“Modulation of adult neurogenesis as a potential therapeutic tool for Alzheimer’s disease”


Objectives: Alteration of adult neurogenesis has been reported in several Alzheimer’s disease (AD) animal models, and recently in AD subjects (Moreno-Jimenez et al., 2019). Nevertheless, a causal link between this phenomenon and oligomeric A-beta (AβOs), the most neurotoxic species in AD, has not been demonstrated yet. Moreover, defective neurogenesis at early stage of AD has not been fully explored. We addressed this issue in Tg2576 transgenic mice, which represent a well-characterized animal model for AD and Aβ accumulation.

Methods: In 1.5 months old Tg2576 mice, that is considered a pre-symptomatic age in terms of Aβ accumulation, we analyzed the proliferative and differentiative features of both resident and SVZ- or dentate gyrus (DG) hippocampal-derived adult neural stem cells (aNSCs), in relationship with the amount of Aβ expression. In established Tg2576 neurospheres cultures we measured intracellular and extracellular Aβ and AβOs biochemical patterns, by western blot and dot blot approaches. We exploited an intrabody targeting of intracellular AβOs both in vitro and in vivo; finally, we performed contextual fear conditioning (CFC) memory test to evaluate cognitive improvement linked to rescue of hippocampal neurogenesis.

Results: Tg2576 aNSCs express high level of AβOs and display alteration in proliferation, compared to their control counterparts. Tg2576 neurospheres are enriched in DCX+ neuroblasts, which failed to terminally differentiate, and give rise to less GFAP+ astrocytes with an aberrant morphology. These defects have been confirmed also in vivo, where both olfactory bulbs and hippocampal neurogenesis were reduced. Proliferation and differentiation impairment of Tg2576 progenitors are likely to be due to Aβ accumulation, as both defects can be rescued in vitro by the expression of scFvA13 intrabody, that interferes with intracellular AβOs in a selective and conformational manner (Meli et al., 2014). Strikingly, lentiviral delivery of scFvA13 into the SVZ and the DG of young Tg2576 increased neurogenesis in both niches and rescued CFC memory deficit at 3 months of
age, as demonstrated in collaboration with Dr. S. Middei (IBBC). We also showed (in collaboration with Dr. Amadoro, IFT) that scFvA13-mediated AβOs targeting alleviates the pathological tau-mediated microtubule hyperstabilization of both neurons and astrocytes (Scopa et al., 2020).

**Conclusions:** Our results demonstrate a causal link between Aβ accumulation and defective neurogenesis, involving tau-dependent mechanism(s) and occurring prior to neurodegeneration, at presymptomatic age. Notably, the intracellular interception of AβOs by scFvA13 intrabody in aNSCs rescues adult neurogenesis, both in vitro and in vivo. We also provided an innovative gene therapy approach to neutralize intracellular natural-occurring AβOs in aNSC, exploitable to counteract disease onset and progression. This knowledge would be of benefit in the development of new therapeutic tools aimed to restrain neuronal degeneration in AD.

**References:**


**Keywords:** adult neurogenesis; Alzheimer's disease; Ab-oligomers; intracellular targeting; intrabody; contextual fear conditioning.

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