Scientists discover cause of destructive inflammations

March 3 2010

The signaling molecule CD95L, known as "death messenger," causes an inflammatory process in injured tissue after spinal cord injuries and prevents its healing. This discovery was published by scientists of the German Cancer Research Center. In mice, the researchers found out that if they switch off CD95L, the injured spinal cord heals and the animals regain better ability to move. Therefore, substances which block the death messenger might offer a new approach in the treatment of severe inflammatory diseases.

A couple of years ago, Dr. Ana Martin-Villalba of the German Cancer Research Center already succeeded in reducing the effects of spinal cord injuries in mice. She was able to improve the animals' ability to move by neutralizing the signaling molecule CD95L. In her research work now published, Martin-Villalba and her team were studying the question of how CD95L exerts its harmful effect in injured nerve tissue.

So far, scientists had assumed that the CD95L molecule, which is also known as 'death messenger', attaches to the death receptor, CD95, on the surface of neurons, thus triggering programmed cell death, or apoptosis, and further damaging injured nerve tissue. After the recent discoveries, this view needs to be revised.

Martin-Villalba's team observed in mice that after spinal cord injuries there is a prolonged inflammatory reaction in the surrounding tissue. Within 24 hours after an injury, large numbers of white blood cells migrate to the affected site in the spinal cord. These are primarily cells

of what is called the innate immunity - macrophages and neutrophils. Researchers found out that during the same time the amount of CD95L on the cell surface of white blood cells in the blood stream increases significantly - apparently as a result of a still unidentified chemical signal sent out by the injured tissue.

In their latest study, Martin-Villalba's team has proven that the signaling molecule CD95L is responsible for the migration of immune cells to the injury site. When the investigators blocked the death messenger using specific agents, the migration came to an end. The researchers identified a previously unknown signaling pathway by which CD95L activates immune cells to become mobile and migrate from the blood stream into the injured spinal cord. This mobilization is not restricted to the inflammatory reaction in spinal cord injuries; in mice with severe peritonitis, the researchers also found CD95L mediated migration of immune cells into the affected tissue.

CD95L promotes tissue-damaging inflammatory reactions

What does CD95L cause in injured spinal cord tissue? To explore this question, the DKFZ researchers investigated genetically modified mice whose immune cells are unable to form CD95L. If the spinal cord of such animals is injured, their neurons are protected from death; the mice recover and perform better in subsequent mobility tests than normal mice.

It seems that the migrated immune cells boost the tissue-damaging inflammatory reaction. When the researchers switched off the CD95L molecule on immune cells and subsequently studied the gene activity in the injured tissue, they observed a decrease in the activity of genes promoting cell death and inflammation. In contrast, more genes which

promote neuronal growth were active.

Does death messenger CD95L really exert its harmful effect in injured spinal cord by causing programmed cell death (apoptosis)? The investigators explored this question in mice whose neurons lack the CD95 receptor, i.e. the docking site for death messenger CD95L. In these animals it became obvious that CD95L contributes to the demise of neurons by recruiting inflammation-promoting immune cells to the injured spinal cord and not by programmed cell death.

Blocking CD95L as a new treatment approach for inflammatory diseases

"We assume that CD95L causes harmful inflammatory reactions in the human body, too," said project leader Ana Martin-Villalba. An analysis of blood samples from patients with spinal cord injuries showed that here, too, the amount of CD95L on immune cells rises within a few hours after the injury.

This is an encouraging indication suggesting that blocking CD95L might be a promising treatment approach for severe inflammatory diseases such as autoimmune disorders, e.g. rheumatoid arthritis or multiple sclerosis. An agent acting against the death messenger would prevent the migration of inflammation-promoting immune cells into the affected tissue and the resulting intensification of the tissue damage. Most recent research results even suggest that inflammatory reactions promote the invasive capability of cancer cells, so that using a CD95L blocker could be helpful in such cases, too.

Such an agent might soon be available. On the basis of inventions from DKFZ, a biotech company is already developing an inhibitor which specifically switches off the human CD95L molecule.

More information: Immunity 2010, DOI:10.1016/j.immuni.2010.01.011