Universität Basel

Research Project

Molecular mechanisms of oncogenesis versus tumor suppression by Notch in glioma subsets

Third-party funded project

Project title Molecular mechanisms of oncogenesis versus tumor suppression by Notch in glioma subsets
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Project start 01.05.2019
Probable end 30.04.2022
Status Completed

Accumulating evidence supports a critical role for the Notch pathway in the development of many cancers and various strategies to modulate Notch for cancer therapy are being actively pursued. However, the outcomes of Notch signal activation are remarkably varied depending on cellular context, including in different tumor types. Understanding the basis of Notch tumor-promoting and tumor-suppressive activities is a prerequisite for designing efficacious therapeutic agents that target Notch signaling and for implementing them in the treatment of cancer.

Malignant gliomas are the most common and aggressive primary brain cancers, and the prognosis for glioma patients is very poor. Although we start to understand some of the causes of glioma in humans, current therapies are not effective. These tumors are still invariably lethal and therefore there remains much to be learnt and new therapeutic targets to be discovered. Treatment options for glioma patients remain very limited, which is in part attributed to the presence of therapy-resistant glioma stem cells. Notch signaling has been implicated in the development of brain tumors, primarily by virtue of its stem cell promoting activity and well-established role in supporting maintenance and self-renewal of neural stem cells during brain development and in the adult. This has made Notch pathway components compelling targets for the development of new drugs, some of which have already progressed into the clinic. However, the role of Notch in glioma formation remains controversial. Some data indicate that the Notch pathway can be oncogenic in glioma by promoting survival, radio-resistance and stem cell character within these tumors. In contrast, other experimental evidences indicate that Notch activity can promote a less proliferative glioma phenotype, which leads to less aggressive tumors. Inactivating Notch mutations similar to those identified in epithelial cancers have also been detected in subtypes of human glioma, in line with Notch being tumor-suppressive. The source of this heterogeneity in the responses to Notch activity remains puzzling, but it is becoming clear that human gliomas are heterogeneous entities that differ at the genetic, epigenetic and transcriptional levels. Whether Notch signaling has a different or perhaps even opposite role in distinct forms of the disease has not been rigorously addressed.

Our research has focused on studying Notch signaling in neural stem cell maintenance and brain tumor formation and we have made important contributions to these fields. Our preliminary genetic data in multiple mouse models of human glioma represent proof of principle experiments demonstrating that Notch can be either tumor-promoting or tumor-suppressive in distinct glioma entities *in vivo* and provide a potential rationale for this context-dependency, which may have dramatic implications for glioma therapy in humans. The proposed project will address the cellular and molecular mechanisms behind

Notch oncogenic and tumor-suppressive functions in glioma. Conditional gene deletion experiments will address the interaction between known glioma drivers and Notch activity, and how distinct oncogenic alterations can skew the outcome of Notch activation towards tumor-promoting or tumor-suppressive effects. Novel Notch targets affected following modulation of Notch activity within the tumor will be identified by transcriptome analyses.

Financed by
Foundations and Associations

Follow-up project of 3183457 A novel tumor suppressor function of Notch receptors in glioma

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