The Complexity of Natural Killer Cells

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References

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In Response: We read with interest the comment by Sconocchia et al. describing a cell population with $CD56^{dim}$ $CD16^{low/negative}$ phenotype derived from interleukin 2/stem cell factor–cultured $CD34^{+}$ cells which lack cytotoxic markers and cytotoxicity. Based on CD33 expression, the authors propose that these cells define a new type of myeloid natural killer (NK) cells with antiproliferative capacity and assume a linkage to the noncytolytic low–NK/tumor-infiltrating lymphocyte population that we described recently (1).

This assumption foremost raises the question of how an NK cell is defined. It is accepted that expression of CD56 alone does not characterize NK cells sufficiently because other cell types, including certain T cells, tumor cells, and monocytes, can positively stain with anti-CD56 antibodies. Defining NK cells functionally through their killing ability is also insufficient because environmental conditions, such as chronic viral infection and tumor burden, can impede with this ability. Nevertheless, some criteria have been accepted as characteristics for NK cells. Foremost, it is the lack of lineage markers CD3, CD19, and CD14 and then, as recently described, the expression of NKp46, which is present on every NK cell independent of CD56 and CD16.

Minding these considerations, more information on other markers (CD14, NKp46) is required to appropriately discuss the question raised by Sconocchia et al.

In our study, tumor-infiltrating lymphocytes were stained with a combination of CD3, CD56, and CD16 and either perforin, granzymeA, granzymeB, or NKp46. Additionally, an electronic gate was set on the small lymphocyte subset using forward and side scatter characteristics. Within this gate, NK cells were uniformly identified as $CD3^{-}CD56^{+}$ and $NKp46^{+}$. Due to low cell numbers, CD33 was not included in our analysis. In some cases, a combination of CD14, CD56, and CD3 was tested. A low level of CD56 staining was regularly observed for $CD14^{+}$ cells of healthy donors and patients. These cells corresponded to the larger and more granular cells and were absent within the small lymphocyte gate, which we used for tumor-infiltrating lymphocyte analysis. Thus, our low–NK/tumor-infiltrating lymphocyte cells are, at least morphologically, different from the myeloid cells of Sconocchia et al. In spite of this, it is undisputable that various populations of NK cells exist, some of them with other functions than cytotoxicity. $CD16^{-}CD56^{bright}$ NK cells, whose prominent role seems to be cytokine secretion, are described (2), some of them being cytostatic for a variety of cell types. NK cells also have a key role in dendritic cell biology and adaptive immune activation (3). Whether a distinct NK cell subpopulation is involved is yet unknown. We, therefore, strongly agree with Sconocchia et al. that noncytolytic NK cells are of particular interest and need further attention.

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