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Death Receptor Regulates Brain Regeneration

The so-called death receptor is well known among experts – it induces programmed cell death. In brain stem cells, however, this molecule has an entirely different function, as shown by scientists of the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) in an article published in *CELL Stem Cell.* Here, signals to the death receptor cause the formation of new nerve cells (neurons). When the researchers switched off the receptor molecule in mouse neural stem cells, they found that regeneration of the brain is affected and learning ability is restricted.

Learning and cell death are closely connected: The hippocampus is the “learning center” of the brain where young neurons are permanently formed. However, most of these die by programmed cell death, or apoptosis, before being permanently integrated in the brain circuits. If apoptosis is suppressed so that these superfluous neurons survive, this even leads to impaired learning ability.

The protein CD95 is one of the best studied apoptosis-inducing receptors on the cell surface where it receives the “death message”, the signaling molecule CD95L. However, when studying neural stem cells, which are responsible for supplying the brain with new nerve cells, Dr. Ana Martin-Villalba and her team at DKFZ made a surprising discovery. Here, signals to the CD95 receptor cause the neural stem cells to differentiate into new neurons.

This happens not only in the culture dish but also in the living organism. When the scientists increase the production of death messenger CD95L in the brains of mice, the CD95 receptors on the neural stem cells receive particularly many signals, and the number of young, immature neurons rises.

Under certain conditions, young neurons are also formed outside the hippocampus in the brain, for example, as a reaction to a lack of blood supply such as in a stroke or cardiac arrest. As Ana Martin-Villalba has shown previously, such tissue damages increase the formation of death messenger CD95L in the brain.

To find out whether this rise in CD95L is a signal for brain tissue repair, the investigators artificially induced a lack of blood supply in the brains of mice. Since the scientists expected that the number of stem cells in the brain tissue would not be enough for them to contribute significantly to regeneration, they transplanted additional neural stem cells into the mouse brains. A few weeks later they found numerous young neurons and the animals had good results in a special learning test. In a control experiment, the investigators transplanted neural stem cells with a defect in the CD95 signaling pathway into mice after a lack of blood supply. This time, no new nerves were formed and the animals’ learning ability was comparatively poor.

Running supports supply of new nerves

When the researchers specifically switched off CD95 production in mouse neural stem cells, significantly less neurons were formed in the hippocampus of these animals, as expected. The results of these mice in the learning test were correspondingly bad. However, if the animals were given the opportunity to run in an exercise wheel, their test results improved. Running increases the formation of new nerve cells. This effect, however, continues only for a few weeks after termination of the exercise program, because the working memory needs a continuous supply of newborn neurons.

Possible use for treating brain damages?

“We were able to show, for the first time, that the death receptor and its ligand, CD95 and CD95L, play a central role in the regeneration of the brain,” Martin-Villalba says. In her opinion, it is too early to say whether these results might contribute to improving the treatment of brain damages after a stroke. “We believe that the natural number of neural stem cells in the brain is not sufficient to achieve a noticeable regeneration with CD95L alone. But it is possible that a combination of CD95L and a substance stimulating stem cell multiplication might have a stronger effect.”

For regenerative medicine, the result obtained at the German Cancer Research Center is already an advance. Medical researchers are now able to specifically differentiate tissue stem cells into nerve cells in the culture dish. Such cells might serve as biological replacement material for destroyed tissue in the future.

Nina S. Corsini, Ignacio Sancho-Martinez, Sabrina Laudenklos, Desiree Glagow, Sachin Kumar, Elisabeth Letellier, Philipp Koch, Marcin Teodorczyk, Susanne Kleber, Stefan Klussmann, Benedict Wiestler, Oliver Brüstle, Wolf Müller, Christian Gieffers, Oliver Hill, Meinolf Thiemann, Mathias Seedorf, Norbert Gretz, Rolf Sprengel, Tansu Celikel, Ana Martin-Villalba: THE DEATH RECEPTOR CD95 ACTIVATES ADULT NEURAL STEM CELLS FOR WORKING MEMORY FORMATION AND BRAIN REPAIR. Cell Stem Cell, August 2009
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