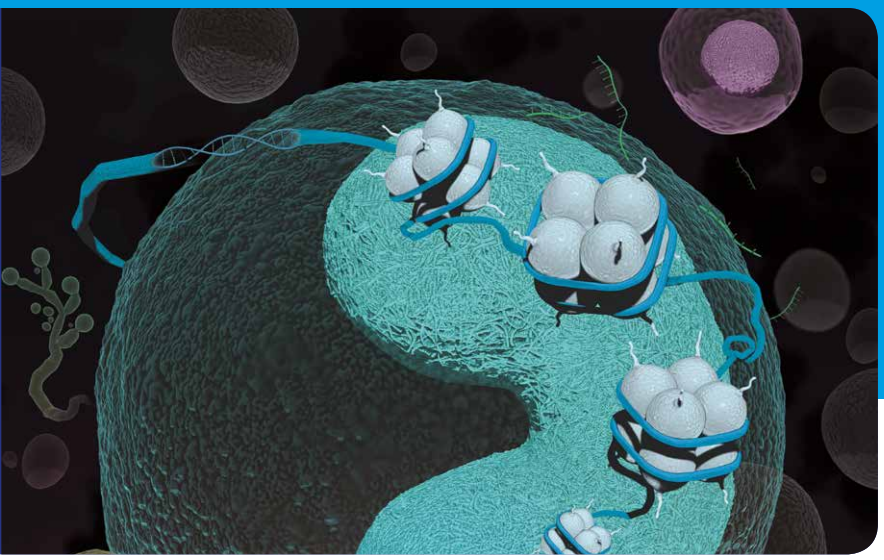

When B cells go rogue

BLUEPRINT partners clarify the origins of two devastating forms of lymph node cancer

Many types of blood cancers are thought to arise from cells that experience defects as they develop. Immune cells called B cells seem particularly susceptible because as they specialize, they rearrange and mutate parts of their genomes to produce a huge variety of antibodies needed to combat infections. B cells undergo this process of maturation partially in compartments of the lymph nodes called germinal centers.

Here cells sometimes cut and paste regions of DNA into the wrong locations, which can disrupt crucial genes and lead to tumors. Normally such defective cells are eliminated. But scientists have suspected for years that in Burkitt and follicular lymphomas, two types of B-cell cancer that arise from improper rearrangements of the genome, cells escape this negative elimination, and the result is a population of cells, produced by accident, with the mutations seen in lymphomas.

An important cornerstone has now been added to this hypothesis in a comprehensive study by researchers from the BLUEPRINT partners at the Universities of Kiel and Leipzig, together with the team at the German Cancer Research Center (DKFZ), other BLUEPRINT partners and the German ICGC MMML-Seq project. The authors show that the two types of tumors, which are different in terms of their aggressiveness, are locked into cellular programs that are typical for different cells of the germinal center. Comparisons between the tumors and healthy cells have revealed patterns of genetic and epigenetic alterations that are helping to explain the origins of cancer cells and the biologial programs that are disrupted within them.

The study was led by Helene Kretzmer of the University of Leipzig, working with scientists across Germany who take part in ICGC MMML-Seq, a project coordinated by Reiner Siebert from Kiel University. The team collected tumoral B cells from lymphoma patients and normal B cells from healthy individuals for a comparative epigenomic study. The goal was to determine the molecular differences between the two types of cancerous cells and their healthy counterparts, and to find patterns that might account for the frequent genetic and epigenetic changes observed in the lymphomas.

Burkitt and follicular lymphomas are two B-cell cancers that resemble mature B cells. The aggressive Burkitt lymphomas predominately affect children, while slower-forming folllicular lymphomas normally arise during adulthood. In both lymphomas, genes become translocated from their regular positions in chromosomes into genomic regions that usually undergo rearrangements in B cells. Other genes frequently experience mutations while remaining at their normal positions in the genome. These distinct mutation events are thought to be linked to the different steps of maturation that B cells

undergo during development and within the germinal centers of lymph nodes.

It is within these centers that B cells normally rearrange their genomes to produce billions of unique and different antibodies. Cells with improper rearrangements are usually eliminated. This happens when maturing B cells shuttle between dark and light zones of the germinal centers. Scientists had advanced a hypothesis that in the distinct lymphomas, cells not only have lost the capacity to shuffle between the zones, but also got stuck in either the dark or the light zone of the germinal centers. The hypothesis proposed that in Burkitt lymphomas cells become fixed in the dark zone, while in follicular lymphomas, cancer cells bear similarities to those of the light zone. Healthy cells of the two types activate different sets of genes as they move between the regions of the germinal centers.

The study examined both the “on” and “off” pattern of gene activation and patterns of DNA methylation within their sequences and nearby regions. This is a process by which chemical tags called methyl groups are applied or removed from DNA sequences as cells specialize. The development of these tags during B-cell maturation (See „The life of a B-cell“) has an impact on which genes are active and which are silenced.

