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When the brain's clock goes awry

Mutations in the genes of a protein complex called SWI/SNF are one of the most common causes of cancer in humans. But until now it wasn't clear how these changes in the genome lead to tumors. Using a fruit fly as a model organism, Jürgen Knoblich and his team from the Institute of Molecular Biotechnology (IMBA) at the Austrian Academy of Sciences (ÖAW) have now been able to discover how the growth of progenitor cells spins out of control as a result of genetic defects. This understanding of the mechanism that causes tumors is important for the targeted development of medicines to fight them.

The formation of organs such as the brain is nourished by a pool of stem cells that have the fascinating ability to divide asymmetrically. One part is a new stem cell, and the other is a cell that continues to divide until it becomes a nerve cell.

„In this stem cell sequence, the cells always progress from unspecialized to specialized,“ explains Jürgen Knoblich, team leader and last author of the current study in *Cell*, a professional journal. „That process never reverses – except in a tumor.“ With dire consequences: the cells then regain their ability to regenerate. That leads to unchecked growth and eventually to fatal cancers.

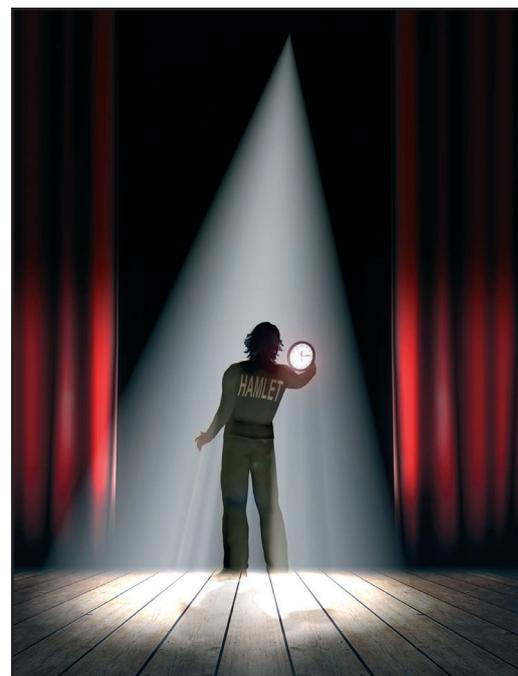
Fruit flies with cancer

Jürgen Knoblich and his post-doctoral research fellow Elif Eroglu suspected they would find the culprit in the SWI/SNF complex. Like many other proteins in the cell, this protein complex has a regulatory function. It changes the chromatin, the structure containing the DNA hereditary molecule, and thus ensures that a gene is read at the right time. Interestingly, both fruit flies and humans have this complex. In cancers such as brain tumors or leukemia, researchers have observed that the genes containing the „construction manual“ for SWI/SNF have mutated.

But what exactly happens in the cell when the protein complex is missing as a result of a genetic defect? Jürgen Knoblich's team looked into this question using the brain of the *Drosophila* fruit fly. In this model organism, the genes for the complex can be targeted and shut down. The researchers allowed embryos thus mutated to develop into larvae flies, and cancerous tumors then quickly infested the entire brain. The scientists isolated tumor cells and used biometric procedures to examine which genes were active in the cells. What they discovered was a sophisticated molecular clockwork that was severely disrupted in the cancer cells.

SWI/SNF switches on the cell's clock

It became apparent that the SWI/SNF complex is not active in the stem cell. But as soon as the stem cell begins to specialize, the complex goes into action. In that sense the complex is like a clockmaker who switches on a clock – in this case a complicated program of proteins called transcription factors. They ensure that genes are switched on



A protein called „Hamlet“ ensures that cell division is stopped in time. If Hamlet is missing cancer occurs.

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at the right moment so that the cell can develop into a nerve cell step by step.

At the same time, the SWI/SNF clockmaker switches on another important protein: Hamlet. Hamlet is the clockwork, and it ensures that the clock ticks only a few times before cell division is stopped. Humans also have this key protein; it is called Evi1. For example, we already know that Evi1 is often mutated in people with leukemia.

The tumor's cell of origin

„When the SWI/SNF complex is missing, the stem cells still make nerve progenitor cells, but neither the clock nor the clockwork. Although they then look like specialized cells, they divide infinitely,“ said Jürgen Knoblich.

„It's extremely important that we identify the cell of origin of a tumor,“ Elif Eroglu, post-doctoral fellow, agrees. „Tumors in advanced stages comprise various kinds of cells. In some types of cancer we assume that they got their start in stem cells. But in this case it's a progenitor cell that again takes on the characteristics of stem cells.“ Such detailed knowledge of the mechanism of tumor formation is important so that cancer specialists can develop targeted medications to fight it.

IMBA:

The IMBA – Institute of Molecular Biotechnology is an internationally recognized research institute with around 200 employees from 25 countries. Scientists there conduct research into molecular processes in cells and organisms to reveal the causes of the development of diseases in humans. Twelve scientific workgroups work on issues in biology in the fields of cell division, cell movement, RNA interference, and epigenetics, as well as on immediate medical issues in the fields of oncology, stem cell research, and immunology. The IMBA is a 100% subsidiary of the ÖAW. www.imba.oeaw.ac.at

ÖAW:

The Austrian Academy of Sciences (ÖAW) is the leading venue for extra-university academic research in Austria, and has an annual budget of around 75 million euros. The 28 research facilities employ a total of around 1,300 people. They conduct open-application fundamental research in socially relevant fields of the natural and life sciences, technology, as well as the humanities, social sciences, and cultural studies. www.oeaw.ac.at

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