

When hyperactive proteins trigger illnesses

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Cancer researcher Prof. Jürgen Ruland received the 2021 German Research Foundation (DFG) Leibniz Prize – the most important German research award. Credit: Andreas Heddergott/TUM

The immune system can be a mixed blessing: Usually it is highly effective in protecting the human organism against bacteria, viruses and mycosis and even cancer. But these defense cells can also turn against the body's own tissues and trigger autoimmune diseases, including for example rheumatoid arthritis and systemic lupus erythematosus, an illness involving chronic dermatitis and inflammation of the joints, the nervous system and internal organs, or even become cancer cells themselves and develop into leukemias or lymphomas. But what causes these destructive immune system attacks?

"The question has yet to be finally resolved," says Prof. Juergen Ruland, Director of the TUM Institute for Clinical Chemistry and Pathobiochemistry. "B cells, a subgroup of white blood corpuscles produced in the [bone marrow](#), play a central role in regulating immune responses. During a normal immune response, activated B cells produce antibodies which attack foreign substances. Defective activation can result in formation of antibodies which attack the body itself, triggering an autoimmune disease. The activity of B cells is controlled by a variety of signals, some of which we have yet to understand," observes Ruland. The immunologist and physician is also the winner of the 2021 German Research Foundation (DFG) Leibniz Prize, the most important German research award.

Ruland and his team have succeeded in identifying one decisive signal which influences B cell activity: "The objective of our research was to characterize the possible pathological roles of a protein located on the surface of the B cells. This receptor, the Receptor Activator of NF- κ B, or RANK, exhibits increased activity in patients with [systemic lupus erythematosus](#) and in some B cell lymphomas. We wanted to find out if hyperactive RANK receptors actually trigger these illnesses."

Chronic signals lead to chronic illnesses

The RANK receptors work like switches within the cell: They generate a signal in the cell when activated by signal molecules. One such signal molecule is called RANKL, for Receptor Activator of NF- κ B Ligand.

Working in the laboratory to determine the effects of hyperactive RANK receptors, the team compared healthy mice and genetically modified animals with modified RANK receptors. After only a few weeks a large portion of the mice with genetically modified receptors contracted systemic lupus erythematosus, while the animals in the [control group](#) remained healthy, proving that this autoimmune disease

can be triggered by defective regulation of the RANK signals.

And that wasn't all: After about a year, the transgenic mice that survived systemic lupus erythematosus contracted chronic lymphatic leukemia or CLL. "This result was a surprise to us, since it shows that activated RANK proteins are also responsible for the degeneration of B [cells](#) to cancer of the lymphatic system nodes," says Maike Buchner, CLL specialist and junior group leader young scientist at the Institute of Clinical Chemistry and Pathobiochemistry at the university hospital TUM Klinikum rechts der Isar.

Interrupting the cycle of self-destruction

These new findings will help treat [autoimmune diseases](#) and lymphatic leukemia in the future: Therapeutic antibodies which block the interaction of RANK receptors and RANKL ligands were originally developed and used to treat osteoporosis: Here the objective is to counteract the deterioration of bone tissue, which is also triggered by hyperactive RANK [receptors](#). Scientists used these blocking antibodies to successfully treat mice suffering from chronic lymphatic leukemia. "Future clinical studies will have to determine whether or not this therapy is also suitable for humans," Ruland points out.

More information: Begüm Alankus et al, Pathological RANK signaling in B cells drives autoimmunity and chronic lymphocytic leukemia, *Journal of Experimental Medicine* (2020). [DOI: 10.1084/jem.20200517](#)

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