A second chance for dangerous T-cells

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The immune system's T-cells react to foreign protein fragments and therefore are crucial to combating viruses and bacteria. Errant cells that attack the body's own material are in most cases driven to cell death. Some of these autoreactive T-cells, however, undergo a kind of reeducation to become "regulatory T-cells" that keep other autoreactive T-cells under control. A group led by immunologist Professor Ludger Klein of LMU Munich has now shown that the developmental stage of an autoreactive T-cell is decisive to its ultimate destiny.

Young autoreactive T-cells are very readily reeducated into regulatory T-cells. Under identical conditions, however, older T-cells become fully activated and can cause damage - they are in a way resistant to reeducation. "We now intend to study at the molecular level what makes a T-cell accessible for reeducation," said Klein, "because then it may be possible to convert even normal adult T-cells, which can be obtained easily and in great numbers from blood. Possibly, they could then be used as regulatory T-cells in therapies for autoimmune diseases such as type-1 diabetes or multiple sclerosis: these are diseases that are triggered by uncontrolled autoreactive T-cells."

During their development in the thymus gland, a kind of 'T-cell school', every T-cell is fitted out with its own personal receptor. The diversity of these receptors allows the immune system to respond to nearly all pathogens. Since T-cell receptors are all randomly constructed, there is also a constant production of T-cells in the thymus that may recognize and attack the body's own structures. "Most of these dangerous autoreactive T-cells, though, are sorted out in a screening process before

they leave the thymus," Klein reported. "This negative selection, that is the elimination of autoreactive T-cells that would otherwise attack their own organism, is an important requirement for immune tolerance."

But not all autoreactive T-cells are driven to cell death. Some of them are 'reeducated' into so-called regulatory T-cells. While these still possess a T-cell receptor that targets the body's own structures, they have been reprogrammed during their development in the thymus so that they can no longer cause any damage. In fact, it is "quite the opposite," as Klein explained. "They even keep other nearby errant T -cells under control. This is why the mechanisms for the creation of regulatory T-cells are of enormous practical interest. Deciphering these processes could lead to new therapeutic approaches for autoimmune diseases such as multiple sclerosis, rheumatic arthritis and type-1 diabetes, which are triggered by autoreactive T-cells."

Klein and his colleagues are working on a study into unexplained aspects of regulatory T-cells: How can negative selection, i.e. induced cell death, and reprogramming into regulatory T-cells both take place in the thymus gland, right alongside each other? Why does apparently the same trigger drive some cells to 'suicide' while bringing on a 'reeducation process' in others? "One largely popular hypothesis among immunologists in answer to these questions is based on the fact that T-cells can only recognize their target structures if they have them presented to them by other immune cells," said Klein. "Since there are various subspecies of these antigen-presenting cells in the thymus, we tested whether some of them are possibly specialized in controlling one or the other T-cell destinies - with a negative result."

Instead, it turned out that the developmental stage - the 'age' as it were - of the T-cells is crucial. This was even observable in vitro: Young T-cells are very readily reeducated into regulatory T-cells, while older T-cells are largely 'resistant to reeducation' under identical conditions. "It is

important for us to understand this 'educability' at a molecular level," Klein said, "because then we might be able to manipulate adult, non-autoreactive T-cells to our needs, since they can be obtained in the millions from the blood of patients. Young T-cells, on the other hand, only exist in the thymus. We will now investigate whether there is a specific time window in the life of a young T-cell that allows negative selection or reprogramming into regulatory T-cells. We are also trying to decode the molecular switch inside T-cells that controls this cell-autonomous switching as a response to external signals."

Source: Ludwig-Maximilians-Universität München