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Circular RNA circKlhl2 modulates TBI response influencing the BDNF pathway

Marica Pagliarini[1], Zhenghui Li[1], Florian Olde Huevel[1], Francesco Roselli[1,2]
[1] Dept. of Neurology, Ulm University, Ulm, Germany, [2] DZNE Ulm, Ulm, Germany

Traumatic brain injury (TBI) causes widespread disruption of synaptic connections and neural networks, which must be re-established for functional recovery to occur. Recently, a new class of non-coding RNA, known as circular RNA (circRNA), has been discovered and may play a role in post-traumatic plasticity and recovery. Given that circRNAs can originate from synaptic genes and appear to be involved in the modulation of synaptic biology, we hypothesize that circRNAs may contribute to synaptic disruption, regeneration, and neuronal vulnerability in TBI.

We assessed synaptic-gene circular RNA expression in hippocampus using RT-qPCR and we validated that circRNAs were significant up-regulated in whole-hippocampus extracts at different timepoints after blunt TBI. Our initial screening revealed the upregulation of circKlhl2 in neurons of the ipsilateral hippocampus of mice 7 days post TBI. To further investigate hippocampal neuronal and synaptic modulation, we performed AAV-mediated overexpression and knockdown in vivo.

Up- or downregulation of circKhlh2 had functional consequences in TBI in particular; overexpression of circKlhl2 is involved in improving hippocampal related tasks in vivo. Moreover, circKlhl2 is involved in the up-regulation of BDNF by sequestering microRNAs related to BDNF mRNA translation. Specifically, circKlhl2 acts as a molecular sponge for miR-30 family and miR-9, thereby regulating BDNF expression.

Finally, to monitor the effect of circKlhl2 OE and its BDNF regulation in neuronal and synaptic plasticity mechanism we confirmed circKlhl2 role in reduction of synaptic loss and spin maturation.

In conclusion, circKlhl2, through the BDNF pathway, plays a crucial role in the hippocampal recovery processes following TBI.