Embryology and Stem Cell Biology

Verdon Taylor
Department of Biomedicine
Anatomy
University of Basel

Group Members

Dr. Robert Beattie (Postdoc)*
Dr. Marion Betizeau (Postdoc)*
Callum Brien
Laura Cavalleri*
Prof. Dr. Ginetta Collo (Research Associate)
Regina Dönen (Technician)*
Zahra Ehsaei (PhD Student)
Anna Engler (PhD Student)
Andrea Erni (PhD Student)
Dr. Stefania Fedele (Postdoc)
Dr. Claudio Giachino (Postdoc)
Dr. Alice Grison (PhD Student)
Dr. Anna Lisa Gündner (Postdoc)
Dr. Dominik Herzog (Postdoc)*
Niklas Iffländer (PhD Student)
Dr. Dirk Junghans (Postdoc)*
Tanzila Mukhtar (PhD Student)
Dr. Elena Parmigiani (Postdoc)
Dr. Chiara Rolando (Postdoc)
Frank Sager (Technician)
Miriam Vogt (PhD Student)*
Dr. Runrui Zhang (Postdoc)

*left during report period

Regulation of neural stem cell fate

Deciphering the mechanisms of neurogenesis
Development of the brain is controlled in a precise and organized fashion, but the mechanism controlling the differentiation of neuron-types in the cerebral cortex are unclear. The adult mammalian brain contains neural stem cells (NSCs) that continue to generate neurons in defined regions and contribute to brain homeostasis and function. Our understanding of the control of NSC activity and maintenance is rudimentary, but these processes have implications for brain function and cancers including gliomas. Using mouse genetics *in vivo* and in cell culture we are trying to understand the molecular mechanisms controlling NSC activity and fate during development, adulthood and gliomas formation.

Systems biology of forebrain development
As part of the SystemX.ch project NeuroStemX, we analyze neurogenesis during cortical development. NSCs of the developing cerebral cortex generate six layers of cortical neurons in a precise inside-out temporal fashion. The neurons within each layer are functionally distinct, express specific markers and transcriptional regulators, and are born at precise times during development. The number of neurons within each layer is precisely controlled through sequentially modulation of NSC and progenitor cell fate. The mechanisms orchestrating neural progenitor fate in the developing cerebral cortex are not understood. We have addressed, at the systems biology level, whether all NSCs in the developing cortex have the same potential and respond to the same fate cues to contribute to all neuronal cell-types. We generated high-resolution transcriptome analyses of NSCs, progenitors and newborn neurons by next generation RNA sequencing at the population and single cell levels at each day of cortical development. We are using computational modeling of signaling and transcriptional regulatory networks to uncover the complex networks and switches in signaling that control NSC fate decisions.

Regulation of adult NSC fate by Notch and Drosha
Multi-lineage potential is an adult NSC trait. We showed that the RNAseIII Drosha is an intrinsic regulator of adult NSC maintenance and differentiation. Drosha silences NFIB in NSCs by cleaving hairpins in its mRNA thereby repressing expression. Our findings revealed a novel mechanism for the maintenance and oligodendrocyte fate restriction of adult NSCs. We continue to study targets of Drosha in the NSCs in embryonic and adult NSCs. Neurogenesis continues in adult forebrain from quiescent NSCs. To generate neurons, NSCs activate and enter cell cycle. Notch signaling is critical in this process and we found that Notch2 signaling conveys quiescence to adult NSCs by repressing cell cycle genes and neurogenesis. Although neurogenesis occurs at all location of the developing embryonic brain, in adults, neuron production is restricted to specific brain regions. We identified dormant adult NSCs in niches outside the classical neurogenic zones. These NSCs are regulated by Notch2 signaling and retain neurogenic potential responding to pathophysiological stimuli to control mouse behavior. Thus, we identified novel NSCs in the brain that are held in a reversible, inactive state.

Notch in forebrain tumor subtypes
Notch signaling maintains NSC and as been proposed to be oncogenic. However, inactivating mutations in Notch receptors suggest that Notch signaling has tumor suppressor functions in human gliomas. We generated genetic mouse models that simulate different human glioma subtypes. These models enable us to study Notch function in brain tumor formation and growth. We identified a tumor suppressor function for Notch in forebrain tumor subtypes. Inactivating mutations in the Notch1 and Notch2 receptor genes accelerates growth of some gliomas. Conversely, activation of the Notch pathway reduces glioma growth. We could confirm these findings in human glioma data finding that high Notch activity correlates with distinct glioma subtypes, increased patient survival, and lower tumor grade. We are studying the role of Notch in other novel brain tumor models to understand how Notch signaling could be used as a therapeutic target for gliomas.

