Commentary

The downside of human natural killer cell diversity in viral infection revealed by mass cytometry

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Antigen-specific receptor diversity is the hallmark of an immune cell and an asset in adaptive immunity (1). In contrast, natural killer (NK) diversity appears to be detrimental to its antiviral immune functions, as reported by Strauss-Albee and colleagues (2). Adaptive T and B cell diversity is generated by the rearrangement of their receptors during development, giving rise to a vast array of antigen specificities (3). It is estimated that the total diversity of T cell receptors (TCR) generated by somatic recombination in human T cells is in the order of 10^{15}–10^{20} sequences (4). Unlike these adaptive immune cells, innate immune cell diversity, including NK cells, is shaped by random assortment of germline-encoded cell surface receptors. NK cell receptors come in two flavours: activating and inhibitory. Unlike T cell activation, which is mediated by the engagement of TCR and co-stimulatory receptors, NK cell activation is determined by the net balance of signals from the engagement of activating and inhibitory receptors (5). Therefore, the diversity and cell surface expression of these receptors on a per-cell basis can have a profound influence on an NK cell's function.

Recent technological advances in single-cell analysis have allowed us to better appreciate the diversity of immune cell phenotype and function. The use of fluorescence-based flow cytometry in revealing the full extent of immune cell diversity has been limited by the overlap of excitation and emission spectra between different fluorophores (6). Replacement of fluorophores with transitional element isotopes of different masses, which can be detected by a time-of-flight (TOF) mass spectrometry, in a technique called cytometry by time of flight (CyTOF) or mass cytometry, has tremendously increased the number of different parameters that can be analyzed on a single cell (7). Single-cell mass cytometry has been used to measure over 40 different cellular parameters to demonstrate tremendous heterogeneity within the $CD8^+$ T and NK cell compartments in humans (2,8,9).

Using mass cytometry, Strauss-Albee and colleagues have simultaneously analyzed 41 parameters to determine the functional and phenotypic diversity within the human NK cell repertoire, and its implications for anti-viral immune responses (2). They have found that NK cell diversity is low at birth but increases over the lifetime of an individual, possibly through repeated NK cell stimulation. This contrasts with the adaptive T cell compartment in which the TCR repertoire is completed at birth, but diversity diminishes over time due to oligoclonal expansions and formation of memory T cells (10,11). In blood samples obtained from healthy individuals over a 6-month period, receptor expression and NK cell function were stable at the single-cell, as well as population levels, demonstrating that the increase in NK cell diversity in adulthood is a very gradual process. Increased NK cell repertoire diversity in adult humans was found to be associated with a terminally differentiated phenotype

and a skewed function towards cytokine production over degranulation and cell proliferation. Moreover, increased diversity in the NK cell repertoire did not appear to enhance NK cell-mediated antiviral responses since high NK cell diversity was associated with increased susceptibility to acquire HIV-1 infection in a cohort of Kenyan women. This study shows that NK cell diversity appears to be flexible, allowing NK cells to modulate their receptor repertoire rapidly in response to environmental cues. However, increased NK cell diversity as a result of anti-viral immune responses over the lifetime of an individual may come at the cost of decreased functional flexibility.

This seminal work by Strauss-Albee and colleagues highlights the use of multiparametric single-cell technology in defining the human NK cell repertoires in the context of viral infection. This study further demonstrates the need for a better understanding of NK cell diversity and its potential clinical implications in assessing anti-viral immunity and viral susceptibility. Further studies are needed to analyze NK cell diversity in the context of various human diseases, different stages of the NK cell response, tissue-specific NK cell functions, and the recently described adaptive NK cell memory responses. Advances in single-cell technologies are poised to facilitate these studies and revolutionize the phenotypic and functional analysis of immune cells. This information is essential in understanding the processes by which immune cells contribute to disease prevention in order to harness their full potential in immune cell-based therapies.

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Footnote

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