ADAM17 and CD56^{low}CD16^{low} NK cells

Natural killer (NK) cells are important lymphocytes with potent anti-tumor and anti-viral functions. In recent years there has been a significant increase in knowledge about the mechanisms regulating NK-cell functions. Furthermore, NK cells play an important role in preventing relapse in patients with myeloid malignancies after allogeneic hematopoietic cell transplantation.[1,2] Also, due to their anti-leukemia properties, there has been a keen interest in the use of NK cells in novel adoptive transfer protocols for patients with hematologic and non-hematologic malignancies.[3-5]

Human NK cells are negative for CD3 expression but uniformly express CD56, and based on CD56 and CD16 expression, two main subsets are present in the peripheral blood: CD56^{high}CD16$^{low/-}$ and CD56^{low}CD16^{high}. CD16 is the low affinity IgG receptor (FcγRIII) and human NK cells exclusively express CD16a, a transmembrane protein critical for mediating antibody dependent cell cytotoxicity (ADCC) function of NK cells. CD16 is rapidly down-regulated upon NK-cell activation and was recently shown to be mediated primarily by shedding function of ADAM17 (A Disintegrin And Metalloprotease-17).[6,7] CD56^{low}CD16$^{low/-}$ cells, therefore, normally represent NK cells which have been activated and thus shed their CD16.[8,6] ADAM17 also has other substrates such as CD62L on NK cells.

We were excited to read the interesting study by Stabile *et al.* recently published in this Journal which shows an increased population of CD56^{low}CD16^{low} NK cells in the bone marrow (BM) of healthy children as well in leukemia patients.[9] We wonder whether this represents increased activity of ADAM17 in the marrow especially in leukemia patients, perhaps representing an NK-cell-activating event. Therefore, it would be useful to assess for ADAM17 expression and/ or activity in these patients and the expression of other ADAM17 substrates such as CD62L. In fact, BM expression of CD56^{low}CD16^{low} NK cells has lower CD62L, consistent with this possibility. The authors also show increased function of these cells upon their stimulation with K562 leukemia cell line (see Figure 6A of the work by Stabile *et al.*[9]). However, this assessment of the degranulation function by gating on the CD56^{low}CD16^{low} NK-cell subset using bulk NK cells is problematic as shedding of the CD16 is dynamic and rapid during co-culture with K562 perhaps leading to biased gating of the degranulated (CD107a positive) NK cells in the CD56^{low}CD16$^{low/-}$ gate. This issue has been discussed in previous studies[8,10] and could be addressed by repeating this assay using flow cytometry sorted subsets (without activation) as the authors have done for their cytotoxicity assay (see Figure 6D of the work by Stabile *et al.*[9]). Furthermore, if CD56^{low}CD16^{low} is truly a unique NK-cell subset, it would be important to determine their differentiation and maturation schema in human NK-cell development.

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doi:10.3324/haematol.2015.129213

Key words: natural killer cell function, ADAM17 expression, CD56^{low}, CD16^{low}, cell development.

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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