

# **Study unveils neural pathway promoting regeneration after traumatic injuries**

December 20 2022, by Ingrid Fadelli

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An illustration representing the team's work. The wizard symbolizes microglia that orchestrate the brain regeneration process in adult zebrafish telencephalon.

Granulins, represented by wizard's cane, hold the power to clear out TDP-43 condensates and lipid droplets in microglia and lead to successful brain regeneration. Credit: Oliver Hoeller.

Studies exploring the neural processes involved in cell regeneration are of crucial importance, as they could pave the way towards the development of more effective treatments for many pathologies associated with the mutations or deterioration of cells. Microglia, the brain's resident immune cells, become active in response to pathologies, sometimes leading to chronic inflammation and the scarring of tissue.

Cell regeneration mechanisms thus regulate the reactivity of different glial cells, including microglia, preventing further damage and promoting recovery. While many past studies have explored the processes involved in inflammation, many questions about how the brain can successfully recover after injuries or pathologies remain unanswered.

Researchers at LMU Munich, Helmholtz Zentrum Munich, Johannes Gutenberg-Universität (JGU), and other institutes in Germany have recently carried out a study on zebrafish aimed at better understanding the processes underpinning brain regeneration in both animals and humans. Their findings, published in *Nature Neuroscience*, unveiled a microglial state characterized by the accumulation of lipid droplets and TDP-43<sup>+</sup>, a RNA-binding protein, which delayed or prevented post-injury brain regeneration.

"Our logic is to understand the regeneration process in the model systems endorsed with endogenous repair and then apply this logic in the mammalian system, including humans, to achieve better regeneration," Jovica Ninkovic, one of the researchers who carried out the study, told MedicalXpress. "Therefore, we set out to explore how the zebrafish

timely inactivates microglia to prevent long-term inflammation after [brain injury](#)."

The overreaching goal of the recent work by Ninkovic and his colleagues was to identify neural pathways involved in the regulation of microglial activity, which could be potentially targeted by pharmacological drugs. The researchers used their understanding of zebrafish biology to identify possible therapeutic targets that might also be applicable to the mammalian brain. In their experiments, they essentially inflicted small injuries in zebrafish and observed how the brain regenerated damaged areas.

"One soon realizes that such simple experimental outcome depends on a number of regulatory processes that are even differing from cell to cell," Ninkovic explained. "We used sophisticated methods to analyze the changes at the single cell level and follow the reaction of single cells to the injury. Only using this approach, we managed to identify the 'dangerous' microglial population that needs to be eliminated to achieve proper regeneration."

The researchers observed a microglial state following traumatic injuries, characterized by the accumulation of lipid droplets and TAR DNA-binding protein 43 (TDP-43). To validate the hypothesis that this state hindered regeneration, they experimentally manipulated the brains of zebrafish to achieve different duration of microglial reactivity and TDP-43 accumulation.

This ultimately allowed them to identify pathways regulating the reactivity of microglia and thus promoting brain regeneration. Specifically, they found that Granulin, a protein known to regulate cell growth and survival, mediated the clearance of both lipid droplets and TDP-43<sup>+</sup> condensates. As a result of this process, microglia went back to their basal state and the zebrafish's injured tissue regenerated without

scarring.

The researchers have already tried to assess the extent to which their findings might generalize to humans, using post-mortem human tissue. In the future, their work could pave the way towards the development of new pharmacological drugs that promote tissue [regeneration](#), which could be valuable for treating various pathologies.

"I think that the identification of the drug-targetable pathway that should be activated to prevent the long-lasting neuroinflammation is very exciting, because neuroinflammation is not only arising after injury, but also in other pathologies and processes, including neurodegeneration, stroke and brain cancers," Ninkovic added. "It will be extremely interesting to see to which extend the mechanisms that we find are applicable to these conditions. A screen for [small molecules](#) resolving the TDP-43 aggregates in microglia will be the logical next step in our work."

**More information:** Alessandro Zambusi et al, TDP-43 condensates and lipid droplets regulate the reactivity of microglia and regeneration after traumatic brain injury, *Nature Neuroscience* (2022). [DOI: 10.1038/s41593-022-01199-y](#)

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