into non-lytic NK cells, capable of binding their targets, independently of an intact bone marrow microenvironment. In the second phase, the bone marrow microenvironment is absolutely required for immature NK cells to acquire their full cytotoxic potential.

Using in vitro culture systems or in vivo transplantation assays, early precursors in the bone marrow that could give rise to B, T, NK, and DCs were identified as Lin^{-} (CD3^{-} CD19^{-} Ter119^{-} Gr1^{-}) c-Kit^{hi} Sca-1^{+} fms-related tyrosine kinase 3 (FLT3)$^{+}$ CD34^{+}. These cells, which are lymphoid specified and have greatly reduced non-lymphoid differentiation potential, have been termed early lymphoid progenitors (ELPs) [65–67]. Common lymphoid progenitors (CLPs), which derive from these early precursors, are Lin^{-} Kit^{lo} Sca-1^{lo} IL-7Rα^{+} and cannot generate myeloid-lineage cells [68]. Although ELP and CLP precursors have the potential to give rise to B, T, and NK cells in vitro and in vivo, it is not clear whether mature NK cells must transit through these intermediates. For example, the c-kit-deficient Vickid mice lack CLP but have normal numbers of peripheral NK cells [69, 70]. Further differentiation of CLP results in the acquisition of IL-2/IL-15Rβ (CD122) by committed NK precursors (NKP), which become IL-2 or IL-15 responsive and are restricted to the NK lineage. NKP have been identified and characterized in the fetal thymus and the bone marrow of the adult mice with the following phenotype: Lin^{-} CD122^{+} NK1.1^{-} DX5^{-} [71, 72]. Importantly, while signals such as transcription factors (TFs) and cytokine receptors have been implicated in imposing lymphoid commitment, those responsible for generating NKP in the bone marrow and thymus are still poorly understood. The bone-marrow-derived NKP express CD122 but neither NK1.1 nor DX5 (pan-NK cell markers), and they give rise exclusively to functional NK cells in vitro. The next stages of NK cell development, identified in the bone marrow of the adult mice [41, 73], are characterized by the sequential acquisition of NK1.1 (Nkrp1c; with CD94/NKG2, NKG2D, and integrin α_v, stage II), c-kit and Ly49 receptors (stage III), and the differential modulation of integrin α_2 (DX5) and integrin α_v (stage IV; Fig. 1). At this stage, developing NK cells proliferate vigorously and undergo a substantial and specific expansion in the bone marrow. Thereafter, as NK cells upregulate the expression of Mac-1 (integrin α_M) and CD43 (stage V), they become fully competent to kill their target and secrete cytokines. Finally, a recent detailed repertoire analysis revealed that mature Mac-1^{hi} NK cells can be further divided into CD27^{hi} and CD27^{lo} subpopulations, representing effector cells and long-lived terminally differentiated mature NK cells, respectively [60, 74]. Interestingly, in the C57Bl/6 strain (H-2^{b}), a higher proportion of the CD27^{lo} NK cell subset expresses self-recognizing Ly49 and KLRG1 inhibitory receptors, their cytotoxic activity being more tightly regulated than that of the CD27^{hi} subset. As for human NK

