Side effects of possible anti-cancer strategy discovered

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The Malt1 protein is one of the most important control centers in human immune cells and a real all-rounder. Genetic defects in it can lead to the development of lymphatic cancer (lymphoma). A possible therapeutic approach is therefore to specifically block certain functions of Malt1, thus destroying the cancer cells. Now, however, scientists at Technische Universität München (TUM) have shown in a mouse model that such a blockade can cause serious side effects.

The Malt1 protein carries out a variety of tasks in immune cells, known as lymphocytes. Among other things, it acts as an enzyme - specifically, a protease - that breaks down messenger substances and thus controls their quantity. Until now it was not known what role the specific protease function plays in the development of immune cells. Several years ago Prof. Jürgen Ruland and his team at TUM's Klinikum rechts der Isar turned their attention to this question.

Blockade as a therapeutic approach

The scientists were able to show in earlier cell culture experiments that a blockade of the protease function of Malt1 kills lymphoma cells. The idea was therefore conceived that this strategy could be used against lymphomas, in which Malt1 is often excessively active due to a genetic defect. "A promising therapeutic approach is believed to be the development of substances that specifically inhibit the protease function of Malt1," explains Andreas Gewies, lead author of the study.

The next step was therefore to test this blockade strategy in an animal model in order to shed light on the exact function of Malt1 protease. "It's only possible to study complex interactions in the immune system, which comprises a finely orchestrated interplay of various cell types, in an intact organism - not in cell cultures. The processes are too complex to recreate in cells outside the body," says Ruland, in explanation of the step to using an animal model.

Unexpected effects in the mouse model

The mice used were genetically modified so that their Malt1 protein could no longer act as a protease but was still able to carry out all its other functions. The scientists were surprised to find that the mice developed severe signs of inflammation. Moreover, the immune system attacked and destroyed key neurons that coordinate movements. Consequently, the animals had difficulty controlling and coordinating their movements.

The scientists were able to explain how this serious malfunction of the immune system occurred and in doing so discovered an unexpected function of Malt1. They found that in the absence of the protease function, the mice were unable to produce a specific subset of lymphocytes known as regulatory T cells (Tregs). These cells are crucial for the precise control of immune responses. They ensure that immune responses are damped and, most importantly, finely controlled. Without Tregs, the mice's immune responses went out of control.

The researchers also found that normal lymphocytes can be activated without the protease function of Malt1, but they then release messenger substances uncontrollably, which causes inflammation. "Our study showed that Malt1 protease is surprisingly important for the development of regulatory T-cells and for damping the immune response in general," Ruland says, summarizing the results. "Since the blockade of

the protease function in the organism produces undesirable effects, new alternatives should urgently be sought for the treatment of lymphoma."

More information: A. Gewies, Gorka O., Bergmann H., Pechloff K., Petermann F., Jeltsch K. M., Rudelius M., Kriegsmann M., Weichert W., Horsch M., Beckers J., Wurst W., Heikenwälder M., Korn T., Heissmeyer V. und J. Ruland, Uncoupling Malt1 threshold function from paracaspase activity results in destructive autoimmune inflammation, *Cell Reports*, 2014. DOI: 10.1016/j.celrep.2014.10.044

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