Molecular 'on switch' could point to treatments for pediatric brain tumor

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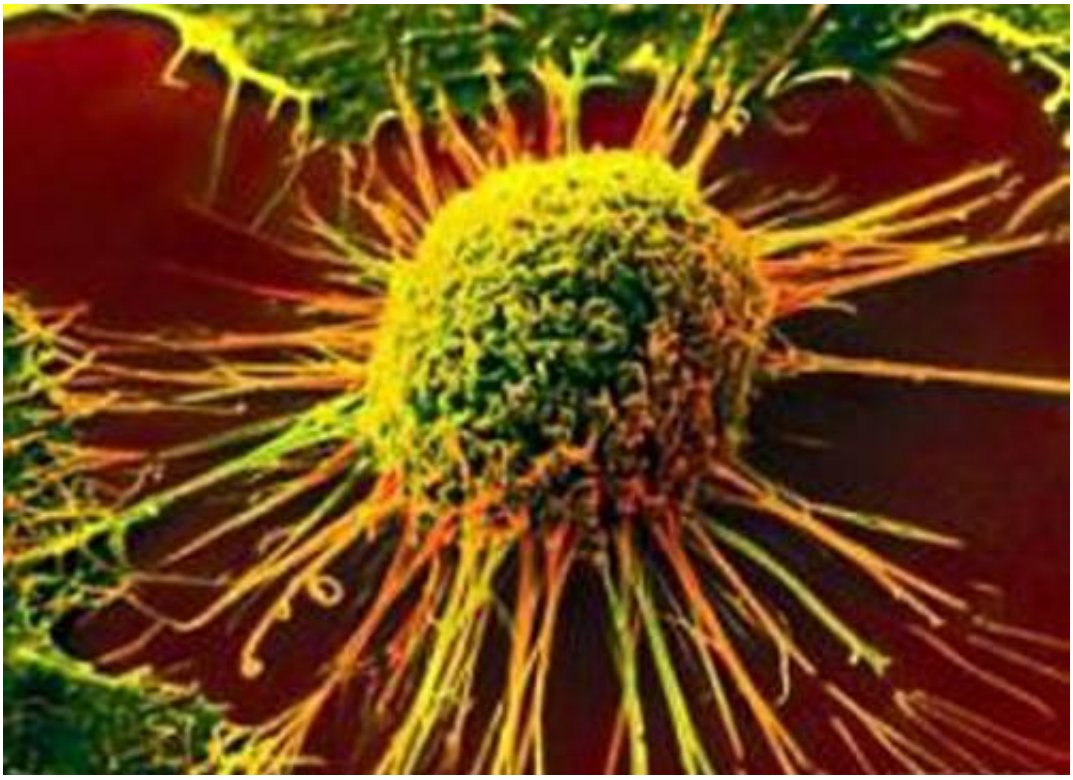

Massachusetts General Hospital (MGH) researchers have identified a mechanism that controls the expression of genes regulating the growth of the most aggressive form of medulloblastoma, the most common pediatric brain tumor. In their report published online in *Cancer Discovery*, the team also identifies potential targets for future treatments.

"We set out to find the most important regulators of gene expression programs in medulloblastoma," says senior author Miguel Rivera, MD, of the MGH Department of Pathology / and the Center for Cancer Research. "To do that we used a powerful genomic technology called chromatin profiling to map all the genomic elements contributing to transcription regulation in Group 3 medulloblastoma - the most aggressive subtype. This goes beyond measuring gene expression because it tells you how genes are turned on and off."

Medulloblastoma is a fast-growing tumor that arises in the developing brain and most commonly affects children under the age of 10. Four molecular variants, each with different patterns of DNA alteration and gene expression, have been identified. Subtypes WNT and SSH are the best understood; the other two - Group 3 and Group 4 - are poorly understood and account for 60 percent of tumors.

Cells regulate whether specific genes are transcribed into RNA through the action of transcription factors, proteins that bind to DNA and either stimulate or suppress the expression of their target genes. Rivera's team used advanced genomic technologies to identify key DNA elements called enhancers that were active in primary Group 3 medulloblastoma samples and cell lines. The transcription factor OTX2, which plays a role in normal brain development and is known to be highly expressed in Group 3 medulloblastomas, was present at the majority of active enhancer sites in tumors, suggesting it may have a role in promoting the expression of tumor-associated genes.

Subsequent experiments revealed that OTX2 can function as a "pioneer factor," opening up chromatin - which consists of DNA wound around proteins called histones - to activate enhancers and that its function is amplified by a second transcription factor called NEUROD1. The investigators then identified a set of genes the expression of which was significantly reduced when OTX2 was suppressed. Among these genes,

they found that expression of the kinase NEK2 responded to OTX2 levels and that its depletion or pharmacologic inhibition strongly reduced the growth and survival of medulloblastoma cells.

"Overall, our findings show that OTX2 is a critical factor in regulating gene expression programs in Group 3 medulloblastoma and possibly in the WNT and Group 4 subtypes, where it is also expressed," says Rivera, who is an assistant professor of Pathology at Harvard Medical School. "This work points to OTX2 itself and its target genes - including NEK2 - as potential therapeutic targets. Disruption of the relationship between OTX2 and NEUROD1 may also be a potential treatment strategy. We now need to get a more a detailed picture of the mechanisms OTX2 uses to activate enhancers and improve our understanding of the function of NEK2 and other target genes regulated by OTX2."

More information: Gaylor Boulay et al, OTX2 Activity at Distal Regulatory Elements Shapes the Chromatin Landscape of Group 3 Medulloblastoma, *Cancer Discovery* (2017). DOI: 10.1158/2159-8290.CD-16-0844

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