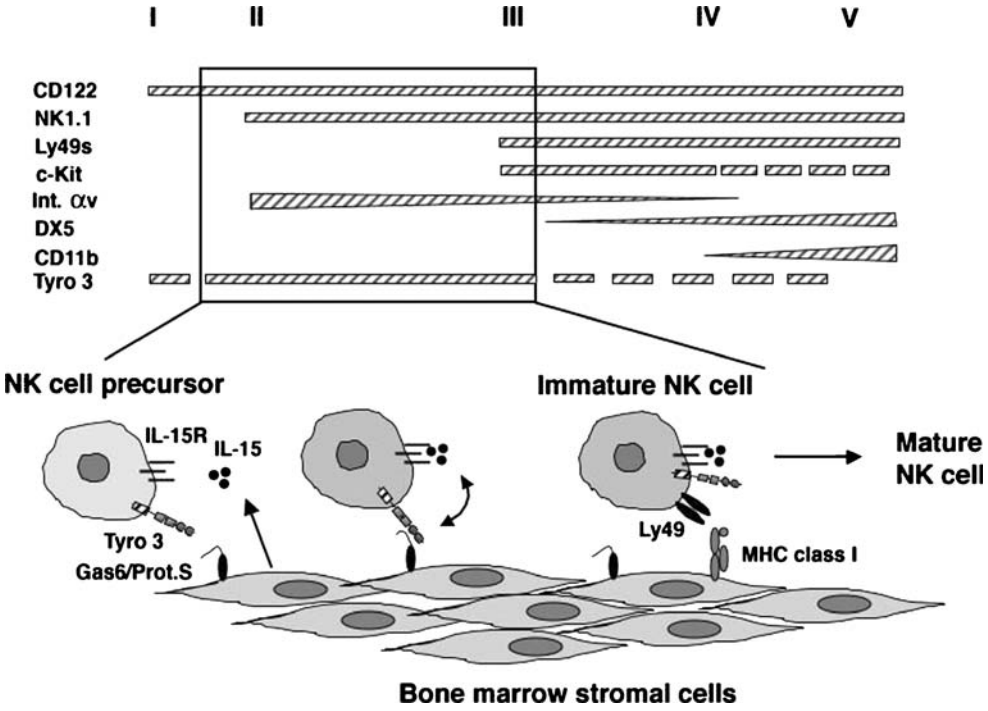

Fig. 1 Phenotypic markers expressed by developing NK cells in the bone marrow. NK precursors (*NKP*) are characterized by CD122 expression (*stage I*), but they lack other NK cell markers. Immature NK cells expressed NK1.1 (*stage II*), Ly49 molecules (*stage III*), and DX5 and CD11b integrins (*stage IV*), whereas they downregulate the expression of integrin α_v (*stages IV* and *V*). A hypothetical model of the different signals intervening during interactions between NKP and bone marrow stromal cells underlines the role of Tyro 3/ligand interactions and IL-15 signaling in driving NK cell differentiation between stages II and III of NK cell development

cells, the $CD56^{dim}$ subset has a high expression of KIRs and cytotoxic granules and exhibit higher cytotoxic activity than the $CD56^{bright}$ subset [74, 75].

Signals delivered by the bone marrow environment

1 "Early" signals and NKP generation

While the bone marrow represents the generative site for NKP, which undergo further maturation both in the bone marrow itself and in other sites, it remains to be determined whether it is sufficient to support all the stages of NK cell development. It is possible, for example, that treatments leading to bone marrow ablation could affect the capacity of NK precursors to respond to maturation signals in other sites than the bone marrow itself. The identification of NK cell precursors and immature NK cells in the spleen and the liver that express the effector molecule TRAIL and the recent identification of thymus-derived GATA-3^+ $CD127^+$ NK cells in the thymus are in agreement with the prediction of an organ-specific maturation of NK precursors. In line with this model, the mature and functional NK cells found in the bone marrow could thus constitute a reservoir for other sites, which can be mobilized quickly upon infection or stress [76].

In the bone marrow environment, the generation of NKP from hematopoietic stem cells (HSC) appears to be subtly controlled by the coordinated action of TFs and signals derived from bone marrow stromal cells. Briefly, these TFs include those involved in the generation of NKP from ELP, such as PU.1, Ikaros, Ets-1, and Id2, those involved in the further maturation of immature NK cells (Gata-3, IRF-2, and T-bet), and those involved in the functional differentiation of mature NK cells [CCCAAT/enhancer-binding protein-γ (CEBP-γ), myeloid ELF1-like factor (MEF), and microphthalmia-associated transcription factor MITF] [29]. Among the signals delivered by the bone marrow environment, c-kit-L, Flt3L, and gamma-chain-dependent cytokines play a general role in lymphoid and in NK cell commitment, as ELP, CLP, and NKP, respectively, express receptors for these cytokines and are therefore sensitive to these growth factors. However, none of these cytokine alone is essential for the generation of committed NK precursors, as shown in mutant animals (c-kit-, γc- or FLT3L-deficient) that have a normal or only a slight reduction in the absolute number of NKP [70, 77]. In fact, close interactions between ELP precursors and stromal cells are required for NKP generation, as shown in vitro using irradiated long-term bone marrow cultures (LT-BMC) as stromal cells [78, 79]. Along those lines, interactions between lymphotoxin (LT) α1β2-expressing hematopoietic cells and LTβ receptor (LTβR)-expressing stromal cells were shown to induce the activation of stromal cells and the expression of IL-15 receptor on NK precursors rendering them IL-15 sensitive [71, 80]. In addition, an instructive role of a stress-response gene, named vitamin D3 upregulated protein 1 (VDUP-1) in the induction of CD122 expression has been recently highlighted, as NKP ($CD122^+$) cells are undetectable in VDUP-$1^{-/-}$ mice [81].

2 "Late" signals acting downstream NKP

2.1 Transcription factors

Several TFs, including T-bet [82], IFN-regulatory factor-2 (IRF-2) [83], and GATA-3 [59], which could act in a

sequential fashion [56], exert their roles in controlling the differentiation of immature NK cells in the bone marrow and their subsequent migration in other peripheral sites. In the absence of these TFs, bone marrow NK cells are increased, whereas there is a reduction in the number of peripheral, splenic, or liver NK cells. NK cells from mice lacking these TFs share the same phenotype with a low expression of CD11b and CD43, a reduced capacity to secrete IFN-γ, and a normal cytotoxic activity against sensitive target cells, suggesting that some effector functions could be detected on phenotypically immature NK cells. Other TFs such as the MEF, the MITF, and the CEBP-γ influence the effector functions of NK cells, as revealed by the normal NK cell development, but impaired cytotoxicity and cytokine production in NK cells deficient in these TFs [84–86].

