Activation of the RAGE/NF-κB axis mediates proneurogenic effect of HMGB-1 andAβ-oligomers

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The Receptor for Advanced Glycation End-products (RAGE) is a membrane-bound receptor of the immunoglobulin superfamily activated by several ligands. Literature data suggest that RAGE plays a deleterious role in AD and neurodegeneration (Takuma et al., 2009; Fang et al., 2010). Recently, we demonstrated that activation of the RAGE/NF-κB axis promotes both proliferation and neuronal differentiation of adult SVZ neural progenitor cells (NPC) *in vitro* (Meneghini et al., 2010). Based on these observations, we decided to investigate the role of the RAGE/NF-κB axis in the modulation of adult hippocampal neurogenesis and its relevance in AD pathophysiology.

We initially demonstrated that a RAGE ligand, the alarmin HMGB-1, promoted neuronal differentiation of adult hippocampal NPC via RAGE activation. Moreover, activation of the NF-κB signaling pathway appeared to be involved in the proneurogenic effect elicited by HMGB-1.

To better understand the potential involvement of the RAGE/NF-κB axis in AD we evaluated hippocampal neurogenesis in TgCRND8 mice, a FAD animal model characterized by age-dependent accumulation of amyloid deposits (Chishti et al., 2001). TgCRND8 mice, at 8 months of age, had significantly more BrdU-IR cells in the SGZ, compared with WT animals, suggesting an increased cell proliferation in the region in which neural stem/NPCs lie and divide. This change was accompanied by a significant increase in the absolute number of DCX^+ neuroblasts as well as of CR^+ postmitotic adult-born neurons in the hippocampi of TgCRND8 mice compared with WT.

By using TgCRND8- and WT-derived hippocampal NPC, we further investigated the molecular mechanisms potentially involved in the increased number of progenitors, neuroblasts, and postmitotic neurons in TgCRND8 hippocampi. We demonstrated that, also *in vitro*, TgCRND8-derived NPC had a higher neurogenic potential compared with WT-derived progenitors and that this increased effect could be abolished by blocking activation of the RAGE/NF-κB axis. Additionally, conditioned media from TgCRND8 NPC cultures also increased the number of neurons generated *in vitro* by adult WT NPC cultures, and again, this effect correlated with NF-κB activation. In an attempt to identify the soluble factors that were responsible for that effect, we could prove the presence of human $A\beta_{1-42}$ in TgCRND8-conditioned media and that only $A\beta_{1-42}$ oligomers but not monomers or fibrils could act as proneurogenic signal when added to cultures of adult hippocampal NPC (Meneghini et al., 2013).

Altogether our data propose a novel molecular mechanism that may regulate hippocampal neurogenesis in AD brain and rely on $A\beta_{1-42}$ oligomers and HMGB-1-induced activation of RAGE/NFκB axis in adult NPC. The significance of these findings in the pathophysiology of AD is currently under investigation.

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