Natural (born) killers: What do they really do?

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Our immune systems contain three fundamentally different types of cell: B-cells, T-cells and the mysteriously named Natural Killer cells (NK cells), which are known to be involved in killing tumour cells and other infected cells. Experiments to investigate the function of NK cells have proven difficult to interpret because the interactions between the various components of the immune system make it almost impossible to isolate effects of individual cell types. This has changed with the development of a mouse in which individual genes can be knocked out (eliminated) only in NK cells, thereby providing scientists with a tool to study the importance of NK cells and indeed of individual pathways in these cells. The mouse was generated in the group of Veronika Sexl, who has recently moved from the Medical University of Vienna to the University of Veterinary Medicine, Vienna. An initial characterization is presented in the current issue of the journal *Blood*.

The development of a tool alone would not normally generate headlines but this case is different: the new mouse can be used to knock out any gene completely and exclusively in NK cells. It thus permits researchers to examine the functions of NK cells in the entire organism or even to investigate the importance of individual genes in this particular cell-type.

Sexl herself has naturally used the tool already. She has been able to show that a particular transcription factor known as Stat5 is essential for the correct development of NK cells – when this factor is eliminated, the cells fail to develop properly. The upshot is a mouse with an immune system that lacks NK cells but is otherwise fully intact. This is the first

time it has proven possible to remove this particular cell type without affecting the rest of the animal. Finally, then, it is possible to learn what NK cells actually do in the intact organism.

Sexl and her collaborators have shown that mice lacking NK cells have normal T-cell responses to tumours, although their NK cell-mediated responses are naturally dramatically reduced. This experiment proves conclusively that the mouse can be used to untangle the web of interactions among the various cells of the immune system.

Sexl's work has immediate implications for the treatment of cancer in humans. As an example, leukemia is sometimes treated by inhibiting the STAT5 protein. Sexl's findings make it clear that this approach has a real drawback: inhibition of STAT5 will lead to a drop in the number of NK cells and so interfere with one of the body's own mechanisms for fighting the cancer. It will be important to assess whether NK cells normally play a part in fighting diseases before inhibiting STAT5. For the first time, the newly developed mouse provides a tool to do so. Not surprisingly, it is already attracting a great deal of interest – as Sexl says, "They've been going like hot cakes ever since the word got out."

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