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LFA-1 antigen identifies immature stages of human NK cell differentiation

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Background. Human Natural killer (NK) cells are characterized by NK cell receptors (NKRs) with inhibitory and activatory function that finely control their functional activities. In particular, they express inhibitory receptors for MHC class I molecules, named killer cell immunoglobulin (Ig)-like receptors (KIRs) and C-type lectin CD94-CD159a, and many triggering molecules like NKp30, NKp44, NKp46, (called natural cytotoxicity receptors, NCRs), NKG2D, CD161, and CD244. The majority of peripheral blood human NK cells are characterized by a phenotype with a low density expression of CD56 ($CD56^{dim}$) and a high expression of CD16 ($CD16^{bright}$), whereas a minority (approximately 5–10%) shows a bright expression of CD56 ($CD56^{bright}$). This latter NK subset presents relatively high expression of some cytokine receptors (CD117 and CD25) and the CD94-CD159a heterodimeric inhibitory receptor. CD56bright NK cells are widely expressed in lymphoid tissues and can be generated from CD34+ cells when cultured with combinations of flt-3 ligand (FL) or stem cell factor plus IL-15 or IL-2. During their development, NK cells sequentially acquire many different antigens but there is still limited knowledge on differentiation antigens able to identify immature human NK cells and the specific sequence through which developing NK cells acquire the expression of NKR.

Methods. NK cells obtained from human CD34+ hematopoietic progenitor cells after 30-day culture with FL plus IL-15, or from peripheral and umbilical cord blood samples were characterized.

Results. Virtually, all CD56 NK cells differentiated in vitro expressed CD117, CD25, NCRs, NKG2D, CD161, and CD244, while only a subset expressed CD18-CD11a (LFA-1), and CD94 molecule, defining an immature $CD56^{bright}$/NCRs+/NKG2D+/$LFA\text{-}1^{-}$/$CD94^{-}$ subset. Another small subset of cells expressing CD94 but not LFA-1 integrin was also identified, suggesting that during NK differentiation LFA-1 might be upregulated later than CD94. To verify this hypothesis in vivo, we evaluated the NK cell expression of LFA-1 in both peripheral and umbilical cord blood samples. Interestingly, in these blood fluids, we have identified a lineage negative CD34-/$LFA\text{-}1^{low}$/$NKp46^{dim}$/$NKG2D^{dim}$/$CD94^{-}$ subset that resembled an immature stage of NK cells present in lymph nodes.

Conclusions. Altogether, the results indicate that CD18-CD11a integrin, as well as CD11b in mice, may be a useful marker to identify immature stages of human NK cell differentiation.

Keywords: Natural killer cells, differentiation, phenotype