

Implication of human NK cells during mycobacterial infection and vaccination. Damien Portevin & Douglas Young, MRC National Institute for Medical Research, London NW7 1AA, UK.

Natural Killer (NK) cells are large granular lymphocytes of the innate immune system that have been implicated in early immune responses against cells infected by viruses, bacteria and parasites. NK cells can provide a source of IFN γ prior to induction of the adaptive immune response, and have a cytotoxic function that can kill infected cells and possibly intracellular mycobacteria. Little is known about the contribution of human NK cells during mycobacterial vaccination or infection. It has been reported previously that exposure of human NK cells to *M. bovis* BCG stimulates production of IFN γ , lymphocyte proliferation, and increased cytotoxic activity. Using CD56⁺ NK cells purified from human peripheral blood, we found that exposure to either live *M. bovis* BCG or *M. tuberculosis* H37Rv induced IFN γ production, but only when cells were provided with exogenous IL-2 or IL-12. Marked qualitative and quantitative differences in mycobacterial sensing were found among donors. This was mainly due to individual variations in the percentage of the CD56^{bright} population, which accounted for most if not all of the IFN γ response, but was also associated with differences in the influence of cytokine environment. While stimulating IFN γ production, *M. bovis* BCG had a marked inhibitory effect on IL-2-induced proliferation of CD56^{bright} NK cells measured by CFSE dilution and BrdU incorporation. Cytokine activated CD56^{bright} NK cells were also shown to have direct bactericidal activity on mycobacteria. Exposure to *M. bovis* BCG had no effect on the cytotoxic activity of NK cells measured using the K562 tumour cell line as target. When monocyte-derived macrophages were used as target cells, autologous cytotoxicity was observed following infection with the virulent strain *M. tuberculosis* H37Rv but not with *M. bovis* BCG.

We have shown that human NK cells are able to recognise free mycobacteria as well as mycobacteria-infected cells, resulting in differential induction of proliferative, cytotoxic, and cytokine functions. While these results are consistent with a beneficial role of NK cells during mycobacterial infection and vaccination, individual variations in the CD56^{bright} compartment suggest that NK cells may make an important contribution to the diversity of the immune response to mycobacteria found in human populations. NK cell activation represents an important consideration in the rational design of improved mycobacterial vaccines, and also, manipulation of NK cell responses could have benefit in augmenting the treatment of tuberculosis.