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Guardian molecule keeps cells on track – new perspectives for the treatment of liver cancer

A guardian molecule ensures that liver cells do not lose their identity. This has been discovered by researchers from the German Cancer Research Center (DKFZ), the Hector Institute für Translational Brain Research (HITBR), and from the European Molecular Biology Laboratory (EMBL). The discovery is of great importance for cancer medicine because a change of identity of cells has come into focus as a fundamental principle of carcinogenesis for several years. The research team was able to show that the newly discovered guardian is so powerful that it can slow down highly potent cancer drivers and cause malignant liver tumors to regress in mice.

As a rule, the identity of cells is determined during embryonic development. They differentiate into nerve cells or liver cells, for example, and their fate is sealed. Only stem cells retain the ability to develop in different directions. However, once cells have differentiated, they usually stay on course.

Cancer cells can change their identity

Cancer cells are different. They have the amazing ability to reactivate embryonic programs and thus change their identity – their phenotype. This ability is referred to as – unwanted or abnormal – plasticity. It enables tumor cells to break away from the cell network and migrate through the body. Once they have arrived in the target organ, the cells differentiate again, become sedentary again and form metastases at this site.

“It is not long ago that the importance of plasticity as a fundamental phenomenon in cancer was recognized,” explains molecular biologist Moritz Mall of the DKFZ. His team's goal is to reduce the plasticity of cancer cells and thus prevent the development and spread of malignant tumors. To do this, they first need to understand how cell plasticity is regulated. In principle, almost all cells in the body have an identical genome. But how is it possible then that such different and highly specialized cell types as nerve cells or liver cells arise?

The Yin and Yang of cell differentiation

“This is only possible because cells have a sophisticated control network,” explains Moritz Mall. „Similar to Yin and Yang, complementary forces are at work here.“ These ensure that only certain genes are switched on, depending on the cell type, while others are permanently silenced. Master regulators play a central role in this process. They switch on genes that influence specialized cells to change their identity and even acquire stem cell properties.

However, little is known about the antagonists – the control instances that prevent unwanted (re)transformation of differentiated cells by switching off certain genes. Together with Judith Zaugg, EMBL, Moritz Mall wanted to find out more about such guardians. The researchers used a computer program to search for gene switches that could potentially serve as guardians. “We developed a special computer program to screen candidates for the essential properties that a guardian molecule must possess,” explains Judith Zaugg. “We then ran the profiles of more than a thousand gene switches through the computer, accessing large databases of research results.”

Guardians undermine cancer drivers

The research team found almost 30 different guardian candidates and decided to pursue one of them further: PROX1 (Prospero homeobox protein 1). Studies on the liver cancer model showed that the team had hit the mark. Moritz Mall explains: “It turned out that PROX1 is a very influential guardian in liver cells. If it is missing, the liver cells change their phenotype. And conversely, the versatility of tumor cells can be reduced by experimentally inducing an increase in the activity of the guard. We were surprised by how powerful PROX1's influence is. We tested the guardian molecule in mice that had highly potent cancer mutations in the p53 and Myc genes. PROX1 was able to override the influence of such strong cancer drivers and suppress the

formation of tumors despite their presence."

And the researchers found more: the PROX1 guardian must be constantly active around the clock to fulfill its function. This is different from many other gene switches, which, like a toggle switch, only need to be activated briefly.

There are still many unanswered questions, but it is already clear that the discovery of the guardian molecule could open doors to new therapies. If it were possible to increase PROX1 activity locally in the liver, it could be an innovative approach to the prevention and treatment of liver cancer. It is unclear whether there are similar guardians in other organs. Moritz Mall and Judith Zaugg are convinced that there are and want to continue their successful research alliance in the future.

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