Identification of new molecular targets for human medulloblastoma using RNA interference screening

Summary / Zusammenfassung

Medulloblastoma is the most common malignant brain tumor in children and is associated with poor survival rates. This is due to resistance of tumor cells to conventional treatments such as chemotherapy or radiotherapy and to tumor metastasis. Novel therapies are thus urgently required and will arise from a better understanding of the disease biology. Protein and lipid kinases have been shown to play a key role in the biology of human medulloblastoma. Indeed, receptor tyrosine kinases (RTKs) such as ErbB-2, ErbB-4, insulin-like growth factor-I receptor (IGF-IR) and platelet-derived growth factor receptor (PDGFR) have been shown to be expressed and to control cell proliferation, survival and metastasis in human medulloblastoma cells. Promising new therapies for medulloblastoma are emerging, which are based on blocking signalling by these RTKs to some of their downstream signalling targets such as phosphoinositide 3-kinase (PI3K), protein kinase B (PKB)/Akt, the mammalian target of rapamycin (mTOR) or mitogen-activated extracellular signal-regulated kinase activating kinase (MEK).

To identify new molecular targets for medulloblastoma, we will perform a RNA interference (RNAi) screen using a library of retroviral constructs targeting most of the known human protein and lipid kinases (500-600 genes). The screen will be limited to kinases, since these enzymes are potentially easy to subsequently target using pharmacological approaches. We will use the RNAi constructs to down-regulate the expression of the endogenous kinases in human medulloblastoma cell lines. The analysis of the impact of these constructs on tumor cell proliferation, chemoresistance, resistance to radiotherapy, and metastasis should reveal which protein and lipid kinases are important for the biology of medulloblastoma.

Together the planned studies will hopefully lead to the identification of novel targets for pharmacological inhibitors, leading in turn to the development of new drugs for medulloblastoma.

Keywords / Suchbegriffe

RNA interference, medulloblastoma, protein kinase, signal transduction

Project Leadership and Contacts / Projektleitung und Kontakte

PD Dr. Alexandre Arcaro, PhD (Project Leader) alexander.arcaro@kispi.uzh.ch

Other Links to external Webpages / Andere Links zu externen Webseiten


Funding Source(s) / Unterstützt durch

Foundation Berger-Janser Stiftung

In Collaboration with / In Zusammenarbeit mit

Dr Julian Downward United Kingdom
CRUK London Research Institute, Lincoln's Inn Fields
London

Dr M. Grotzer Switzerland
Dr T. Shalaby

**Duration of Project / Projektdauer**
Feb 2005 to Dec 2009