Pediatric brain tumors: Regulatory protein represents potential drug target

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Medulloblastomas constitute the most frequent class of malignant childhood brain tumor. Tumors of this type arise due to the uncontrolled proliferation of immature nerve cells in the developing brain, and there is no targeted treatment available. A research team based at LMU's Center for Neuropathology and Prion Research and led by Privatdozent Dr. Ulrich Schüller has now demonstrated that the regulatory protein FoxM1 is essential for the continued growth of these tumor cells. Moreover, the level of FoxM1 expressed in the cells is significantly, and negatively, correlated with a patient's survival time. The protein therefore provides a useful prognostic marker, which should allow oncologists to gauge the malignancy of tumors and select the most effective therapeutic strategy for the individual patient. Furthermore, FoxM1 may provide a novel point of attack for the development of new ways to treat the condition. Schüller and his team were able to reduce FoxM1 levels in tumor cells by exposing them to the antibiotic siomycin A, and showed that the drug also inhibits tumor growth. "If further work on laboratory cell cultures and in living organisms confirms these results, siomycin could turn out to be an effective drug for the treatment of medulloblastoma," Schüller says. (*Clinical Cancer Research*, published Online First 14.September 2011)

Research conducted over the past 10 years has shown that medulloblastomas arise as a result of aberrant activation of certain molecular signaling pathways. Schüller and his team set out to determine whether the transcription factor FoxM1 plays a role in supporting the growth of this type of tumor and, if so, whether it might serve as a drug

target for the development of an effective therapy for the disease.

Transcription factors determine the suite of proteins present in a given cell by defining which of the genes encoded in the genomic DNA are transcribed into RNA copies that can program protein synthesis. The so-called Forkhead-box (Fox) proteins are transcription factors that are particularly concerned with the regulation of cell growth, division and differentiation, and fully differentiated cells do not proliferate further. FoxM1 activates genes that promote cell division and simultaneously turns off genes that inhibit proliferation. Since uncontrolled proliferation is the basic hallmark of cancer cells, understanding and manipulating the function of FoxM1 has become a focus of cancer research. In several different types of cancer, including cancers of the breast, lung and prostate gland, increased amounts of FoxM1 have been found in tumor tissue. Indeed the protein has been shown to be necessary for growth of these tumors. Schüller and his team have now shown that this also true for medulloblastomas.

"One important result was that the amount of FoxM1 present in medulloblastoma cells is correlated with patient survival time," says Schüller. Since it is relatively easy to estimate FoxM1 levels using laboratory tests, the molecule could possibly be used as a prognostic marker to guide the choice of treatment for each patient. Modern therapeutic options for medulloblastoma involve surgical removal of the tumor, followed by radiation and chemotherapy to eliminate any surviving tumor cells, but this approach is associated with serious side-effects. Furthermore, there are six different subtypes of medulloblastoma, which differ markedly in their malignancy and clinical prognosis. "That is why a good prognostic marker with which one could predict the aggressivity of tumors would be so useful," says Schüller. The clinician could then adapt the therapeutic approach to the patient's individual needs, and thus avoid using a sledgehammer to crack a nut.

Since FoxM1 is indispensable for the growth of medulloblastoma cells, it represents a potentially ideal drug target. With the aid of the antibiotic siomycin A, which specifically inhibits the production of FoxM1, Schüller was indeed able to inhibit the growth of medulloblastoma cells. These findings confirm and extend results obtained by other groups who have reported that siomycin A also hinders the growth of breast cancer cells. – And most importantly, Schüller's experiments showed that although FoxM1 is essential for tumor growth, other factors can apparently substitute for it during normal development. Hence blocking the action of FoxM1 by administering siomycin A should have no untoward effects on normal cells. Thus the antibiotic may make it possible, for the first time, to intervene directly and specifically in the process that gives rise to medulloblastomas, and provide the first therapeutic option that targets a major driver of the growth of such tumors.

More information: Expression of FoxM1 is required for the proliferation of medulloblastoma cells and indicates worse survival of patients.
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