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Cancer Cell

Pervasive H3K27 Acetylation Leads to ERV Expression and a Therapeutic Vulnerability in H3K27M Gliomas

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Dr. Claudia Kleinman and her team performed the comprehensive epigenomic data analysis in order to delve deep into the histone 3K27M driver mutations that characterize more than 80% of high-grade gliomas (HGG), a leading cause of cancer-related death in children and young adults. The study was the result of an interdisciplinary collaboration with the teams of Dr. Nada Jabado, a pediatrician at the MUHC, and Dr. Stephen Mack, from the Baylor College of Medicine.

HGG are highly aggressive tumors, which have a two-year survival rate of less than 10% and for which there are no existing therapies. Moreover, it is challenging to target because the gene itself serves critical functions so it is not as simple as deactivating gene expression. The intention of the study was to identify vulnerabilities within the tumor that can be targeted while circumventing a direct assault on H3K27M.

Using animal models, patient tumors and patient-derived cell lines, the researchers knocked out the mutation and discovered a side effect of the mutation that caused stress in cells. This revealed a vulnerability that may not be directly related to oncogenic properties, but which may be exploited by existing drugs to interfere with the progression of disease. This paper illustrates proof of principle for deploying epigenetic therapies against repeat elements as a pathway to combating high-grade gliomas.