Knowing that acquisition of Ly49 receptors on immature NK cells represents a crucial step before expansion and functional maturation, numerous studies have attempted to identify the molecular signals involved in the acquisition of Ly49 molecules on developing NK cells in the bone marrow. They have notably shown in vitro and in vivo that Ly49 receptor expression depends on cellular interactions between NK precursors and stromal cells and is induced in an ordered and cumulative way, although the precise order varies as a function of the culture system and the detection method used [87–90].

Using a transgene containing the entire *Ly49a* gene, Tanamachi et al. [91] defined a critical regulatory element, upstream the Ly49a transgene, which is essential for normal Ly49A expression in NK cells, in a variegated manner similar to endogenous Ly49A expression. This element was shown to correspond to a distal promoter element, called Pro1, that is active only in immature NK cells [92]. Evidence that Pro1 is conserved in other Ly49 genes and exhibits bidirectional promoter activity led to a molecular model to account for variegated expression of Ly49 genes, in which activation of gene expression is a probabilistic function dependent on the relative strengths of the forward and reverse promoter activities of Pro1, which then influence stable activation of the Pro2 and Pro3 promoters used in mature NK cells [93].

Several TFs have been shown to control the formation of the Ly49 repertoire in developing NK cells. Indeed, TCF-1 positively regulates the expression of Ly49A and D receptors and negatively regulates the expression of Ly49G and I molecules [94, 95], whereas the LEF-1 TF appeared to have only a minor impact on Ly49G2 receptor expression [96].

2.2 Cytokines

Among the multiple factors interacting with the γc-dependent cytokine receptors, IL-15 is the main cytokine that controls the activation of IL-15Rβ^{+} NKP precursors as well as immature and mature NK cells. This factor, which is essential for the development and the survival of mature NK cells in the periphery [76, 97–100], was shown to be associated with the IL-15Rα subunit on hematopoietic and non-hematopoietic cells and presented *in trans* to NK precursors expressing the β and γ chains of the IL-15 receptor [101]. However, while its implication in the early steps of NK development has been clearly established, its exact role in the late stages of NK cell differentiation is still a question of debate. Some studies have indeed shown a nearly normal Ly49A, D, and CD94 and a reduced Ly49G2 and C/I repertoire expression in RAG2$^{-/-}$×IL-15$^{-/-}$ animals [77], while others have found more profound abnormalities in Ly49A, G2, and I receptor expression in IL-15$^{-/-}$ mice [83, 102]. These differences in the Ly49 repertoire observed in IL-15-deficient NK cells could be due to differences in the genetic backgrounds of mice in which the repertoire was studied, the RAG-deficient animals providing a better environment for a subpopulation of NK cells to proliferate and/or differentiate in vivo, independently of IL-15 [76]. Other molecules, such as membrane LT, may also participate in the formation of the NK cell Ly49 receptor repertoire, although the results were not in complete agreement [103, 104]. The fact that exogenous IL-15 could correct the Ly49 receptor repertoire in LTα$^{-/-}$ mice and that LTβR signaling induces IL-15 production by stromal cells strongly suggests that Ly49 regulation is mediated at least in part by signals mediated by LTβR through the activation of IL-15 [103].

2.3 MHC class I molecules

Although it has been known for many years that NK cells with mature phenotype develop in normal numbers in MHC class I deficient mice and humans [105, 106], NK cells arising in the absence of MHC class I molecules are functionally hyporesponsive, meaning that they exhibit reduced but still significant functional activity in most assays [17, 107]. Furthermore, a subset of NK cells lacking self-MHC-specific inhibitory receptors (Ly49 in mouse or KIR in human) was shown to exist in both species, and this NK subset exhibited hyporesponsive functional activity similar to that of the NK cells in class I deficient animals [42, 44, 108]. These studies demonstrated that engagement of inhibitory MHC-specific receptors influences the functional status of NK cells. Indeed, the cytoplasmic immunoreceptor tyrosine-based inhibitory motif (ITIM) of an inhibitory Ly49 receptor was shown to be critical for NK cells to attain higher functional activity [44]. It remains controversial, however, whether the engagement of inhibitory receptors is necessary for NK cells to undergo a terminal differentiation step where full functionality is attained. The alternative interpretation is that NK cells mature fully without engaging these receptors but are subsequently "anergized" because they are persistently stimulated by other cells in the body (reviewed in [43, 109]). Whichever

hypothesis is correct, and they are not mutually exclusive, the recent studies have shed new light on NK cell self-tolerance.

