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Missing Self, NK Cells, and *The White Album*

Lewis L. Lanier¹



In 1986, Joe Phillips and I published a paper in *The Journal of Immunology* identifying the CD56^{bright+}, CD16⁻, and CD56⁺, CD16⁺ NK cell subsets in humans that began, “Natural killer (NK) cells are a population of lymphocytes derived from an unimmunized host that lyse certain tumor cell lines and virus-infected cells without major histocompatibility (MHC) restriction” (1). The conventional wisdom, that NK cell recognition did not involve the MHC, stemmed from a decade of studies, starting with the first article on the subject in 1976 by Eva Klein titled “The ‘natural killer’ cell in the mouse does not require H-2 homology. . . .” (2). In an age when attention was focused on the discovery by Zinkernagel and Doherty that T cell recognition required “restriction” by the MHC (3), NK cells didn’t play by these rules. Indeed, the ability of NK cells to efficiently kill cells lacking MHC (4) apparently confirmed the notion that MHC was irrelevant to the function of NK cells.

Fortunately, Klas Kärre was not so quick to dismiss the importance of MHC to NK cells. In experiments that began in his doctoral thesis work and were premiered at the 2nd Natural Killer Cell Workshop held near Detroit in 1984, Kärre proposed the heretical notion that NK cells were inhibited, not activated, by interacting with MHC class I (5). This was the equivalent of playing The Beatles’ *The White Album* backwards and hearing: “Paul is dead, Paul is dead. . . .” Hard to believe, but could one dismiss the possibility in the face of such compelling evidence?² Having presented the Doherty and Zinkernagel papers in journal club as a student, this seemed all backwards; how could recognition of H-2 *inhibit* an immune response? Reading Kärre’s paper in *Nature* (6), I was skeptical. Experimental results from our lab and others clearly indicated that human NK cell had the capacity to kill tumors expressing MHC class I, so how could one reconcile these facts with Kärre’s stunning results? But then again, NK cells always behaved differently—how could NK cells in an F₁ mouse reject a parental bone marrow graft? (7)—this too was backwards. Even in 1989, in the definitive review on NK cell biology by Giorgio Trinchieri, the consensus was: “Overall studies suggest that in some cases class I MHC Ag expression prevents the triggering of

NK cells. . . ; however, in other cases this negative control is ineffective, possibly because other structures are present on the target cell membrane and are recognized by NK cells” (8).

Was this phenomenon just a peculiarity of a variant of the mouse RMA lymphoma or was Kärre onto something significant? In 1991, my skepticism dissipated when it was shown that mouse NK cells in wild-type mice rejected β_2 -microglobulin-deficient bone marrow cells (9, 10). At that time, our lab committed to determining whether NK receptors for MHC class I existed in humans—as they say, the rest is history.

Rereading Kärre’s letter to *Nature* for *The JI Pillars of Immunology* series, his seminal finding not only predicted the existence of NK inhibitory receptors for MHC class I, but also illustrated several other general features of NK cell responses that have stood the test of time (18 years to be precise). First, the inhibition of NK cell killing by MHC class I is quantitative; the more class I on the target, the more profound the inhibition (i.e., a balance between activation and inhibition). Second, unlike T cells, NK cells do not demonstrate a recall response, i.e., NK cells don’t have memory.

Today, the concept that “a balance of inhibitory and activating signals regulates NK cell responses” (11) is universally accepted, but in 1986, it was the equivalent of “Revolution #9” (another song from *The White Album*) in the immunological community; hard to comprehend—esthetically pleasing—and ultimately a classic.

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² Because The Beatles ceased giving public concerts in 1966, there was a growing rumor that Paul McCartney had died in a 1966 automobile accident, but that this was being kept a secret. The album cover of *Sgt. Pepper’s Lonely Hearts Club Band* depicted a funeral, the cover of *Abbey Road* showed Paul in his funeral clothes, and the ultimate supporting data was when one played the song “I’m So Tired” on *The White Album* backwards on the turntable, you clearly (if in the right state of mind) heard “Paul is dead.”