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https://www.gesundheitsindustrie-bw.de/en/article/press-release/mutation-non-coding-dna-worsens-leukaemia-prognosis-ulm-study-uncovers-previously-unknown-disease-promoting-mechanism

Mutation in non-coding DNA worsens leukaemia prognosis Ulm study uncovers previously unknown disease-promoting mechanism

Why is blood cancer particularly aggressive in some patients? Researchers at Ulm University Hospital have characterised a mutation in the so-called NOTCH1 gene that significantly influences the prognosis of chronic lymphocytic leukaemia (CLL). Remarkably, this mutation is located in the non-coding region of the gene – an area of DNA long considered less relevant for disease mechanisms. The findings suggest that this mutation could serve as a biomarker for patients who need a timelier treatment decision. Published in the prestigious journal Blood, the study highlights that DNA segments which had previously received little attention play a much greater role in understanding diseases than previously assumed.

Chronic lymphocytic leukaemia (CLL) is the most common form of blood cancer. In this disease, B lymphocytes multiply and do not – as is normally their task – form specific antibodies, but instead displace healthy immune cells. CLL usually affects people over 50 and in many cases initially develops slowly. Many patients with CLL can live for a long time after diagnosis without treatment. In other cases, however, the disease progresses much faster, requiring earlier therapy. This not only carries more risks but is also linked to a poorer prognosis. In a study, scientists at Ulm University Hospital have now identified a molecular mechanism that indicates accelerated disease progression. Their findings centre on a familiar player: the NOTCH1 gene switch. However, the discovery, led by researchers from a working group at the Department of Internal Medicine I, takes the research in a completely new direction.

Clinical data put the researchers on the right track

"We used clinical data from CLL patients to investigate an already known disorder of the NOTCH signalling pathway in more detail," explains Professor Franz Oswald. The research group leader from the Department of Internal Medicine I in Ulm coordinated the study. The NOTCH1 protein is located on the surface of cells and receives signals from neighbouring cells. When a signal binds, part of the NOTCH receptor is cleaved off and migrates into the nucleus of the recipient cell. There, NOTCH regulates the activity of genes and determines whether the cell divides or continues to develop. Normally, the NOTCH1 protein is very short-lived and is rapidly degraded once it has fulfilled its task. In CLL, however, this degradation is impaired.

"We already knew that there are mutations in the coding region of the NOTCH1 gene, i.e. in the section of DNA that contains the blueprint for the protein. Such mutations lead to the protein being stabilised and thus remaining active for longer," says Oswald. "This permanently switches on precisely those genes that promote the growth of cancer cells. Surprisingly, however, our analysis of patient data has now also revealed a mutation in the non-coding region of the NOTCH1 gene that is specifically associated with poorer survival rates in patients. We therefore asked ourselves how this mutation affects the course of the disease at the molecular level."

Tumour tricks defence mechanisms with artificial protein

The researchers discovered that the mutation in the non-coding region of the NOTCH1 gene changes the shape of the NOTCH1 RNA – with the effect that the 'end product' changes: instead of the NOTCH1 protein, a new variant of the gene switch is created – the so-called NOTCH1-152. "This modified protein is characterised by a perfidious property," explains Oswald. "The new protein segment acts like a magnet on the degradation machinery that is actually intended for the NOTCH1 protein: an artificial protein is created that blocks the degradation processes and thus stabilises the normal NOTCH1 protein – as if it had mutated itself. This eliminates control mechanisms that normally slow down cancer growth." In order to visualise these processes, the research team combined various modern analysis methods: using the CRISPR-Cas9 gene editing technique, mutations could be introduced into cells in a targeted manner and their consequences analysed. AI-supported programmes calculated the interfaces in the RNA and thus made the effects of the mutation comprehensible.

New biomarker for therapy

"The course of the disease should be monitored particularly closely in patients with this mutation," emphasises Dr Min Guo. The medical scientist from the Department of Internal Medicine I is the first author of the study, as is doctoral student Tuğba Memis. The study team therefore suggests using the NOTCH1-152 protein as a biomarker in clinical practice. This could help to determine the right time to start therapy. After all, an important aim of medical care for patients with CLL is to delay chemotherapy as far as possible, as this does harbour certain risks: if too many of the pathological B lymphocytes are destroyed, this can upset the balance between fewer and more reinforced malignant cell clones. The possible consequence: a very aggressive form of the disease – the so-called Richter transformation – with a significantly shorter life expectancy compared with the original CLL.

For a long time, little or no attention was paid to changes in non-coding areas because it was assumed that they had no significance. "However, our study now clearly shows that mutations not only play a role in the known coding sections of genes. In fact, supposedly irrelevant regions of the genome can make a decisive contribution to the course of the disease. We should therefore also take a much closer look at these non-coding regions in future. This could provide the answers to understanding serious diseases," says Professor Franz Oswald.
Other researchers from Ulm University Medicine, as well as scientists from the DKFZ, Charité, the University of Giessen, the University Hospital of Cologne and the German Red Cross, were involved in the Ulm Leukaemia Study, which was led by the Department of Internal Medicine I and funded by the German Research Foundation (DFG) and German Cancer Aid.

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Further information

Prof. Dr. Franz Oswald
Department of Internal Medicine I
Ulm University Hospital
E-Mail: franz.oswald(at)uni-ulm.de

- Ulm University