2.4 Other signaling pathways

Among the signaling molecules that influence the formation of the Ly49 repertoire, PLCγ-2, a key regulator of intracellular calcium mobilization, was shown to be critical for the final stage of NK cell development, as revealed by the partial reduction of Ly49 expression and the dramatic impairment of functional activity in NK cells deficient for this enzyme [110, 111].

More strikingly, using an in vitro stroma-dependent system to induce NK cell differentiation [87], an analysis of differentially expressed transcripts from different bone-marrow-derived NK clones allowed the identification of receptors for stromal factors involved in NK cell development [112]. These factors, Gas6 and protein S, are the endogenous ligands for the Tyro 3/Axl/Mer (TAM) family of protein tyrosine kinase (PTK) receptors [113–119], which are expressed on NK precursor cells. A clear demonstration of the role of these ligands and their receptors in NK cell development was provided by the analysis of NK cell differentiation and functional maturation in mice deficient for one or more members of the Tyro 3 receptor family. In mice deficient for all three receptors, not only was the repertoire of inhibitory and activating NK cell receptors greatly altered in the bone marrow but the NK cells were also deficient in killing sensitive targets and in initiating cytokine production in response to immune stimuli [112]. In addition, the reduced expression of the integrins Mac-1 and DX5 and the increased expression of integrin α_v in the receptor knockouts suggested that Tyro 3 receptors are required between stages II and III of NK cell development. Finally, an instructive role for these Tyro 3 receptors was indicated by studies using fibroblasts expressing Gas6/protein S to support NK cell differentiation in cell culture. In clonal conditions, recombinant versions of these ligands drove growth and differentiation of NK cell precursors in vitro, confirming the direct involvement of these ligands in NK cell development. Important issues that need further investigation include defining the stage of NK cell development, where precursors express these Tyro 3 receptors, and whether Axl, Tyro 3, and Mer are sequentially expressed. Considering the lack of functional activity in NK cells deficient for the Tyro 3 receptors, it will also be important to determine whether Tyro 3 receptor signaling on subpopulations of mature NK cells can directly induce their functional activation or if these PTK receptors induce NK cell functions through the expression of still unknown activating receptors. Interestingly, Tyro 3 receptors contain a conserved ITIM motif [118, 120], which could act in conjunction with inhibitory Ly49 molecules in the acquisition of NK cell effector functions [44].

More strikingly, these results fit very well with the recent demonstration of an interaction between Axl and the IL-15Rα subunit. In murine fibroblasts, Axl stimulation through Gas6 could indeed induce a significant upregulation of IL-15Rα, and IL-15 could transactivate Axl and its associated signaling pathway, leading to tyrosine phosphorylation of both Axl and IL-15Rα and activation of the phosphatidylinositol 3-kinase/Akt pathway [121, 122]. While this heterotypic association remains to be validated in NK cells, one possibility could be that Axl expressing NK precursors could respond to bone-marrow-derived Gas6/ProtS signals, leading to the expression of IL-15Rα chain by early NK precursors (before the NKP stage), which thus become sensitive to IL-15 signals provided by the surrounding bone marrow stromal cells. The analysis of Axl and IL-15Rα protein expression on various populations of committed NK precursors should give some clues on the respective role of these receptors in the early steps of NK cell differentiation. As for the expression of IL-15Rα, which is induced upon Axl signaling in fibroblasts [121], it remains to be determined whether this holds true for NKP cells or their immediate progenitors, which express low levels of IL-15Rα transcripts [72]. Identification of the signals that regulate the expression of both the IL-15Rα and the IL-15Rβ chains on NK-committed precursors should provide crucial information on the mechanisms involved in NK cell development.

Conclusion

Despite considerable progress in identifying activating and inhibitory receptors that guide natural killer (NK) cell specificity for their target cells, little is known about the molecular signals required for their differentiation in the bone marrow, the main site of NK cell differentiation in the adult. For instance, the nature of the interactions between NK progenitors and the bone marrow microenvironment that promotes receptor acquisition and NK cell maturation remains poorly understood. Identification of these signals, which act on developing intermediates, should help in understanding how NK cells acquire a complete and functional repertoire. In the adult, this repertoire ensures that NK cells are self-tolerant (unresponsive to normal self cells) and maximally effective against target cells (responsive to abnormal or missing self). Clearly, the identification of receptors regulating NK-cell function, as well as the signals that promote their expression, should give a more complete picture of NK development and shed light on the pathogenesis of certain immune disorders. It may also offer novel tools for molecular intervention in these diseases.

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