Commentary

Trace Evidence: Identifying Natural Cancer Killers After the Crime

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NK cells possess tremendous diversity with respect to receptor repertoire, with the average person having between 6000 and 30,000 different phenotypes (Horowitz et al., 2013). With variegated expression of over 30 activating and inhibitory receptors, identifying which among these many phenotypes is responsible for recognition and elimination of specific viral infections or malignancies has not been feasible in most circumstances. In this issue of *EBioMedicine*, Krzywinska et al. (Krzywinska et al., 2015) have identified CD45RO as a unique marker of activated natural killer (NK) cells. CD45 is a phosphatase associated with lymphocyte signaling (Tonks et al., 1988; Ledbetter et al., 1988; Charbonneau et al., 1988) which is expressed in several forms that can be discriminated by antibodies to extracellular determinants. The splice variant CD45RO is the short isoform of CD45, which is expressed on memory T cells (Sanders et al., 1988; Thomas and Lefrancois, 1988). An NK cell population expressing both CD45RA and CD45RO was identified in patients with hematological malignancies, and these cells possessed features of having recently been activated. By further demonstrating evidence of recent interaction with leukemic cells in vivo, the authors suggest that CD45RO identifies a subpopulation of NK cells with anti-leukemic activity. If CD45RO proves to be a reliable in vivo marker of activated NK cells, it could be of potential use in identifying or selecting NK cells with context-specific activity (e.g., anti-tumor, anti-viral, auto-immune, decidual).

The novel CD45RO^{pos} NK cell subset is identified as mature by being CD56^{dim} and having co-expression of CD16, killer cell immunoglobulin-like receptors (KIR), and the NK maturation marker, CD57. The CD45RO^{pos} NK cells are large in size with increased granularity, indicative of an activated or primed state. Interestingly, these cells have decreased granzyme B content when compared to the CD45RA^{pos}RO^{neg} expressing NK cells, suggesting recent degranulation. The authors also show that the CD45RO^{pos} NK cells from patients acquire surface antigens specific to the patient's leukemia type, most likely mediated by trogocytosis (Somanchi et al., 2012), suggesting recent interaction with the leukemia cells and possible anti-leukemic activity. It is important to note that although the patients have this activated and mature NK cell subset that appears to interact with their leukemia, these NK cells are not sufficient for clearing the cancer. It is not clear whether this is a result of non-cytotoxic interactions, resistance mechanisms, or inadequate effector numbers. If larger numbers of these NK cell subsets are needed, this raises the possibility of using CD45RO to identify leukemia-reactive subsets that can be expanded ex vivo for therapy (Denman et al., 2012) without a priori knowledge of their receptor repertoire.

Determining the NK cell subsets that are tumor-reactive in cancer patients remains a challenge. In non-cancer settings in which the target cells cannot be so easily propagated — or in some cases is unknown — this may represent an approach for identifying the relevant NK cell subsets for mechanistic, diagnostic, or therapeutic purposes. Additional work is needed to determine whether CD45RO is a generalizable marker of recent NK cell activity or is specific to leukemic or malignant cell interactions, whether CD45RO^{pos} NK cells are present at diagnosis, how they are affected by chemotherapy, radiation, and immunotherapy, whether they represent a cytotoxic, regulatory, or exhausted phenotype, and whether quantitation of these NK cells during therapy can be used as a biomarker for survival or response to therapy. Work done in this study has demonstrated an NK cell subset that has both basic and clinical interest, and further research will determine the importance of this subset in human disease.

Conflict of Interest

The authors declare no conflict of interest.

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