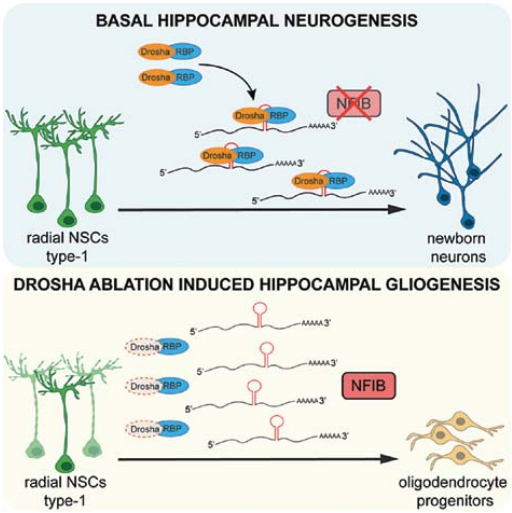

Fig. 1: The RNAse Drosha is a key component of the microRNA microprocessor but also regulates cell fate by directly destabilizing mRNAs of fate determining factors. Drosha is known for its cleavage of pri-miRNA transcripts to generate pre-miRNAs, the precursors of mature microRNAs. Drosha also processes hairpin structures in mRNAs of the proneural transcription factors Ngn2, NeuroD1 and NeuroD6 in NSCs during development (Knuckles *et al.* 2012). In the adult brain, NSCs generate neurons, astrocytes and oligodendrocytes, except in the hippocampus where oligodendrocytic differentiation is blocked. We have recently shown that NSC maintenance in the hippocampus, and their bias against oligodendrocytes differentiation, is controlled by repression of NFIB expression. Under normal conditions (basal hippocampal neurogenesis), hippocampal NSCs do not express NFIB protein as its mRNA is rapidly degraded. We showed that Drosha is responsible for this degradation of NFIB mRNA by cleaving specific hairpin structures formed by the transcript. This intrinsic regulation of NFIB expression enables NSCs to remain and self-renew but also prevents them from differentiating into oligodendrocytes. If Drosha is inhibited or blocked, NFIB mRNA stabilizes, the transcript factor is expressed and hippocampal NSCs erroneously differentiate into oligodendrocytes (Drosha ablation induced hippocampal gliogenesis) (Rolando *et al.* 2016).

Selected Publications

Rolando C, Erni A, Grison A, Beattie R, Engler A, Gokhale PJ, Milo M, Wegleiter T, Jessberger S and Taylor V. (2016) Multipotency of Adult Hippocampal NSCs *In Vivo* Is Restricted by Drosha/NFIB. Cell Stem Cell *19*, 653–662

Giachino C, Boulay JL, Ivanek R, Alvarado A, Tostado C, Lugert S, Tchorz J, Coban M, Mariani L, Bettler B, *et al.* (2015) A Tumor Suppressor Function for Notch Signaling in Forebrain Tumor Subtypes. Cancer Cell *28*, 730–742

Giachino C, Barz M, Tchorz JS, Tome M, Gassmann M, Bischofberger J, Bettler B and Taylor V. (2014a) GABA suppresses neurogenesis in the adult hippocampus through GABAB receptors. Development *141*, 83–90

Giachino C, Basak O, Lugert S, Knuckles P, Obernier K, Fiorelli R, Frank S, Raineteau O, Alvarez-Buylla A and Taylor V. (2014b) Molecular diversity subdivides the adult forebrain neural stem cell population. Stem Cells *32*, 70–84

Rolando C and Taylor V. (2014) Neural stem cell of the hippocampus: development, physiology regulation, and dysfunction in disease. Curr Top Dev Biol *107*, 183–206

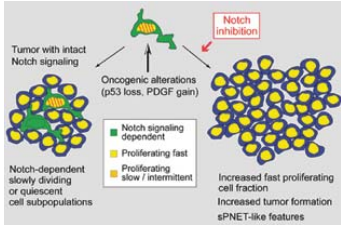

Fig. 2: Gliomas are some of the most devastating cancers and the prognosis for patients with high-grade gliomas is very bad with only ineffective and highly aggressive treatments being available. Notch signaling has been implicated as being oncogenic and inducing gliomas, particularly in the most aggressive forms of the disease, glioblastoma multiforma. We generated murine models of human gliomas that lack the tumor suppressor p53 and express the growth factor PDGF. We assessed the role of Notch signaling in these tumors by genetic ablation and over expression. We could show that these model glioblastomas contain cells where Notch is active, however, in contrast to expectations, deleting Notch signaling increases tumor growth indicating that Notch signaling, in this form of brain tumor, functions as a tumor suppressor. We were able to support these findings by analyzing human tumor data that also indicated that in some human gliomas sub-types, Notch signaling likely functions as a tumor suppressor (Giachino *et al.* 2015). These results open up important new directions for potential therapies for patients with gliomas.