Regulation of neurogenesis by transgenic expression of activated Ha-Ras in adult hippocampus: impact on spatial working memory

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Transgenic expression of constitutively activated V12-Ha-Ras in mice under the direction of the promoter for synapsin 1 (synRas mice: Heumann et al. 2000, J Cell Biol 151:153) promotes protection against lesion-induced neuronal degeneration. Here we investigate the possible effect of Ha-Ras-enhanced granule cell survival on the production of migrating precursor cells of the adult hippocampus. Proliferation or survival rate of newborn cells was determined at day 1 or day 28 after BrdU injections. There was a significant 69% reduction in the number of BrdU-labeled cells in the dentate gyrus of synRas mice as compared to wild type (wt) siblings at day 1. In spite of this reduction, the relative number of surviving cells was strongly enhanced in synRas mice as compared to wt mice, where only 35% of newborn cells were present after 28 days. Double labeling experiments using BrdU and glial fibrillary acidic protein (GFAP) or calbindin markers, respectively, showed that the reduction in BrdU positive cells in synRas mice at day 28 was mainly due to a decrease in the neuronal population. Consistently, doublecortin positive cells were strongly reduced in the subgranular zone of the dentate gyrus of synRas mice as compared to wt siblings. Intraperitoneal injections of the cytokine erythropoietin re-increased the number of doublecortin positive cells in the dentate gyrus. These results indicate that we were able to partially revert the synRas phenotype with respect to the generation of neuronal precursor cells.

In order to investigate a possible relationship between neurogenesis and memory functions we analyzed the spatial memory abilities in a 8-arm radial maze task. Our results showed that there was a significant impairment of spatial working memory in synRas mice while water maze test did not reveal any differences to wt mice. Our results support the hypothesis of a correlation between neurogenesis in the adult hippocampus and short-term memory abilities.

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