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Scientists tackle the aberrant epigenetic programming underlying childhood cancers

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Several childhood cancer cell types show features of immature neural cells, and there is evidence suggesting that these tumors may arise from neural crest stem cells that underwent abnormal changes during embryonic development. One such cancer is Ewing sarcoma. Although combinatorial treatment protocols encompassing chemotherapy, surgery, and radiotherapy have improved outcomes, many patients still suffer from a poor prognosis.

Typically, the pathogenesis of Ewing sarcoma includes fusion of the EWS and FLI-1 genes. The resulting EWSR1-FLI-1 protein induces aberrant epigenomic reprogramming, which alters acetylation and methylation, leading to chromatin remodeling. Chromatin is a structurally condensed form of DNA, and its condensation state regulates gene expression patterns epigenetically. Highly condensed chromatin can suppress the expression of genes that control differentiation, thereby keeping cancer cells in a poorly differentiated, stem cell-like state that facilitates tumor progression.

A team of researchers at the Cancer and Neurobiology Laboratory and the Pediatric Oncology Service at the Federal University of Rio Grande do Sul (UFRGS) and its university hospital (Hospital de Clínicas de Porto Alegre, HCPA), and the Children's Cancer Institute (Instituto do Câncer Infantil, ICI), in Porto Alegre, Brazil, in collaboration with Dr. Carol J. Thiele, Deputy Chief of the Pediatric Oncology Branch at the National Cancer Institute, National Institutes of Health (NIH), in Bethesda, MD, USA, have targeted proteins that regulate the chromatin

state of DNA in Ewing sarcoma cells with the goal of hindering malignant tumor growth. In a new study published in the journal *Molecular Neurobiology* (preprint available at biorxiv.org), lead author Dr. Barbara Kunzler Souza and colleagues were able to induce chromatic relaxation in Ewing sarcoma cells by treating them with a compound that inhibits histone deacetylases. The treatment reduced expression of the EWSR1-FLI-1 oncogene as well as expression of other genes associated with pluripotency and cell viability, while impairing the cells' ability to survive and proliferate. Decreased survival of stem-like cancer cells and re-expression of a neuronal differentiation marker were also observed.

In a previous study by the same group, Dr. Viviane Rösner de Almeida and colleagues demonstrated that treating human neuroblastoma cells with epigenetic agents that inhibit either histone deacetylases or DNA methyltransferase potentiated the ability of a retinoid-based therapy to impair cell proliferation and reduced the expression of oncogene products, including c-Myc and Bmi1. Neuroblastoma—the most common extracranial solid childhood cancer accounting for ~15% of pediatric cancer deaths—is another pediatric cancer thought to originate from a developmental malfunction of embryonic neural crest cells. Dr. Rafael Roesler, associate professor of pharmacology at UFRGS and senior author of the studies, has said that "targeting epigenetic processes that regulate chromatin state, such as histone acetylation and DNA methylation, seems to be an effective experimental approach to inducing desirable biological changes in cells from childhood tumors that may arise from defects in embryonic development."

Dr. André T. Brunetto, Research Diretor at ICI, added, "It is our hope that uncovering molecular mechanisms involved in childhood cancer progression will result in translational opportunities that can be explored in clinical studies." Dr. Caroline Brunetto de Farias, ICI Head of Cellular and Molecular Research, says the findings from cell culture experiments are helping the team identify clinically useful drugs that target epigenetic

mechanisms and have the potential to be investigated as putative adjuvant therapies in animal and human studies.

More information: Bárbara Kunzler Souza et al, Targeting Histone Deacetylase Activity to Arrest Cell Growth and Promote Neural Differentiation in Ewing Sarcoma, *Molecular Neurobiology* (2018). DOI: 10.1007/s12035-018-0874-6 , www.biorxiv.org/content/early/2018/01/16/191700

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