Anti-viral rapid reaction force

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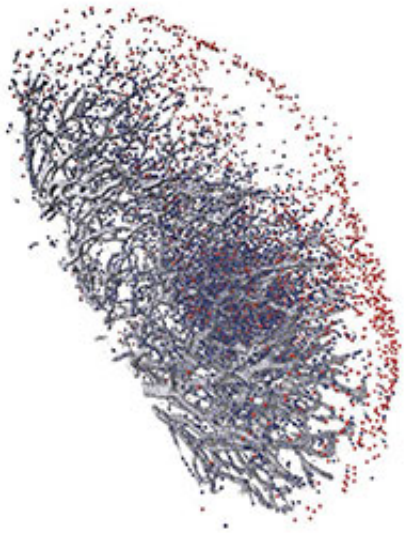

The textbooks tell us that killer cells have to match their antigens exactly if they're to fulfil their task. Researchers in Bern, however, have also found that loosely attached white blood corpuscles also play a role in the immune system. Credit: Swiss National Science Foundation

After host cells have been attacked by a virus, they present parts of the pathogen on their surface. Thanks to these virus components, the killer cells patrolling in the body (CD8+ T lymphocytes) can recognise the infected cells and kill them, thereby preventing the virus from spreading further.

Until now, the orthodoxy was that killer cells were the primary component in the body's immune response. These so-called high-affinity

killer cells attach themselves firmly to the antigens presented on the surface of the host cells. Then, one or two weeks after infection, we only find high-affinity killer cells in the blood. The low-affinity killer cells that carry fewer matching receptors have always been believed to be rejects from the production of these white blood corpuscles.

However, Jens Stein and his colleagues at the University of Bern have for the past four years been busy investigating the behaviour of the low-affinity killer cells, and they now doubt the current wisdom. They have found indications that these less precise cells also make a contribution to the immune response. After a brief activation phase, they launch an initial, quick attack on an intruder while high-affinity killer cells are proliferating in massive numbers in order to attack the pathogen in a mighty, second wave. "This is still just a hypothesis, but our experiments suggest that it is the case", says Stein.

The researchers injected killer cells into test mice that had been provided with a receptor against a specific antigen such as might come from a virus. In addition, the animals were given dendritic cells that present assorted antigens to the killer cells, activating them and thus prompting an immune response. Using a special two-photon microscope, the researchers followed what happened in the lymph nodes of the anaesthetised mice. Stein and his colleagues developed this method specifically for this type of experiment, and it enabled them to determine precisely where and when the cells interacted with each other.

Quicker, but less thorough

"To our surprise, all the killer cells reacted with the dendritic cells – regardless of which peptide the dendritic cells presented", says Stein. "So all the T cells prepare themselves for their role as killer cells. They initiated the differentiation and began to proliferate".

However, there was a major difference among these encounters: if there was a strong link between dendritic cells and the killer cells, the molecular dialogue lasted longer. If dendritic cells had the lesser matching version of the molecule on their surface, and if the link was looser, then the T cells were activated and were prompted to begin proliferating. But these T cells abandoned their contact with the dendritic cells very quickly and then migrated to the exits of the lymph nodes in order to go virus-hunting. At the same time, these low-affinity cells acquired their killer function more quickly than the cells whose receptors were highly suited to the peptide on offer. The high-affinity T cells, meanwhile, did not remain very long in contact with the dendritic cells and proliferated; their daughter cells were also activated and made to proliferate.

"We interpret this and other data as meaning that low-affinity cells are a small, rapid-response group", says Stein. "High-affinity killer cells come into play later, but are all the more numerous, presumably more accurate and quite possibly more effective". At least, this was the case in the mice. There has as yet been no verification of this in human tests.

More information: Aleksandra J. Ozga et al. pMHC affinity controls duration of CD8T cell–DC interactions and imprints timing of effector differentiation versus expansion, *The Journal of Experimental Medicine* (2016). DOI: 10.1084/jem.20160206

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