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Role of the transcription factor NRF2 in hippocampal neurogenesis and in a mouse model of Alzheimer´s Disease.

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Introduction: During adulthood, new hippocampal granule neurons are generated in the hippocampus by differentiation of neural stem/progenitor cells (NSPCs) in the subgranular zone (SGZ). The implication of hippocampal neurogenesis in learning and memory functions point it as a therapeutic strategy to face the cognitive deficits related with aging and neurodegenerative diseases. Hippocampal neurogenesis can be modulated by oxidative stress, neuroinflammation and proteinopathy. Here, we hypothesized that Nuclear Factor-Erythroid 2-Related Factor 2 (NRF2), as a master regulator of cellular homeostasis, might modulate the fate of NSPCs at the hippocampus.

Material and methods: immunohistochemistry analysis of hippocampal coronal sections of WT, NRF2-/-, APP/TAU/WT and APP/TAU/NRF2-/- mice at indicated age points. Long term potentiation (LTP) and Morris water maze test assays in 6 month- old mice of indicated genotypes. Immunocytochemistry of primary cultures of NSPCs of mice in postnatal day 0 to 4 (P0-P4) and 3 months of age in proliferation and differentiation conditions and lentiviral silence and overexpression of NRF2.

Results: NRF2-/- mice showed an impairment in LTP, correlating with an exacerbated reduction in hippocampal NSPCs from birth to adulthood. In vitro analysis using neurosphere assay corroborated this data, showing a reduced proliferative capacity of SGZ-derived NSPCs from newborn and 3-month-old NRF2-/- mice. Differentiation analysis pointed that NRF2-deficiency alters proper differentiation profile, favouring an abnormal rate between glial and neuronal differentiation. Ectopic expression of NRF2 in Nrf2-deficiency NSPCs attenuated the impact in their clonogenic, proliferative and differentiating capacity. Furthermore, when we performed the knockdown of the NRF2 gene in wild type NSPCs, data showed the alterations described previously for NRF2-/- NSPCs. Subsequently, to further analyse NRF2 implication in pathology, we used mice that express human mutated forms of TAU(P301L) and the amyloid protein precursor APP(V717I), in the presence or absence of NRF2. We report cognitive deficits in APP/TAU/NRF2-deficient mice considering the registered decrease in hippocampal LTP and poor performance in the Morris water maze test. Immunohistochemistry analysis of SGZ evidenced the detriment of NSPCs pool and neuronal differentiation in APP/TAU/NRF2-deficient mice at different age points.

Conclusions: The data support that NRF2 is important in the maintenance of proper proliferation and differentiation rates of hippocampal NSPCs. Our findings highlight the importance of NRF2 pharmacological upregulation to preserve the neurogenic functionality of the hippocampus and improve cognitive functions in AD.

Keywords: neurogenesis, NRF2, NSPCs.
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