Universität Basel

Research Project

Glioma subtype dictates oncogenic versus tumor suppressive potential of Notch signaling during tumor growth

Third-party funded project

Project title Glioma subtype dictates oncogenic versus tumor suppressive potential of Notch signaling during tumor growth
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We and others have previously shown that Notch signaling regulates neural stem cell (NSC) self-renewal and differentiation in the adult brain. NSCs are a candidate cell type at the origin of brain tumors including gliomas. Notch signaling has been implicated in the development of many malignancies. This has made Notch pathway components compelling targets for drug development, and some have already progressed into the clinic. However, the role of Notch in brain tumor formation remains controversial. Notch signaling has been proposed to be oncogenic in glioma, primarily by virtue of its stem cell promoting activity. In contrast, we recently uncovered a surprising tumor suppressor function for the Notch pathway in mouse models of glioma. These findings, together with the knowledge that human gliomas are heterogeneous entities, raise the question of whether Notch can be tumor promoting or tumor suppressive depending on the oncogenic alterations driving initiation of a particular glioma subtype.

In the proposed project we aim to identify whether Notch has opposite functions in distinct glioma subtypes and the molecular mechanism underlying these differences. To this end, we developed two novel mouse models of glioma that are driven by different oncogenic mutations and mimicking distinct human glioma subtypes. We will exploit conditional genetics and lineage tracing approaches to interfere with Notch function and study unperturbed tumor growth *in vivo* in these two models. We will address oncogenic and tumor suppressive effects of blocking Notch in the distinct glioma subtypes. Novel Notch targets affected following modulation of Notch and that may be associated with oncogenic or tumor suppressive activity will be identified by transcriptome analyses. Our findings may uncover fundamental differences in the molecular requirements of distinct glioma subtypes, possibly leading to the identification of targets for differential therapeutic intervention in the distinct forms of this disease.

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