VIRAL INFECTION

# Human NK cells control HIV infection in a mouse model

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Natural killer (NK) cells are an important line of immune defence against HIV infection; NK cells recognize HIV-infected cells and inhibit HIV replication in vitro, and transfusion of human NK cells into humanized mice suppresses HIV infection.

Yet studies of how human NK cells respond to HIV infection in vivo are hampered by a paucity of appropriate animal models. Now, researchers from Washington University School of Medicine have developed a mouse model that better mirrors human NK cell function than previous models, and used it to show that human NK cells regulate HIV-1 infection in vivo.

The authors' mouse model was based on an existing humanized model, MISTRG mice, which due to the lack of a murine immune system and expression of several human cytokines, develop a human immune system when injected with human hematopoietic stem cells. With the aim of improving NK cell function in these mice, the authors generated MISTRG mice containing two additional human cytokines, interleukin (IL)-6 and IL-15.

The resultant mice, termed MISTRG-6-15 mice, had higher levels of human NK cells with better functionality than NSG mice, a commonly used humanized model. Overall, the functionality of human NK cells in MISTRG-6-15 mice mirrored that of NK cells in samples from human donors; namely NK cells in spleen, liver, and lung were functional, but NK cells in lymph nodes Ð a major site for HIV-1 infection and reservoirs of latent HIV-1 Ð were immature and non-cytolytic.

Next, the authors monitored ex-vivo NK cell function from HIV-1-infected MISTRG-6-15 mice over a period of five months. Their results showed that NK cells in non-lymphoid organs underwent degranulation, were cytotoxic, and produced cytokines during acute infection. Although NK cells had increased functionality during acute infection, this response waned, with chronic infection causing NK cells to become continuously activated and functionally impaired.

The researchers then asked if endogenous NK cells can impact HIV-1 replication. When NK cells were depleted in acutely HIV-1-infected MISTRG-6-15 mice with an NK-targeted antibody, plasma and tissue HIV-1 RNA levels increased. This result suggests that NK cells directly suppress HIV-1 replication in vivo.

The study did not compare the new MISTRG-6-15 mice with MISTRG mice or other recent humanized models; nevertheless, the authors highlight that MISTRG-6-15 mice will be important for dissecting the molecular and cellular mechanisms by which NK cells supress HIV-1 infection.

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