Static killers?

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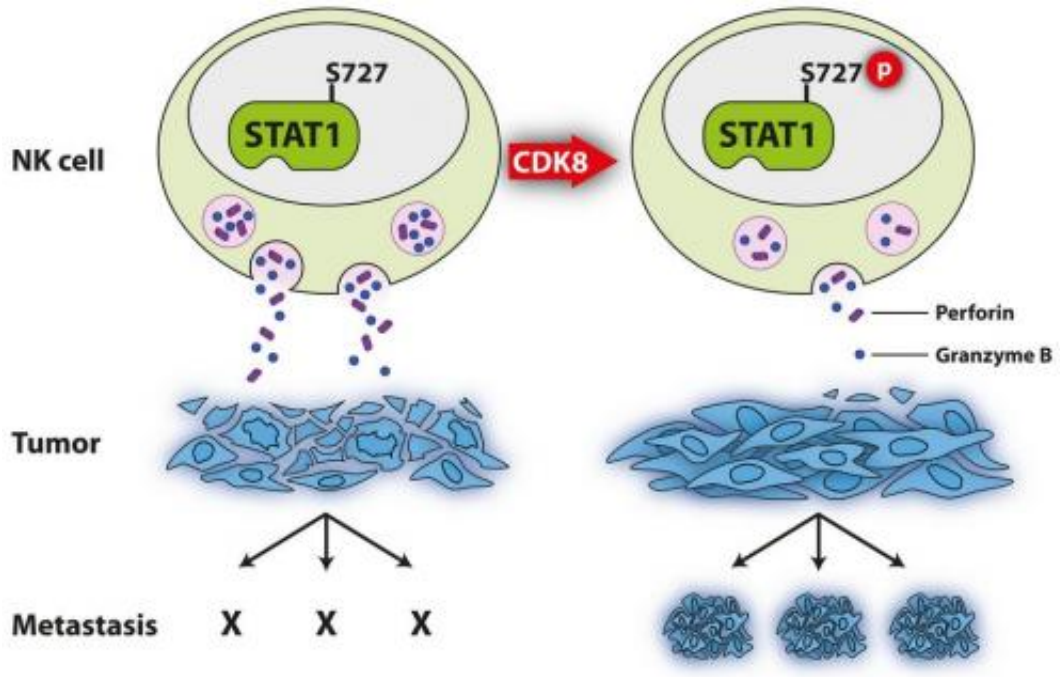

Inhibition of NK cells by phosphorylation of STAT1-Serin 727 mediated by CDK8. Credit: Eva-Maria Putz/Vetmeduni Vienna

Mammals contain cells whose primary function is to kill other cells in the body. The so-called Natural Killer (NK) cells are highly important in defending our bodies against viruses or even cancer. Scientists at the University of Veterinary Medicine, Vienna (Vetmeduni Vienna) provide evidence that NK cell activity can be influenced by phosphorylating a protein (STAT1) in NK cells. The results, which could be of immediate therapeutic relevance, are published in the journal *Cell Reports*.

Since its discovery in the early 1990s, the protein STAT1 (Signal Transducer and Activator of Transcription 1) has been found to be central in passing signals across immune cells, ensuring that our bodies react quickly and appropriately to threats from viruses or other pathogens. Animals without STAT1 are also prone to develop cancer, suggesting that STAT1 is somehow involved in protection against malignant cells. The STAT1 protein is known to be phosphorylated on at least two positions: phosphorylation of a particular tyrosine (tyr-701) is required for the protein to enter the cell nucleus (where it exerts its effects), while subsequent phosphorylation of a serine residue alters the way it interacts with other proteins, thereby affecting its function.

Natural Killer (NK) cells are among the first cells to respond to infections by viruses or to attack malignant cells when tumours develop. When they detect cells to be targeted, they produce a number of proteins, such as granzyme B and perforin, that enter infected cells and destroy them from within. Clearly, the lethal activity must be tightly controlled to prevent NK cells from running wild and destroying healthy cells or tissues. How is this done?

Eva Maria Putz and colleagues at the Institute of Pharmacology and Toxicology of the University of Veterinary Medicine, Vienna (Vetmeduni) have now investigated the importance of STAT1 phosphorylation in NK cells. The researchers found that when a particular serine residue (ser-727) in the STAT1 protein is mutated, NK cells produce far higher amounts of granzyme B and perforin and are far more effective at killing a wide range of tumour cells. Mice with the correspondingly mutated Stat1 gene are far less likely to develop melanoma, leukaemia or metastasizing breast cancer. On the other hand, when the same serine residue is phosphorylated, the NK cells are less able to kill infected or cancerous cells.

The Vetmeduni researchers have accumulated a body of evidence to

suggest that the cyclin-dependent kinase CDK8 phosphorylates STAT1 on serine 727. Surprisingly, this phosphorylation does not require prior phosphorylation of the activating tyrosine residue, at least in NK cells. Instead, it seems to represent a way in which the lethal activity of the NK cells is kept in check. Putz is keen to note the potential significance of the finding. As she says, "If we can stop CDK8 from inactivating STAT1 in NK cells, we could stimulate tumour surveillance and thus possibly have a new handle on treating cancer, harnessing the body's own weapons against malignant cells."

More information: Putz, E. et al. The paper CDK8-mediated STAT1-S727 phosphorylation restrains NK cell cytotoxicity and tumor surveillance, *Cell Reports*. dx.doi.org/10.1016/j.celrep.2013.07.012

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