GERMAN CANCER RESEARCH CENTER
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DNA tags as targets for new therapy against brain cancer

Ependymoma is an aggressive type of brain cancer that primarily affects infants. A comprehensive molecular analysis of these tumors has now been carried out with the major participation of scientists from the German Cancer Research Center (DKFZ) and Heidelberg University Hospital. They discovered that ependymomas with a good prognosis differ significantly from those with a poor prognosis. In aggressively growing tumors, a large number of genes are turned off as a result of methylation, a particular type of chemical change involving DNA. Drugs can remove methyl tags and this slows down the growth of cancer cells. The scientists have published their findings in the latest issue of Nature.

Ependymoma is the second most frequent type of brain cancer in children. In some patients, tumor growth comes to a halt following surgery and radiotherapy, but in about half of the affected infants, the disease rapidly takes a severe course: The tumor continues to grow and patients often succumb to their condition. “We need a better understanding of the aggressive tumors in these children in order to find new starting points for therapies,” says Dr. Hendrik Witt of the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) and Heidelberg University Hospital.

Ependymomas develop in various areas of the brain and the central nervous system, frequently in the cerebellum. A few years ago, Stefan Pfister’s team at the DKFZ discovered that cerebellar ependymomas can be differentiated into two subtypes: Group B tumors primarily affect older children and young adults and have a relatively good prognosis. Tumors of group A, however, often recur after intensive treatment, and they tend to metastasize, which is eventually the cause of death in many patients.

An international team of scientists and pediatricians from the DKFZ and Heidelberg University Hospital, Canada and the United States has now analyzed the genomes of 47 cerebellar ependymomas.

The researchers noticed that ependymomas undergo fewer gene mutations than other cancer types. The scientists found it particularly striking that of the few mutations they discovered, none affected more than one of the tumors. “We generally find fewer mutations overall in pediatric tumors. In ependymomas mutations seem to play an extremely minor role,” says Witt, a pediatrician and molecular geneticist.

However, an analysis of so-called epigenetic changes in the tumor genomes produced quite a different picture. Epigenetic changes influence the function of genes through chemical modifications that do not change the gene sequence as such. Compared to group B ependymomas, tumors of group A revealed a high level of DNA methylation, one of the types of epigenetic alterations that have been studied most thoroughly so far. The difference was so marked that the scientists could use the pattern of DNA methylation alone as a biomarker in establishing a prognosis for the disease.

The epigenetic alterations observed in group A ependymomas might be responsible for the aggressive growth of these tumors. The researchers therefore investigated whether drugs that reduce methylation are effective against the tumors. In experiments with mice affected by aggressive group A ependymomas, one such substance in fact caused tumors to shrink.

“We think that these results are extremely promising,” says Pfister, a pediatrician and molecular geneticist. “Since the drugs we used have already been approved, we will now carry out a clinical trial to investigate whether children with dangerous group A ependymoma benefit from this treatment. This would be the first targeted therapy against a type of cancer for which we currently have very few options for treatment.“

Epigenomic alterations define lethal CIMP-positive ependymomas of infancy
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