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A life-or-death decision

Programmed cell death, or apoptosis, kills off billions of cells in the human body every day, but without it life would not be possible. A team of researchers led by Professor Klaus Rajewsky, an immunologist at the MDC, has now published a study in the journal Genes & Development that sheds new light on cellular survival strategies.

With another four MDC labs Labi und Rajewsky studied microRNAs.
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It is like a call to suicide. When a cell is no longer needed, certain cellular signaling pathways turn on a program that eventually leads to self-destruction of the cell. In many cases this is beneficial, for example, during embryonic development when organs first begin to form. The immune system, which renews itself regularly, also needs to get rid of damaged or old cells in order to make room for new ones. In addition, programmed cell

death, called apoptosis, offers significant protection against cancer. Mutated or already malignant cells can usually be eliminated with its help.

The Bim protein drives cells to suicide

"We used a mouse model to investigate how tiny RNA segments, so-called microRNAs, regulate the concentration of Bim in cells"

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Dr. Verena Labi

Former Postdoc at Klaus Rajewsky's lab

Apoptosis is regulated by various genes. Particularly well understood is the gene that codes the protein known as Bcl-2, the prototype member of the protein family of the same name. A high concentration of Bcl-2 protects cells from suicide. This molecule is counteracted by the protein Bim, which triggers cells death. The team led by Klaus Rajewsky, head of the research group on Immune Regulation and Cancer at the Max Delbrück Center for Molecular Medicine (MDC) in Berlin, focused on this protein in their recent study. Bim also belongs to the Bcl-2 family and is found in almost all mammalian cells.

"We used a mouse model to investigate how tiny RNA segments, so-called microRNAs, regulate the concentration of Bim in cells," explains the study's lead author and former postdoc in Rajewsky's lab, Dr. Verena Labi, now an associate professor at the Institute of Developmental Immunology of the Medical University of Innsbruck. Four other MDC labs were involved in the study: those of Professor Carmen Birchmeier, Dr. Stefan Kempa, Professor Markus Landthaler, and Professor Nikolaus Rajewsky.

The researchers generated mice with a mutated Bim gene

The four microRNAs studied differ in their nucleotide sequence, but are coded together by a gene called miRNA-17~92. "Before the study it was already known that these

microRNAs possess vital functions," says Klaus Rajewsky. "When they are turned off in mice, the animals die during or shortly after birth because their lungs do not develop properly. Such mice also exhibit an impairment in the development of certain immune cells, the B lymphocytes, as well as skeletal abnormalities. In addition, it is known that an elevated concentration of microRNAs of the miRNA-17~92 gene contributes to tumor growth in many tumors, especially in B-cell lymphomas.

"It is probably the lung cells themselves that start the suicide program during lung development in the embryo"

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Klaus Rajewsky

Group leader at MDC

For the current study, Rajewsky and his team first used bioinformatic methods to search for genes with a specific property: Their protein precursor molecules, the messenger RNAs, needed to be capable – as a result of the matching sequence of the individual nucleotides – of being bound by a large number of miRNA-17~92 microRNAs. This is how the researchers came across the Bim gene. In the next step, which involved complex experiments, the team bred mice in which the Bim gene was modified in such a way that the Bim messenger RNA could no longer be bound by the miRNA-17~92 microRNAs. This model enabled the researchers to find out whether – and in which cells of the body – the regulation of the BIM concentration by miRNA-17~92 microRNAs has functional consequences.

Most of the mice died shortly after birth

"Mice in which the Bim gene is altered already in the germline die within an hour after birth for the same reasons as animals whose miRNA-17~92 cluster is shut down do," reports Labi. "The air sacs in their lungs do not expand with their first breaths."

The researchers do not yet now why this happens. "It is probably the lung cells themselves that start the suicide program during lung development in the embryo,"

speculates Rajewsky. “The miRNA-17~92 microRNAs protect these cells from an unplanned apoptosis and thus enable lung tissue to develop optimally in the embryo.”

In around 16 percent of the cases, however, the mutated mice survived. “The animals were somewhat smaller than usual, but their lungs developed normally,” says Rajewsky.

B lymphocytes were unaffected by the mutation

The scientists got a big surprise when they experimented with B lymphocytes in which they had altered the Bim gene so that it could no longer be regulated by the miRNA-17~92 cluster. “Based on the scientific literature, we expected that the mutations would impair the survival of B lymphocytes during their development in the bone marrow – just as we had experienced in experiments with microRNAs that had been turned off,” says Rajewsky.

However, the B lymphocytes, whose most important task is to produce antibodies and protect the body from pathogens, did not let the mutated Bim gene affect their development. “As with normal B lymphocytes, only those cells were eliminated by apoptosis that either no longer functioned at all or accidentally attacked the body’s own structures,” explains Labi.

The control mechanism is not the same in all cell types

Although the miRNA-17~92 microRNAs in normal B lymphocytes can bind to the BIM messenger RNA, this does not appear, according to our results, to affect the amount of Bim protein in these cells.
“So an important conclusion of our work is that the control of the messenger RNA by microRNAs can distinguish between different cell types and probably messenger RNAs as well, and should therefore be tested separately in each tissue,” says Labi.

However, the study also showed that in certain stress situations B lymphocytes need Bim to be controlled by the miRNA-17~92 micro-RNAs to survive. “Consequently, this mechanism could play a role in many other contexts concerning the survival of cells in organisms,” says Rajewsky. “This is particularly so because a series of other microRNAs apparently control Bim.”

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Further information

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Immune Regulation and Cancer

Literature

Labi et. al (2019): „Context-specific regulation of cell survival by a miRNA-controlled BIM rheostat“, Genes and Development, DOI: 10.1101/gad.330134.119 (https://doi.org/10.1101/gad.330134.119)