Blood cancer cells initiate signalling cascade

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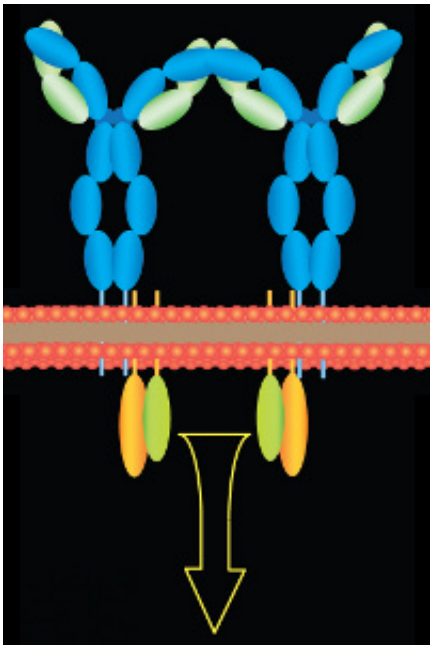

In patients with Chronic Lymphocytic Leukaemia, two receptors dock at the outside of white blood cells (top, in blue) and use receptor components at the inside of the cell (bottom) to trigger a signalling cascade. This in turn is an important step of the conversion into an uncontrolled dividing cancer cell. Image: Dühren-von Minden

Researchers in the group of Prof. Dr. Hassan Jumaa, Centre for Biological Signalling Studies (BIOSS) of the University of Freiburg, Department for Molecular Immunology, have identified a new mechanism that causes immune cells to convert into malignant cancer cells. In Chronic Lymphocytic Leukaemia (CLL), one of the most common types of blood cancer in the Western world, cells themselves

carry the key for the pathogenic transformation, the scientists report in the journal *Nature*. Understanding these underlying mechanisms could facilitate new therapies with reduced side effects.

In healthy humans, a subgroup of white blood cells, so-called B-lymphocytes, are responsible for producing antibodies that fight infections. Special receptor molecules of B-lymphocytes detect pathogenic agents via the key-lock principle and consequently start producing antibodies. In patients with CLL, however, abnormal forms of these receptors lead to uncontrolled reproduction of malignant B-lymphocytes. As a result, healthy cells of the immune system get repressed.

“Up to now, it was assumed that agents produced in the bodies of patients dock at the receptor and thereby activate CLL lymphocytes”, Jumaa says. “In our study we could show that specific components of the receptors are responsible for the development of CLL.” In B-lymphocytes of CLL patients, receptor components FR2 and HCDR3 are formed in such a manner that they represent key and lock of the receptor. “Hereby, neighbouring receptors of the same cells activate each other and trigger a signalling cascade, which finally causes uncontrolled division of cancer cells.”

Currently, approaches like chemotherapy that suppress symptoms in a relatively unspecific manner are applied in CLL treatment. “Based on decoding the molecular basics of CLL, we now strive to translate this knowledge to make it useful for patients”, Marcus Dühren-von Minden says, another author of the study. “It is conceivable to administer numerous copies of the key FR2 to patients, which then dock to the receptors and prevent neighbouring receptors to bind at each other. This stops the consequential signalling cascade.” Through this mechanism, the course of the disease could be precluded much earlier than before, and with less side effects.

More information: M Dühren-von Minden, R Übelhart, D Schneider, T Wossning, MP Bach, M Buchner, D Hofmann, E Surova, M Follo, F Köhler, H Wardemann, K Zirlik, H Veelken, H Jumaa. Chronic lymphocytic leukemia is driven by antigen-independent cell autonomous signaling. Nature, electronic publication ahead of print. DOI 10.1038/nature11309