Do natural killer cells accelerate or prevent autoimmunity in multiple sclerosis?

In an attempt to identify biomarkers, which are able to better characterize the phenotypic heterogeneity of multiple sclerosis, and at the same time dissect disease-relevant mechanisms of this autoimmune disease, de Jager and colleagues (2008) determined flow cytometric profiles of circulating blood cells from untreated patients with clinically isolated demyelinating syndrome (CIS) and relapsing–remitting multiple sclerosis (RR-MS) in comparison to healthy volunteers. Profiles were generated using a panel of 50 monoclonal antibodies which primarily targeted lymphocyte populations and were distributed amongst 56 pools of four antibodies each. The key finding of this discovery-based study was that a population of CD8<sup>dim</sup>CD4<sup>+</sup> cells was reduced in frequency in both RR-MS and CIS patients. Within this population, only the frequency of CD3<sup>−</sup>CD56<sup>−</sup>CD8<sup>dim</sup>CD4<sup>−</sup> lymphocytes, consistent with the profile of natural killer (NK) cells but not CD8<sup>dim</sup>CD4<sup>−</sup> T cells appeared to be lower in multiple sclerosis. Notably, the same NK cell population (CD8<sup>dim</sup>CD4<sup>−</sup>) was reported to expand during interleukin-2 (IL-2) receptor α-targeted immunotherapy (daclizumab) in multiple sclerosis. Among these, the expansion of a specific subset of NK cells, namely CD56<sup>bright</sup> NK cells, was found to correlate with the inhibition of contrast-enhancing lesions on brain MRI during daclizumab treatment (Bielekova et al., 2006). These findings reinforce the notion that NK cells, originally named after their ability to mediate spontaneous cytotoxicity towards certain tumour cell lines, regulate autoimmune responses in multiple sclerosis.

NK cells originate from bone marrow, but can mature in a variety of primary and secondary lymphoid tissues (Freud et al., 2005; Vosshenrich et al., 2006; Romagnani et al., 2007). Access to the latter and interaction with dendritic cells (DCs) seems to be required for optimal NK cell activation (Lucas et al., 2007). The two key effector functions of human NK cells—killing and cytokine production—are mediated by two main subsets of these innate lymphocytes that can be differentiated from each other based on the expression of CD16 and CD56 (Ferlazzo and Munz, 2004; Strowig et al., 2008). CD56<sup>dim</sup>CD16<sup>+</sup> NK cells constitute about 90% of total blood NK cells, efficiently kill target cells and secrete only low levels of IFN-γ. In contrast, CD56<sup>bright</sup>CD16<sup>−</sup> NK cells constitute <10% of total blood NK cells, but are enriched in secondary lymphoid tissues (Ferlazzo et al., 2004) and sites of autoimmune inflammation (Dalbeth et al., 2004).

In contrast to the CD56<sup>dim</sup> NK cell subset, CD56<sup>bright</sup> cells produce a large amount of cytokines upon stimulation, but acquire cytolytic activity only after prolonged activation (Strowig et al., 2008). Therefore, NK cells could mediate tissue damage and regulate autoimmune T-cell responses through cytokine secretion and cytotoxicity in secondary lymphoid organs and in the inflamed CNS.

Because of the lack of mouse strains that are selectively deficient in NK cells, the study of NK cell function in vivo has been challenging in the past (Walzer et al., 2007). Multiple sclerosis animal models provide evidence for both disease-accelerating and disease-protective effects of NK cells (Zhang et al., 1997; Vollmer et al., 2003; Winkler-Pickett et al., 2008). It has been suggested that NK cells could be pathogenic by shaping Th1-polarized adaptive immune responses, activating CNS-infiltrating DCs and/or via direct recognition and lysis of glial and neuronal cells (Morse et al., 2001; Winkler-Pickett et al., 2008). However, most studies in the experimental autoimmune encephalomyelitis (EAE) model reported that NK cells protect from autoimmune-mediated tissue damage, presumably by editing initiator and effector cell populations (Zhang et al., 1997; Matsumoto et al., 1998; Huang et al., 2006; Lu et al., 2007). Such apparently controversial findings might be explained, at least in part, by differences in the timing of myelin immunization and NK cell activation/depletion in these animal models: NK cells could assist T-cell polarization and effector function during the initiation of autoimmune responses against neuroantigens, but might acquire a more suppressive function during progression of the established disease. Alternatively, distinct subsets of NK cells could mediate divergent effects on EAE initiation and progression. The observation by de Jager et al. (2008) and others (Segal, 2007) in humans—namely reduced frequencies of NK cells in multiple sclerosis patients together with NK cell expansion during effective immunotherapy (Li et al., 2005; Bielekova et al., 2006; Saraste et al., 2007)—suggests that these innate lymphocytes exert beneficial functions. The mechanisms that could mediate such immunoregulatory NK cell functions in multiple sclerosis are, however, poorly understood.

NK cells have been suggested to edit immune responses by killing human myeloid and lymphoid cells (Moretta et al., 2001; Rabinovich et al., 2003). NK cell cytotoxicity is controlled by germ line encoded activating and inhibitory receptors on these innate lymphocytes and triggering of killer immunoglobulin-like receptors (KIRs) as well as of
the NKG2A/CD94 receptor on NK cells by classical and non-classical MHC class I molecules delivers negative signals that prevent target cell killing (Lanier, 2005). Engagement of activating receptors such as CD16 (FcgRII), NK cell protein 30 (NKP30), NKP44, NKP46, DNAM-1 and NKG2D by antibody opsonization or ligands whose expression is upregulated following infection, transformation or cellular stress, provides an NK cell activating signal (Moretta et al., 2001, 2008). Several cell types of the human lymphoid and myeloid lineages have been suggested as targets of NK cell cytotoxicity. T cells have been shown to upregulate NKG2D ligands following activation and to become susceptible to autologous NK cell-mediated cell lysis in vitro (Rabinovich et al., 2003; Cerboni et al., 2007; Roy et al., 2008). In addition, activated NK cells can kill autologous immature myeloid DCs via NKP30, NKP46 and DNAM-1-mediated recognition (Spaggiari et al., 2001; Ferlazzo et al., 2002; Pende et al., 2006). Furthermore, activated macrophages have been found to be susceptible to NKG2D-dependent cytotoxicity by NK cells (Nedvetzki et al., 2007). Beyond editing of human immune compartments by cytotoxicity, NK cells could downregulate antigen-specific T-cell effector functions by producing immunosuppressive cytokines such as transforming growth factor-β or IL-10 (Takahashi et al., 2001; Laouar et al., 2005; Deniz et al., 2008). Studies investigating these NK cell functions in patients with multiple sclerosis and other autoimmune diseases will potentially generate exciting insights into the reciprocal regulation between NK cell-mediated innate immunity and adaptive immune responses, improve our capacity to target these cells as surrogate marker for disease activity and treatment response and, perhaps, provide new prospects for NK cell-directed therapies in multiple sclerosis.

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Advance Access publication June 27, 2008

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