The patterns of both types of molecular signatures supported the relationship that had been proposed between the lymphomas and the zones in germinal centers where they arrested. The genes active in Burkitt lymphomas corresponded more closely to healthy B-cell patterns found in the dark zone, while gene expression in follicular lymphomas resembled that of healthy cells of the light zone.

Besides clarifying the cellular origins of the lymphomas, the comparisons also revealed that they shared additional, very specific cancer-like features that distinguished them from healthy B cells. In general, the DNA of cancer cells had far less methylation. But particular regions that were untagged in normal B cells had acquired methylation in the cancer cells. Some of the changes could clearly be linked to processes involved in cancer.

In Burkitt lymphoma, for example, the DNA of a master control gene called TCF3 loses its methylation and TCF3 becomes strongly activated. This improper activation triggers continued expression of TCF3 itself as well as that of other „downstream“ genes that are activated in a cascade. One is SMARCA4, a molecule that usually controls the behavior of genes through epigenetic modifications. It is normally produced at moderate levels in healthy B cells. Burkitt cells produce much more SMARCA4, but at the same time the molecule accumulates a range of mutations that block part of its activity. While the mutations affect many different positions in SMARCA4, they all seem to have similar effects on its functions: the defects in SMARCA4 likely block both DNA methylation and the transcription of genes at the same time.

Generally, Burkitt lymphoma cells suppress the production of molecules needed to combat inflammations and infections. Follicular lymphomas lowered the activity of genes involved in controlling the rate of the cell cycle and DNA repair, leading to an accumulation of errors in DNA that could promote cancer.

Most of the similar changes that distinguish the two types of cancer from healthy cells involved regions of the genome that were already undergoing changes during B cell development. This provides fascinating links between the epigenetic and genetic changes in B cells and the processes that underlie cancer development.

Reference:

- *Kretzmer H et al. DNA methylome analysis in Burkitt and follicular lymphomas identifies differentially methylated regions linked to somatic mutation and transcriptional control. Nature Genetics (2015). Published online 05 Octobre 2015. doi:10.1038/ng.3413*

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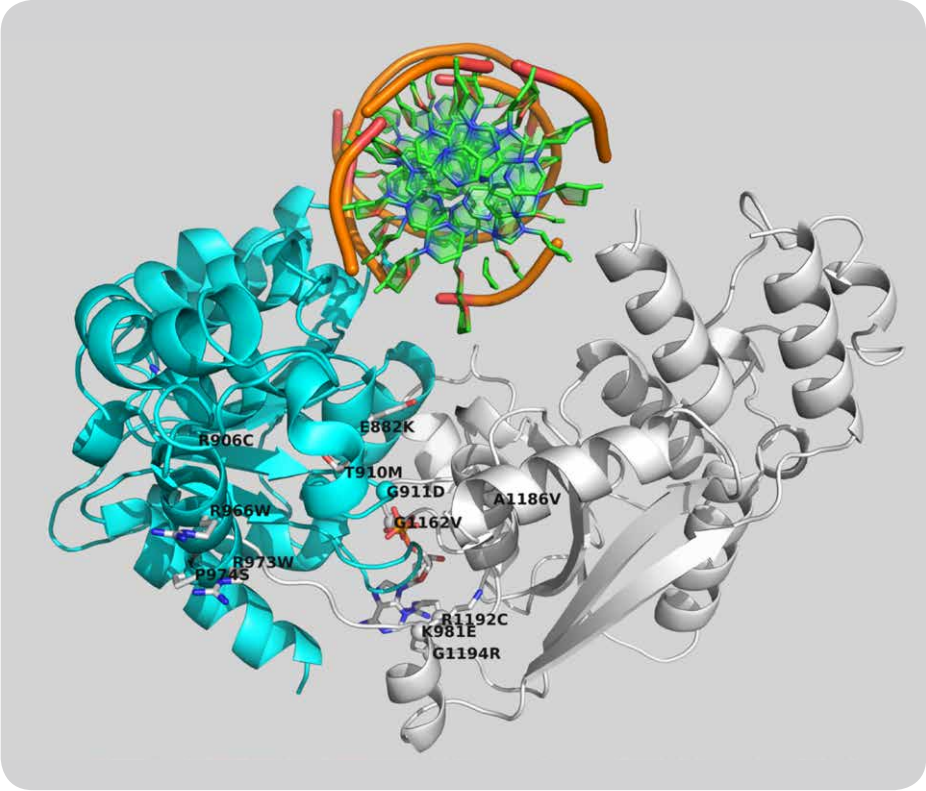

Model of SMARCA4 interaction with a DNA helix. The amino acid residues mutated in Burkitt lymphoma are indicated, but the model suggests that they ablate helicase function rather than DNA binding by interfering with ATP binding, either directly or by obstructing the interaction of the helicase N- and C-terminal domains. Cyan, DEXDc domain; gray, C-terminal helicase domain. ATP is shown with sticks colored by atom type.

Figure published in Nature Genetics (2015).