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Sphingosine-1-phosphate receptor 1 signaling plays a highly selective role during postnatal neurogenesis and negatively modulates the initiation of radial migration

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Postnatal neurogenesis is a spatially restricted form of neural plasticity which affects network remodeling and information processing. Intensive research in the field of postnatal and adult neurogenesis over the last decades led to an enormous increase of our understanding of this process, its regulatory mechanisms, its effects on neural circuitry and animal behavior as well as its effect on and contribution to neurological and psychiatric disorders.
Neural stem cells, which line the walls of the lateral ventricles, proliferate through- out life and give rise to transit amplifying cells and neuroblasts. The latter migrate tangentially along the rostral migratory stream to reach the olfactory bulb, where they detach and migrate radially to superficial layers. There they finally differenti- ate to mature neurons and integrate into the existing neuronal circuits.
These defined steps of neurogenesis in the subventricular zone rely on an orches- trated interplay between mature neurons, neural precursors, ependymal cells and astrocytes as well as on cerebrospinal fluid- and vasculature-mediated signals. The complex interaction and functional regulation of these processes is still not fully elucidated. While significant progress has been made in the understanding of the mechanisms regulating tangential chain migration, strikingly little is known about the switch to radial migration and radial migration itself.

In this study, I introduce sphingosine-1-phosphate, which is known to modulate embryonic stem cell behavior in vitro and which plays an important role in brain development, as a novel signaling molecule in postnatal neurogenesis.
Immunohistochemistry revealed that the sphingosine-1-phosphate producing kinases SK1 and SK2 are expressed by neural stem cells and astrocytes within the subven- tricular zone, the rostral migratroy stream and the olfactory bulb whereas S1P1, a G protein coupled receptor of S1P, is complementarily expressed by transit amplify- ing cells and neuroblasts along the RMS. Furthermore, neuroblasts physiologically downregulate S1P1 upon arrival in the RMSOB, while they switch from tangential chain to radial migration.
I conducted stereotactic intracranial virus injections to perform gain and loss of function experiments in vivo. In addition, SVZ-derived explants were used to further elucidate the mechanism by which S1P1 alters neuroblast properties. Thereby, I show that S1P/S1P1 signaling plays a role in postnatal neurogenesis. Im- munohistochemistry and time lapse imaging of acute brain slices demonstrate that S1P1 signaling does not alter proliferation of neural precursors or apoptosis within neuroblasts. Nevertheless, knockdown of S1P1 leads to an increased number of ar- riving newborn cells within the granule cell layer of the olfactory bulb, whereas S1P1 overexpression attenuates neuroblasts in the RMSOB. This is not caused by alter- ation in tangential migration, but by the induction of radial migration after S1P1 downregulation, which leads to a reduction in cell-cell adhesion between neuroblasts.
In summary, I demonstrate that S1P1 signaling plays a highly specific and selec- tive role during postnatal neurogenesis and negatively modulates the initiation of radial migration

in vivo.

It will be the task of future studies to determine whether S1P1 signaling also affects hippocampal neurogenesis and to elucidate the potential role of S1P2, S1P3 and S1P5 in postnatal and adult neurogenesis. A detailed understanding of the physiological mechanisms of neurogenesis will also lead to an improved understand- ing of associated pathological conditions like cancer, neurodegenerative diseases, movement disorders, stroke and depression. Thereby research in the field of neuro- genesis will ultimately contribute to the important development of new therapeutic approaches to these disorders.