IMBA Press Release

Date: 2011-08-21

A hippo in the head

Stem cells gone rampant cause brain tumors

In healthy larvae of Drosophila, a genus of fruit flies, the developing brain "knows" when it is big enough. Mutant larvae unable to produce the L(3)mbt protein lack this growth monitor. Deadly brain tumors run rampant in their heads; these tumors are made up of rogue stem cells.

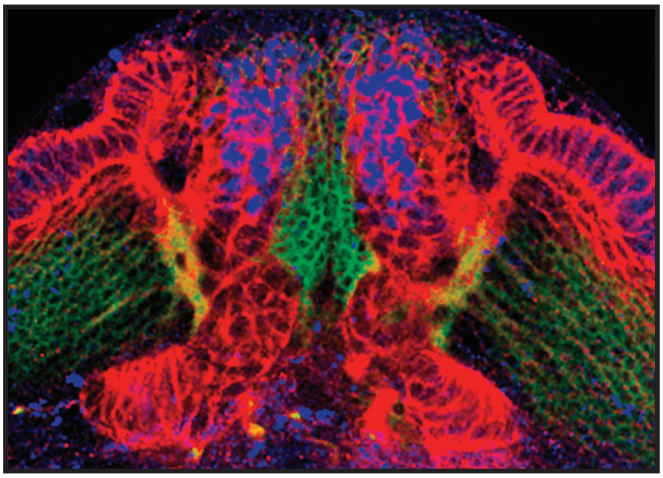
A research team led by Constance Richter and Jürgen Knoblich of the IMBA has identified the source of this uncontrolled growth of stem cells. Without the L(3)mbt protein, certain DNA reads are not isolated and tumor-causing genes go wild. Similar mechanisms of excess are most likely at work in human brain tumors as well.

Gluttony – not knowing when enough is enough – is considered one of the seven deadly sins. That holds true in developmental biology as well: unchecked tissue growth can have disastrous consequences as organs grow beyond their normal size. That's why the developing brain of Drosophilia, a genus of fruit flies, "knows" how long to keep growing and when it's time to stop.

But this mechanism fails in Drosophilia larvae with a defective l(3)mbt gene. These mutants are unable to produce the L(3)mbt protein, and brain tumors are the result. These larvae do produce neuroepithel cells in the optic lobe of the brain, just as healthy larvae do. In the course of normal development, this microscopically thin layer of cells should lead to a pre-determined number of stem cells, as well as specialized nerve cells that allow the brain to process visual information.

Far too many stem cells

But if the larvae lack the L(3)mbt protein, this carefully choreographed dance of development is destroyed at its foundation. A report by post-doctoral researcher Constance Richter and senior scientist Jürgen Knoblich from the IMBA shows that the neuroepithel cells in the optical lobe first become extremely enlarged, then develop into neural stem cells called neuroblasts. This mass of cells undergoes unchecked division, and a tumor is the result.



What does that mean for a fruit fly larva? First the brain tumor, consisting of stem cells, "only" delays development. But within a few days it spreads to the entire larva. Abnormal growth occurs in the anlage for the wings as well. Finally the tumor kills the larva.

No limits, no goals

Up to now no one understood why l(3)mbt mutants displayed such a lack of control. Constance Richter and Jürgen Knoblich wanted to find the answer. For four years they examined the unhealthy larvae. Using methods from biochemistry, epigenetics and bioinformatics, they were finally able to prove that the hippo signaling pathway is severely disrupted in the mutants.

In humans and mice, this information network is responsible for ensuring that organs such as the heart and liver maintain their normal size. Disturbance in the hippo signaling pathway leads to unchecked growth and the development of tumors. It's no coincidence that the gene for this signaling pathway was named after the hippopotamus, a massive animal.

Order through isolation
What exactly happens in the fruit fly larvae? Richter and Knoblich discovered that the L(3)mbt is an isolator that clings to specific DNA reads. In healthy specimens this isolator protein forms a targeted protective shield, keeping the brain free of tumors. This shield ensures that various genes, such as yorkie, expanded and bantam, are activated at only at the right moment, and stimulated precisely.

"Without the isolator protein, the neuroepithel grows out of control. The stem cells it produces do not respond to the external regulation signals the body sends. That is typical behavior for tumors," said Constance Richter.

Learning from the fly
Jürgen Knoblich, the study lead and an expert for stem cell biology, said these findings are particularly interesting because the development of the central nervous system is similar in the Drosophilia and in mammals. The basics of the tumor onset in the fruit fly hold true for humans as well. "One day a cure for this disease might be found based on these results. That's tremendously motivating," Knoblich said.

In 2006 Jürgen Knoblich published a highly-acclaimed report on a different type stem cell tumor that develops in the Drosophilia brain when the brat protein fails. "Tumors resulting from brat mutants and l(3)mbt mutants look identical in afflicted larvae. But their origins are entirely different," said Knoblich. "This is highly relevant to researchers who aim to develop treatments for brain tumor patients. Maybe tumors that have different origins should be treated differently, even if they are anatomically and histologically similar," he added.

Tumor stem cells are the cancer engine
Growing evidence indicates that rogue stem cells can be deadly, not only in Drosophilia. According to a tumor stem cell hypothesis, genetically altered stem cells are the engines that drive at least some forms of cancer in humans.

But standard treatments (chemotherapy, radiation) target differentiated cells that divide quickly and form the bulk of a tumor. They do not assail tumor stem cells, which are far fewer in number and often lie dormant for a long time; that is thought to be the cause of relapses and the formation of metastases. That's why cancer specialists are trying to develop drugs that target tumor stem cells, and to find ways to reprogram rogue stem cells.

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Jürgen Knoblich
Jürgen Knoblich (born 1963) has been a senior scientist and the assistant scientific director at the Institute of Molecular Biotechnology at the Austrian Academy of Sciences (IMBA) since 2004. His team researches the division and growth control of stem cells. Born in Germany, he was the recipient of the Wittgenstein-Preis, the highest award for scientific research in Austria, in 2009.

Scientific publication:
Constance Richter, Katarzyna Oktaba, Jonas Steinmann, Jürg Müller and Jürgen Knoblich. „The tumor suppressor L(3)mbt inhibits neuroepithelial proliferation and acts on insulator elements". 2011. Nature Cell Biology.

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