Website address:
https://www.gesundheitsindustrie-bw.de/en/article/press-release/aggravated-neuroimmune-response-delayed-wound-healing-transcription-factor-nf-kb-astrocytes-critically-affects-outcome-traumatic

Aggravated neuroimmune response, delayed wound healing Transcription factor NF-κB in astrocytes critically affects the outcome of traumatic brain injury (TBI)

Traumatic brain injuries often lead to complications with long-lasting consequences on memory, concentration and movement control. Detrimental secondary inflammatory reactions at the injured tissue sites are often responsible for this. Researchers from Ulm have now shown in a Nature Communications study that the transcription factor NF-κB plays a key role in post-traumatic reactions to TBI. When this gene regulator is activated in astrocytes, i.e., in supporting cells of the brain, an elevated neuroimmune response promotes aberrant inflammation.

A fall on the head, a blow to the skull or a road traffic accident - the causes of traumatic brain injury are diverse, but the severe forms have a common nominator: immune reactions and inflammatory processes are added on top to relevant injuries of bones, skin and brain tissue. Such post-traumatic effects can cause considerable damage to the organism. A research team from Ulm University Medicine has now investigated the functional role of the transcription factor NF-κB in such neuroimmune reactions. NF-κB is found in almost all human cell types and activates a large number of different genes. "NF-κB regulates the immune response, controls inflammatory reactions and can block programmed cell death," explains PD Dr Bernd Baumann, corresponding author of the study. The group leader at the Institute of Physiological Chemistry at Ulm University has been researching this transcription factor, which is also involved in tumorigenesis and development of autoimmune diseases, for many years.

What role does this gene regulator play after a traumatic brain injury? "An earlier study by our research group has shown that the activation of NF-κB in neurons promotes regeneration and healing post TBI," says Professor Thomas Wirth. The Director of the Institute of Physiological Chemistry and Dean of the Medical Faculty coordinated the study together with Baumann. Neurons are the "actual" nerve cells of the brain; they transmit and process signals. However, the new study, which was published in the journal Nature Communications, shows a different picture for astrocytes. These star-shaped cells protect, support and supply neuronal cells. They belong to the glial cells of the central nervous system and, among other things, they form the boundary membranes to the blood vessels - i.e. represent an important part of the blood-brain barrier.

The star-shaped glial cells also play a key role in the wound healing and scar formation process of injured brain tissue. "At the injury/damage site, astrocytes surround the wound core. In this way, they limit further neurodegenerative processes and support healing," explains Professor Leda Dimou. The head of the Department of Molecular and Translational Neurosciences at the Department of Neurology played a leading role in the study. The researchers found a striking gene expression signature in the immediate vicinity of the insult area indicating a particularly high NF-κB activity in astrocytes. To investigate the influence of NF-κB in more detail, the researchers worked with mouse models. In these, NF-κB was either pre-activated or strongly inhibited in astrocytes. The team wanted to know: Does this modulation improve or worsen healing after traumatic brain injury?

Disturbed scar formation inhibits healing processes

The result was clear: If NF-κB was pre-activated, the immune system reacted more rapidly and stronger to the traumatic injury. This excessive neuroimmune response triggered detrimental inflammatory processes and disrupted both wound healing and scar formation. "Certain immune cells such as dendritic cells unexpectedly migrated into the wound area. This prevented coordinated scar tissue formation, which ultimately led to neurological deficits," report the study's first authors, Tabea M. Hein and Ester Nespoli. Surprisingly, similar processes occur in the ageing brain. However, when NF-κB was inhibited in astrocytes, single positive effects were observed: Antioxidant defense and mitochondrial function improved, for example. "However, these changes were not sufficient to significantly improve the healing process in general," explain the researchers.

Even though some questions remain unanswered, the results provide important insights for new therapeutic strategies. The role of certain glycoproteins found in bone metabolism is particularly striking. For example, osteopontin (OPN), which is important for tissue formation and wound healing, is insufficiently produced when there is excessive NF-κB activation in the area of injury thus impairing healing. In contrast, more lipocalin-2 protein (LCN2) is produced. This protein can promote harmful neuro-inflammatory processes and can impair the maintenance of the blood-brain barrier. "This could lead to new therapeutic approaches by specifically regulating the levels of these two factors," says Bernd Baumann. The research project was funded as part of two Collaborative Research Centers based at Ulm University, including CRC 1149 "Danger response, disruptive factors and regenerative potential after acute trauma" and CRC 1506 "Aging at Interfaces".

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