

# Why Hodgkin's lymphoma cells grow uncontrollably

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Histopathologic image of Hodgkin's lymphoma. Lymph node biopsy. H & E stain. Credit: KGH , CC BY-SA 3.0 DE



Although classical Hodgkin's lymphoma is generally easily treatable today, many aspects of the disease still remain a mystery. A team at the Max Delbrück Center led by Professor Claus Scheidereit has now identified an important signaling molecule in the biology of this lymphoma: lymphotoxin-alpha (LTA). It helps the cancer to grow unimpeded—for example, by activating genes for immune checkpoint ligands that protect tumor cells from the body's built-in defense system.

Hodgkin's lymphoma is a cancer that develops in the lymphatic system and is accompanied by swelling of the lymph nodes and other symptoms such as fever, night sweats, and weight loss. It is characterized by the presence of so-called Hodgkin's <u>cells</u> and large multinucleated Reed-Sternberg cells. An unusual feature of this form of lymphoma is that only a small proportion of the tumor mass is made up of <u>malignant cells</u>. The swelling of the lymph nodes is more due to the fact that Hodgkin's cells send out signaling molecules that attract lymphocytes and allow them to migrate into the lymph nodes.

Today, recovery rates for patients with Hodgkin's lymphoma are good: More than 90 percent of patients with localized Hodgkin's lymphoma and more than 80 percent of patients with advanced Hodgkin's lymphoma can be cured. "Given, however, that the disease affects many young people with a long life ahead of them after completing treatment, chemotherapy—the standard form of treatment for the disease—can prove to be problematic," says Professor Claus Scheidereit, head of the research group on Signal Transduction in Tumor Cells at the MDC. Chemotherapy can cause lasting damage to healthy tissue, leading to late effects including heart and lung disease, hormonal disturbances, infertility, and secondary tumors. "We therefore need to develop new therapeutic approaches that help prevent such problems," says Scheidereit.

## NF-kB permanently located in the nucleus of the



#### cancer cells

The researcher and his team are working closely with the research group of Professor Stephan Mathas of the MDC and Charité -Universitätsmedizin Berlin, as well as with other MDC research groups, to closely investigate the mechanisms that contribute to the development of Hodgkin's lymphoma. "We have known for a long time that NF-kB plays a central role in the disease," says Scheidereit. This is a transcription factor that boosts the activity of certain genes. It is usually located in the cell's cytoplasm, and only temporarily migrates into the nucleus when required. Here, it controls gene expression and returns to the cytoplasm once its work is done. In Hodgkin's cells, however, NF-kB is permanently located in the cell nucleus and influences gene activity in such a way that, instead of undergoing programmed cell death, the cells proliferate unchecked and release signaling molecules that lure lymphocytes into the diseased lymph nodes. "Until now, however, we have only partially understood why NF-kB remains in the nuclei of Hodgkin's cells," explains the MDC researcher.

In order to better understand this mechanism, the team of scientists conducted tests on cell cultures to see which of the molecules produced by Hodgkin's cells activate NF-kB. The results of their tests were published in the scientific journal *Blood*. "We identified one single factor that is secreted by Hodgkin's cells and activates NF-kB: a signaling molecule called lymphotoxin-alpha, or LTA for short," says Dr. Eva Kärgel, a research assistant in Scheidereit's team who co-authored the study. An analysis of data from lymph node tissue samples confirmed that Hodgkin's lymph nodes produce a significant amount of LTA. "We were also able to show that, vice versa, inhibiting LTA blocked the NF-kB activity in Hodgkin's cells," says Kärgel.

### A target for new treatment strategies?



With the help of <u>gene expression</u> analyses, Scheidereit's team of scientists was able to prove that LTA plays a central role in Hodgkin's cells: Not only does it activate NF-kB, but it also triggers the release of various signaling molecules that contribute to the migration of lymphocytes into the lymph nodes and create a favorable microenvironment for the cancer cells. It also ensures that the cancer cells express so-called immune checkpoint ligands, which protect them from attacks by the immune system.

There is a reason that LTA is so active in Hodgkin's cells: "We have discovered that LTA upregulates itself through a positive feedback loop," explains Scheidereit. A regulator called A20 can put the brakes on this loop. But it is often mutated in Hodgkin's lymphoma, which causes it to lose its function as a control mechanism.

With LTA, MDC scientists have identified an important player in the disease progression of Hodgkin's lymphoma, as Scheidereit emphasizes: "Our work suggests that LTA could be a good target for diversifying the existing treatment strategies for Hodgkin's <u>lymphoma</u>."

**More information:** Linda von Hoff et al, Autocrine LTA signaling drives NF-κB and JAK-STAT activity and myeloid gene expression in Hodgkin lymphoma, *Blood* (2019). DOI: 10.1182/blood-2018-08-871293

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