Molecular mechanisms for lineage-restricted differentiation of adult neural progenitors

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I. Brederlau A, Faigle R*, **Elmi M***, Zarebski A, Sjöberg S, Fujii M, Miyazono K, Funa K. The bone morphogenetic protein type Ib receptor is a major mediator of glial differentiation and cell survival in adult hippocampal progenitor cell culture.
Mol Biol Cell. 2004 Aug;15(8):3863-75 ***joint second authors**

II. Faigle R, Brederlau A, **Elmi M**, Arvidsson Y, Hamazaki TS, Uramoto H, Funa K. ASK1 inhibits astroglial development via p38 mitogen-activated protein kinase and promotes neuronal differentiation in adult hippocampus-derived progenitor cells.
Mol Cell Biol. 2004 Jan;24(1):280-93

III. **Elmi M**, Faigle R, Yang W, Matsumoto Y, Rosenqvist E, Funa K. Mechanism of MASH1 induction by ASK1 and ATRA in adult neural progenitors.
Mol Cell Neurosci. 2007 Oct;36(2):248-59

IV. **Elmi M**, Matsumoto Y, Yang W, Uemura A, Nishikawa S, Funa K. Nuclear receptor TLX promotes neuronal differentiation in adult hippocampus-derived progenitor cells.
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ABSTRACT

Aims: In the central nervous system of several species, including humans, neurogenesis persists even in the adult life in discrete neurogenic regions of the brain. Adult neural stem cells derived from these neurogenic areas are proliferating cells, which can differentiate to neurons, astrocytes, and oligodendrocytes. The molecular mechanisms and signaling pathways regulating the lineage commitment and differentiation of neural stem cells is now unfolding. Understanding the mechanism underlying these events is essential for the potential future use of neural stem cells for cell therapy in neurodegenerative diseases. In the present thesis, we investigated the role of bone morphogenetic proteins (BMP), apoptosis signaling-regulating kinase 1 (ASK1) and the nuclear receptors, all-trans retinoic acid (ATRA) and TLX, in neural differentiation of adult hippocampus-derived progenitor cells (AHPs).

Results: Overexpression of dominant negative BMP type I (Alk2, 3, and 6) receptors in adult neural progenitors revealed that Alk6 signaling is necessary for differentiation and survival of astrocyte and suppression of oligodendrocyte fate. Blockage of Alk3, on the other hand, increased Alk6 expression, resulting in an increased survival and differentiation towards astrocyte lineage. Blockage of any of the receptors did not alter the neuronal differentiation.

In order to investigate the role of ASK1, we overexpressed either a constitutively active or a kinase mutant form of ASK1. In this study we provide evidence for ASK1 via p38 MAPK activation induces neuronal lineage commitment while inhibiting glial differentiation. We determined that the ASK1-induced glial inhibition was due to a direct repression of the GFAP promoter in a STAT3-independent way.

In search for further downstream mechanisms of ASK1-induced neuronal differentiation, we found that ASK1 in a p38-dependent manner phosphorylated and thereby activated MEF2C. This transcription factor was recruited to the MASH1 promoter along with CaMKII and the co-activator CBP, while the co-repressors HDAC1 and 4 were dismissed. Moreover, we combined ASK1 expression with ATRA treatment. Consequently, we observed a synergistic increase in neuronal differentiation. ATRA also activated the MASH1 promoter however, via the transcription factor Sp1.

Finally, we investigated the role of the orphan nuclear receptor, TLX. By means of over-expressing TLX, we found that TLX induced a transient increase in neural progenitor proliferation and an increase in the number of differentiating and mature neurons, while suppressing glial differentiation. Similar to ATRA signaling, Sp1 was necessary for TLX-induced MASH1 activation.

Conclusions: The results presented in this thesis suggest a new role for both ASK1 and TLX in the regulation of neuronal and astroglial differentiation of adult hippocampus-derived neural progenitors. In addition, we have demonstrated that ASK1 in combination with ATRA yield synergistic effect on the generation of mature neurons. Our results indicate that the Alk6 signaling has an important role for astrocyte survival and differentiation. We have determined the mechanisms involved in these signaling pathways, which might potentially be of benefit for future therapies of neurodegenerative diseases.

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