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Human Natural Killer Cell Activation and Differentiation in Health and Viral Infection

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ABSTRACT

Natural killer (NK) cells are lymphocytes that belong to the innate immune system. They are important for the early defense against viral infections and provide tumor immune surveillance against both solid tumors and leukemias as well as in settings of hematopoietic stem cell transplantation. They also play an important role in human pregnancy via spiral artery modulation, and deliver signals that shape adaptive immune responses. However, despite these insights, several unresolved issues remain with regards to mechanisms by which NK cells respond in these and other conditions. In this thesis, NK cell activation and differentiation in healthy uninfected individuals as well as in defined acute and chronic viral infections are characterized.

Via a detailed analysis of NK cell repertoires in the healthy humans and in two specific settings of immune system development, we have provided evidence that human $CD56^{dim}$ NK cells undergo a previously undescribed differentiation process. This differentiation process can, at steady state, be defined by analysis of expression patterns of NKG2A, KIRs, and CD57 on $CD56^{dim}$ NK cells. Distinct differentiation stages identified are associated with phenotypic and functional changes. This knowledge formed a platform for studies of human NK cells in settings of defined viral infections. In acute human hantavirus infection, the NK cell response encompassed a rapid and vigorous proliferation of activated NK cells followed by long-term persistence of a differentiated NKG2C+CD57+ $CD56^{dim}$ NK cell subset. Surprisingly, this proliferation and persistence occurred only in patients on a CMV seropositive background and was mediated by IL-15 and HLA-E, providing necessary proliferative and anti-apoptotic signals to the expanding cells. When monitoring the NK cell response to immune modulatory IFN-α treatment in the context of acute and chronic hepatitis C virus (HCV) infection, we observed that $CD56^{bright}$ NK cells acquired the capacity to express the apoptosis-inducing molecule TRAIL. These differentiated $CD56^{bright}$ 'killer' cells efficiently inhibited HCV replication in Huh7.5 cells via TRAIL. NK cells could also utilize the activation receptor DNAM-1 to recognize Huh7.5 cells and suppress HCV replication. Chronic HCV-infection was found to cause disturbances in innate cellular immunity. One example of this was the differentiation of NK cells towards a functionally skewed $CD56^{neg}$ NK cell subset. Furthermore, effector CD8 T cells acquired NK cell-like properties, such as expression of CD16 and the capacity to respond independent of the TCR during chronic HCV infection.

Altogether, the described model of human $CD56^{dim}$ NK cell differentiation may serve as a framework for studies of NK cell responses in many disease conditions, here illustrated in studies of viral infections in humans.

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