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The Origin of Hodgkin Lymphoma

Groundbreaking findings in immune cell research reveal how Hodgkin lymphoma develops.

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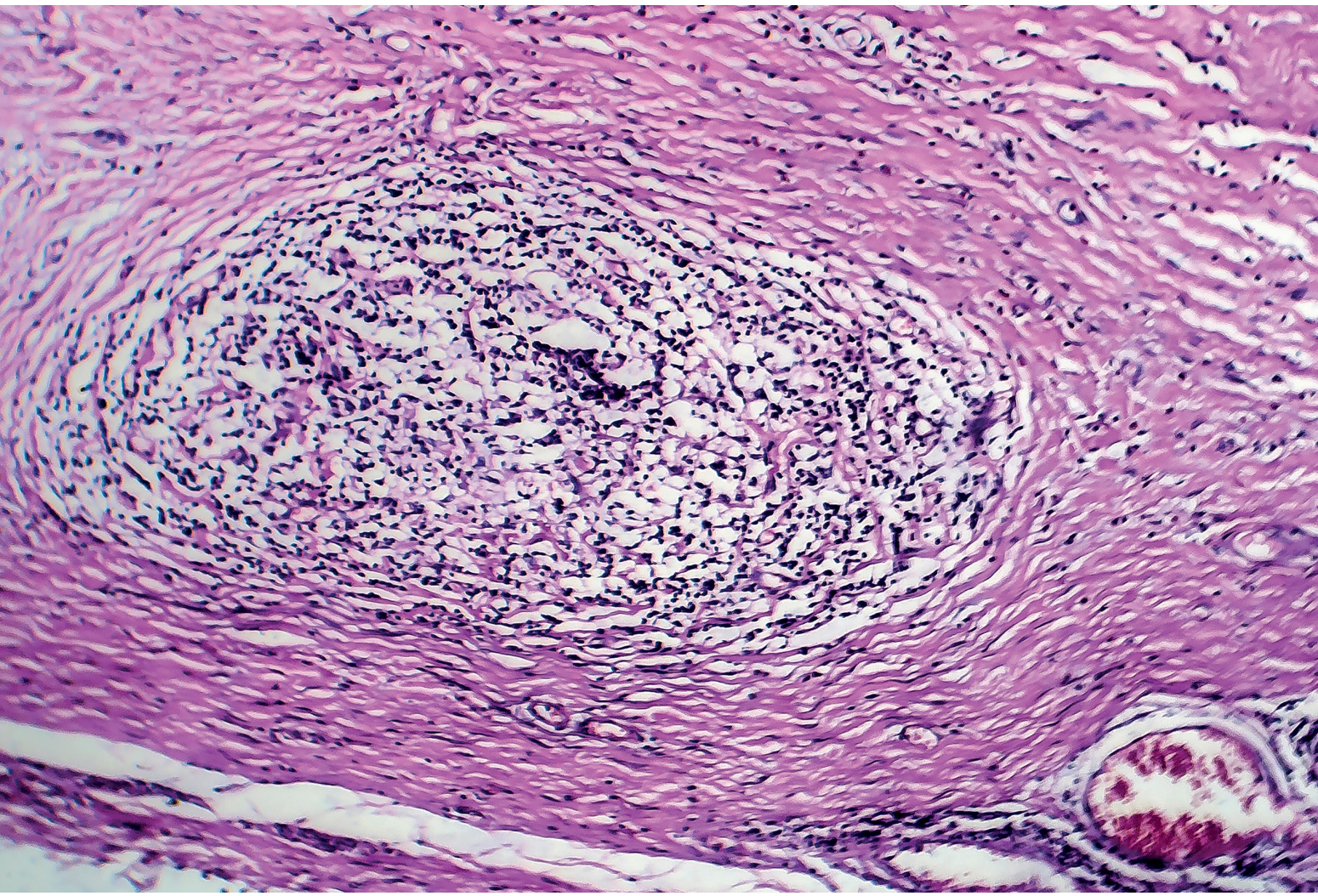

