The role of tenascin-C in adult neurogenesis and glial scarring

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The extracellular matrix glycoprotein tenascin-C (TnC) plays an important role during cell proliferation, migration and neurite outgrowth in embryonal and postnatal development, when it is abundantly expressed in neuronal and non-neuronal tissue. Its expression is downregulated in adult CNS with the exception of areas of plasticity and active neurogenesis, while it is strongly upregulated mainly by astrocytes after CNS injury.

In the present study we examined the role of TnC in adult neurogenesis induced by housing of wild-type (TnC+/+) and TnC deficient (TnC-/-) mice in enriched environment - EE (vs. standard conditions-SC) 8 weeks starting from postnatal day 21. Markers of proliferation Ki67 and newborn neurons doublecortin (DCX) were followed in the subgranular zone of the hippocampus and subventricular zone. In addition, as diverse effects of TnC on cell proliferation were attributed to alternatively spliced isoforms, we further investigated the role of individual recombinant fragments (alternatively spliced domains: FnA, FnC, FnD) of TnC in glial scar formation *in vitro* by scratch wound assay in cortical TnC-/- or TnC+/+ astrocytes cultures. Individual TnC fragments were added to cultures, and scarring was monitored *in vitro* for 48h. Astrocyte activation and proliferation were estimated by GFAP and Ki67 (respectively) analysis with *RT-PCR*, *immunolabeling*, and *Western* blot (WB) for both setups.

We found a significant rise in the number of Ki67 and DCX-positive cells in TnC+/+ mice after EE compared to SC, which was even more pronounced in TnC-/- mice in both housing conditions. Furthermore, application of alternatively spliced fragment FnD, or combination of FnD, FnA and FnC had the strongest effects on deceleration of wound healing. RT-PCR showed higher levels of expression of GFAP in TnC-/- cultures, while the application of fragments led to its reduction. Western blot analysis confirmed the elevation of GFAP in TnC-/- cultures compared to TnC+/+ mice. All TnC fragments significantly lowered cell proliferation.

These results suggest an inhibitory effect of TnC in adult neurogenesis, and reveal an attenuating role of TnC as a whole molecule, and its fragments, in particular FnD alone or combined with FnA and FnC in wound healing. Since exogenously applied fragments lowered cell proliferation, this might be the mechanism of attenuated glial scar formation in the presence of TnC. Thus, TnC could be a target molecule for different regenerative strategies.