T cell receptor ensures Treg functionality

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Christoph Vahl, lead author of the study, investigates Tregs and the role of their T cell receptor. (Photo: C. Vahl / TUM Christoph Vahl, lead author of the study, investigates Tregs and the role of their T cell receptor. Credit: C. Vahl / TUM

Misdirected immune responses that target the body's own tissue can result in diseases. regulatory T cells combat this effect by suppressing excessive immune responses and responses against our own bodies. Until now, scientists had been aware of two molecular properties of regulatory

T cells that control these functions. Researchers at Technische Universitat Munchen have now shown that signals emitted by T cell receptor on the regulartory T cells' surface are also essential for their identity and suppressive functions.

T cells play an important role in the immune system, destroying pathogens and controlling the body's immune responses. Every T cell has its own special T cell receptor (TCR) on its surface that only recognizes one specific substance. Many T cells are generated whose TCR would recognize and destroy endogenous cells if left to develop unchecked. To protect the body, the majority of these autoreactive cells are destroyed before they fully mature.

A small number of these autoreactive T cells are selected to become regulatory T cells. These "guardians of the immune system" play an important role as they are capable of suppressing excessive immune responses. Scientists know that Tregs need the receptors that recognize endogenous material in order to develop properly. They know little, however, about what they need them for after this.

Marc Schmidt-Supprian, Tenure Track Professor at TUM since March 2014, has been exploring this question with his team at the III. Medizinische Klinik at TUM Klinikum rechts der Isar. Working with other research groups in Rijeka (Croatia), Osaka (Japan) and the German cities of Munich, Freiburg and Dresden, he and his team deactivated the T cell receptor at a specific point in time on mature Tregs in genetically modified mice. They then monitored what happened next with the TCR-less cells.

T cell receptor signals are a crucial part of Tregs

Their experiments clearly showed that the defective Tregs were not able to carry out their protective function without the T cell receptor.

Furthermore, the Treg pool fell significantly as these cells were no longer multiplying. The scientists also discovered that two of Tregs' most well-known central molecular properties - the production of Foxp3 protein and specific chemical changes to DNA - were still present in the defective T cells.

"Without their receptor, the Tregs are still clearly identifiable as Tregs. However, they lose a large part of their cellular identity. They also lose their special ability to suppress excessive immune reactions," explains Christoph Vahl, lead author of the study. "The Tregs obviously need continuous contact with their environment to function correctly. This is presumably the reason why they need a receptor that recognizes endogenous substances and continuously sends signals."

"During the course of our research, we uncovered a very important mechanism for suppressing excessive responses and responses targeted against the human body. These findings could be relevant for situations where it would be beneficial to weaken the control of Tregs over immune responses, for example in the treatment of cancer," concludes Schmidt-Supprian.

More information: Vahl J. C., Drees C., Heger K., Heink S., Fischer J.C., Nedjic J., Ohkura N., Morikawa H., Poeck H., Schallenberg S., Rieß D., Hein M. Y., Buch T., Polic B., Schönle A., Zeiser R., Schmitt-Gräff A., Kretschmer K., Klein L., Korn T., Sakaguchi S. and M. Schmidt-Supprian, Continuous T Cell Receptor Signals Maintain a Functional Regulatory T Cell Pool, *Immunity*, 2014.

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