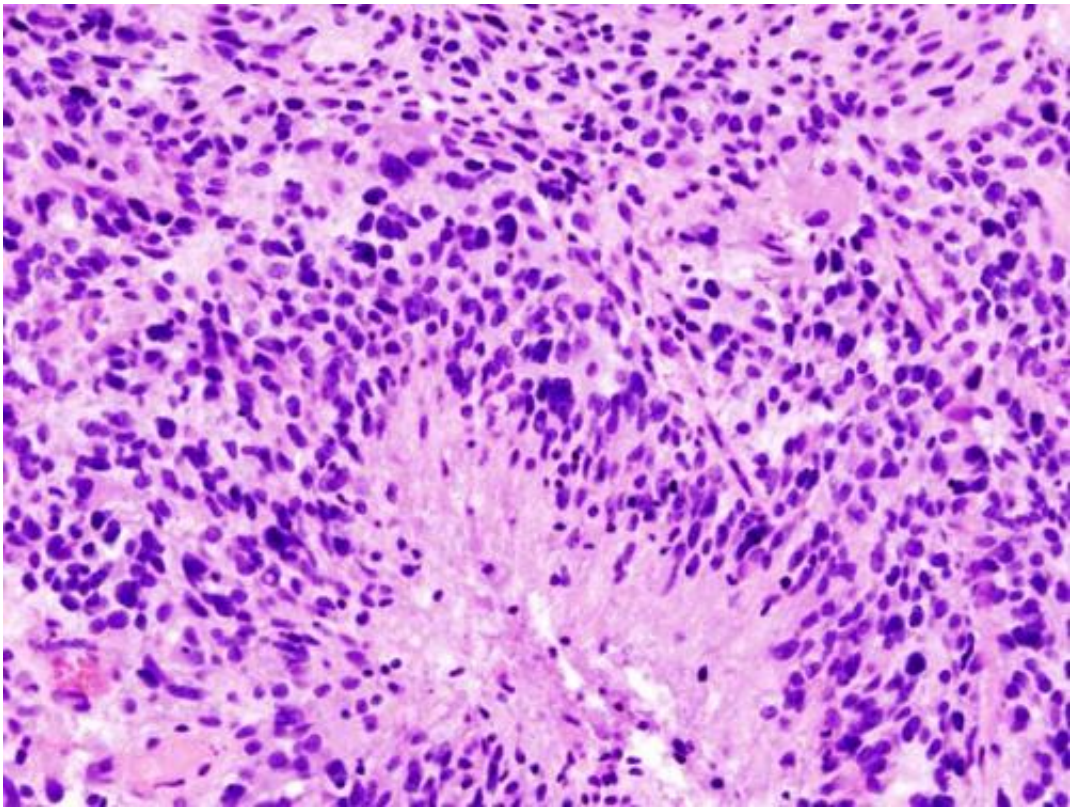
Gene fusions can lead to glioblastoma in children

October 20 2016



Glioblastoma (histology slide). Credit: Wikipedia/CC BY-SA 3.0

Every year, about 60 children and adolescents in Germany are diagnosed with glioblastoma, a very aggressive type of brain cancer, which is still mostly untreatable. Now, scientists from the Max Planck Institute for Molecular Genetics and the German Cancer Research Center undertook a comprehensive sequence analysis of the genomes and the encoded

messenger molecules of pediatric glioblastomas to identify molecular alterations involved in the development of the tumors. The researchers found a recurrently occurring oncogenic alteration in ten percent of the patients that was shown to be a clinically actionable target, potentially offering new therapy options for this dismal cancer type.

Glioblastoma is one of the most dangerous and aggressive types of brain cancer. Although it occurs mostly in adults, each year approximately 60 children and adolescents in Germany are diagnosed with this form of cancer. Glioblastoma is still mostly untreatable in children, established radiotherapy and chemotherapy treatments achieve usually only a slight delay of the progression of the disease.

In one in ten patients, MET was fused with other DNA segments

In a Next Generation Sequencing-based comprehensive molecular analysis of pediatric glioblastomas, the team of Marie-Laure Yaspo at the Max Planck Institute for Molecular Genetics in Berlin and colleagues from the German Cancer Research Center in Heidelberg coordinated by David Jones focused on investigating alterations in the DNA and gene expression profiles (the so-called "transcriptomes") in 42 cases of pediatric glioblastoma. The scientists identified several cancer-associated mutations as well as gene fusions. In about ten percent of the young patients, they discovered a gene defect, where a known cancer gene called MET was fused with other DNA segments, leading to its oncogenic activation. MET functions as a receptor protein in the cell membrane that responds to growth factor signals and controls cell growth. A number of receptor proteins including MET can be targeted and inhibited with clinically approved drugs.

MET has been shown to promote cancer growth, when it is

overexpressed in cells. "Here, we were able to identify a MET fusion in several patients, thus we hope that it might be a new target for a personalized treatment of glioblastoma," said Hans-Jörg Warnatz, one of the first authors of the study. Warnatz belongs to the Max Planck team in Berlin that analyzed the gene activity in the tumors and discovered the MET gene fusion in glioblastoma. MET is a growth-promoting gene, whose activity is normally very strictly controlled. The fusion of MET with other parts of the genome overrides these control mechanisms, leading to abnormal cell growth and cancer.

Treatment with MET inhibitors

Within the joint project, the teams of Stefan Pfister and Peter Lichter at the German Cancer Research Center in Heidelberg conducting the pre-clinical studies were able to demonstrate the contribution of the MET fusion to glioblastoma. They transferred MET fusion genes into brain cells of mice, which recapitulated exactly the same type of brain cancer as in the human patients. Treatment of the mice with a MET inhibitor, a drug that has already been approved in other cancer types, significantly slowed down cancer growth. However, further investigations will be needed, since additional mutations also cooperate with the MET fusion to trigger brain tumors. In addition, resistance against MET inhibitors is a known clinical issue, which needs to be considered in translational settings.

"The high rate of MET fusions that were detected in pediatric glioblastoma underscores the relevance of conducting extensive molecular analyses in cancer. For instance, we discover new cancer gene fusions in a broad range of cancer types, a number of which are targetable", says Marie-Laure Yaspo, head of the group in Berlin that conducted the transcriptome analysis. "The deep molecular analysis of individual tumors, detecting not only mutations but also alterations in the transcriptome, contributes to a much better understanding of the

pathogenesis of each tumor. The more we know the better is the chance to leverage that information to personalized therapies."

More information: Sebastian Bender et al. Recurrent MET fusion genes represent a drug target in pediatric glioblastoma, *Nature Medicine* (2016). DOI: 10.1038/nm.4204

Provided by Max Planck Society