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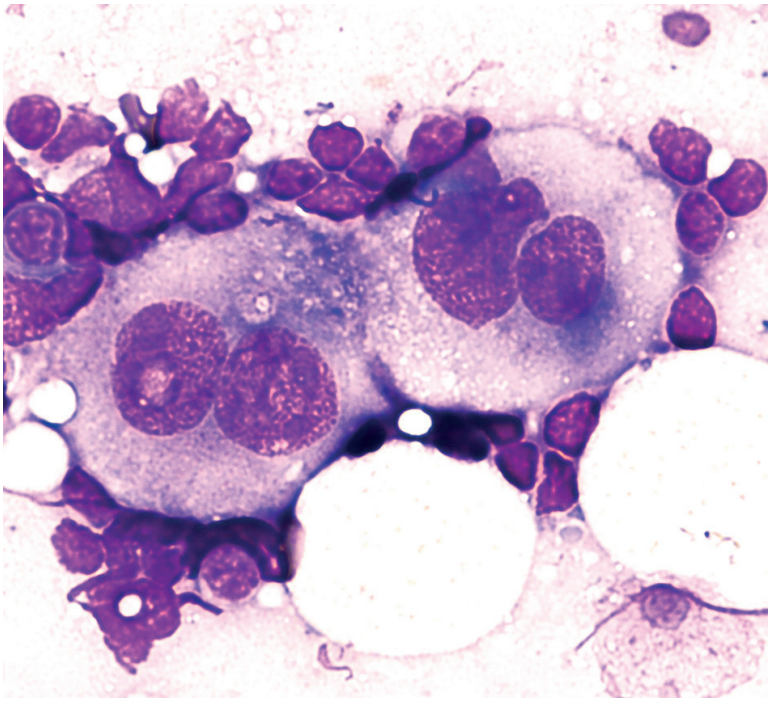
Hodgkin lymphoma, a type of lymphatic system neoplasm, is characterized by a high rate of successful treatment. This, however, was not always true. For years, scientists worked tirelessly to refine therapies that significantly improved survival rates. These advancements, unfortunately, come with the risk of serious side effects. Symptoms such as enlarged lymph nodes that are painful after alcohol consumption, unexplained weight loss, night sweats, persistent fever, or fatigue could be non-specific signs of classic Hodgkin lymphoma. This disease is marked by the uncontrolled growth of cancer-altered B lymphocytes. Initially affecting the lymph nodes, it can also spread to the spleen and other organs in more advanced stages of the disease.

Treatment methods

The progress that has been made in treating classic Hodgkin lymphoma is a remarkable success story in medicine. Once a formidable challenge in the 1960s, with only about 40% of patients surviving beyond five years, it now has an excellent prognosis, with survival rates reaching up to 90% in developed countries thanks to access to contemporary treatments. This leap forward was made possible through decades of comprehensive efforts, including the development of chemotherapy, radiation therapy, and high-dose chemotherapy augmented by stem cell transplants. Crucially, extensive basic research across the globe has led to a deeper understanding of the molecular changes involved in this disease, paving the way for the integration of immunotherapy into treatment regimens. Unlike traditional methods, this innovative approach boosts the patient's immune system, empowering it to identify and eliminate malignantly transformed cells.

Classic Hodgkin lymphoma exhibits two primary age groups of incidence. It is diagnosed in older adults, typically around 60 years of age and, interestingly, there is also a notable incidence rate among teenagers and young adults, between 15 and 35 years old. The implications of treatment at such a young age are profound, especially as many patients are at a pivotal stage of life, possibly considering starting a family. The toxicity of conventional treatments and their long-term side effects pose significant concerns for such patients, as they can lead to an increased risk of secondary cancers and notably impact fertility by damaging the patient's genetic material.

Microscope photograph of lymph node cells obtained from a patient with Hodgkin lymphoma. Visible in the center are multinucleated Reed-Sternberg cells



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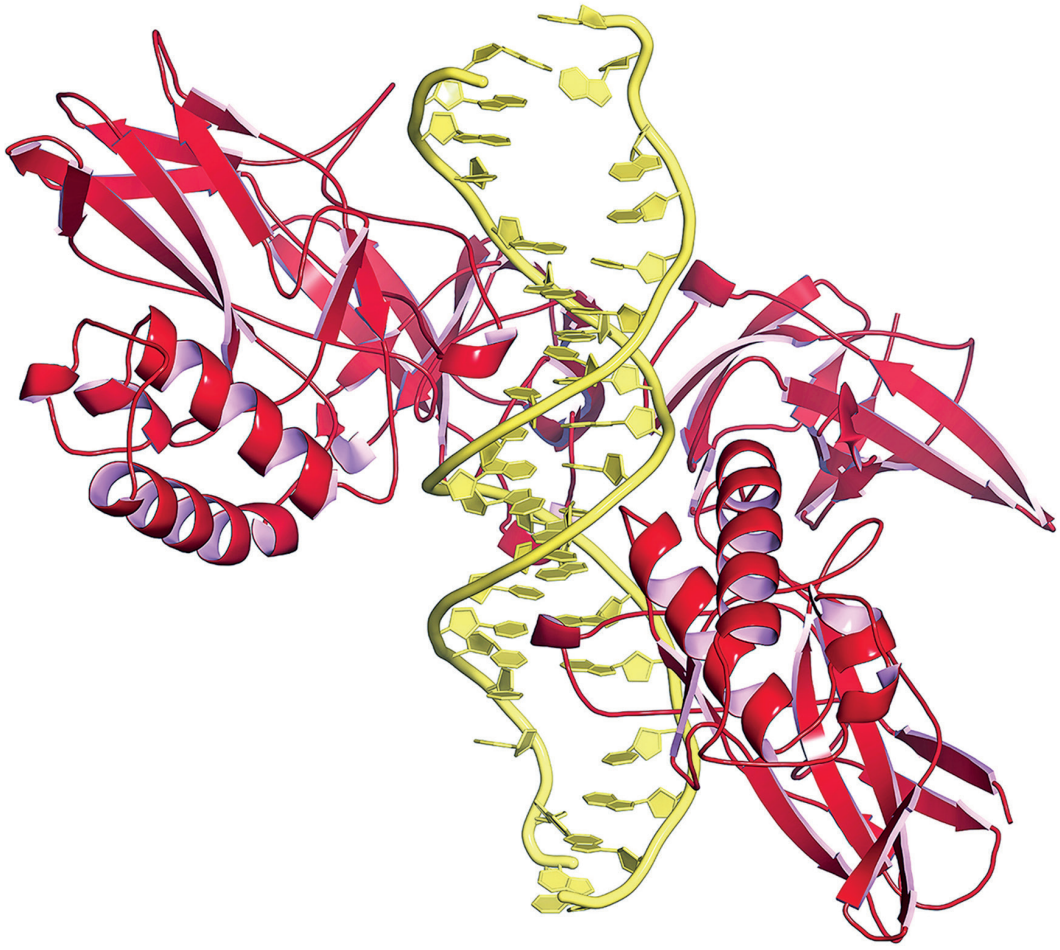
Joining forces

A collaborative effort between German researchers from the Institute of Human Genetics at Ulm University (formerly at Christian Albrecht University in Kiel) and at Charité – Universitätsmedizin and the Max Delbrück Center for Molecular Medicine, both in Berlin, along with Polish scientists from the PAS Institute of Human Genetics in Poznań, has led to fruitful scientific cooperation. The joint mission of the international team is to investigate the genetic and epigenetic alterations that convert a normal B lymphocyte into a neoplastic cell in Hodgkin lymphoma – known as a Hodgkin cell or Reed-Sternberg (HRS) cell.

At the heart of their investigation is the role of transcription factors, crucial proteins that regulate gene activity. Any disruption in these proteins can trigger a series of cellular changes, leading to tumor formation. In cases of classic Hodgkin lymphoma, anomalies in the activity of these transcription factors, including both increases (as seen with transcription factor NFκB) and decreases (as with SPI1 and ELF1), have been observed.

The research specifically targeted activating mutations – those that either cause excessive protein activity or confer new, aberrant functions to the protein. The *IRF4* gene, vital for the development of plasma cells (mature B lymphocytes tasked with producing antibodies to combat pathogens), emerged as a key area of interest. Our team of researchers from Poznań, based on theoretical analyses of the structure and function of the encoded protein, hypothesized



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A model showing the interaction of DNA (yellow) with an example of a transcription factor, NF-kB (red). This type of interaction regulates the activity of genes located in a given DNA fragment

that the changes identified at the DNA level could have significant consequences for its functioning. This assumption was based on the fact that in classic Hodgkin lymphoma, the *IRF4* protein had a mutation (designated as C99R) in a very important part of the molecule responsible for switching on gene activity.

Encouraged by these promising findings, Prof. Stephan Mathas, the group leader, began extensive research on the role of alterations in the gene encoding the IRF4 protein in classic Hodgkin lymphoma. Additional groups from Germany, as well as from the United Kingdom, Canada, and Australia, joined the research. This extensive, multi-center consortium has allowed us to significantly improve our grasp of the significance of the identified *IRF4* gene mutations.

Mutation formation

It seemed intriguing that despite the high expression of *IRF4*, HRS cells stop in the maturation process, ultimately not transforming into plasma cells. This puzzling phenomenon was clarified by the collaborative work of the consortium. The C99R mutation, it was discovered, impairs the *IRF4* protein's ability to recognize and regulate its target genes effectively. Out of nearly three hundred genes typically regulated by *IRF4*, only seven remain unaffected. Conversely, the mutation prompts the activation of almost sixty other genes, initiating cellular reprogramming and the transition to a cancerous state.

It is important to emphasize the dual nature of this mutation's impact. On the one hand, it is a typical mutation that inhibits the normal function of the IRF4 protein, preventing it from accurately identifying its genetic targets. On the other hand, it also adds new functions to the mutated protein, i.e. enabling it to interact with other genes it previously could not. It is worth noting that many of the improperly activated genes, including *GATA3*, *CCL5*, or *TNFRSF8* (CD30), play known roles in classic Hodgkin lymphoma. Thus, the identified single mutation C99R not only results in the global reprogramming of the cell and its transformation into an HRS cell. It also explains why these cells are characterized by a blocked maturation process towards plasma cells.

In summary, the mutation in the *IRF4* gene is one of the key elements of the molecular pathogenesis of this lymphoma, but it is clear that it is not the only one. Observations from the research indicate that the C99R mutation occurs in HRS cells in 15 to 20% of patients with Hodgkin lymphoma. Nevertheless, this insight into the disease's pathogenesis, particularly the interaction between the mutated IRF4 protein and DNA, represents a key step towards a better understanding of Hodgkin lymphoma biology, which might help in the future to develop less toxic treatment strategies. ■

Further reading:

Schleussner, N., Cauchy, P., Franke, V. *et al.*, Transcriptional reprogramming by mutated *IRF4* in lymphoma, *Nat Commun* 14, 6947 (2023). https://doi.org/10.1038/s41467-023-41954-8