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Helping good genes win in brain cancer cells

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Researchers at the Federal University of Rio Grande do Sul (UFRGS) have shown that manipulating an epigenetic mechanism, which regulates gene expression, may promote cell death and favor maturation towards less malignant-prone phenotypes in pediatric brain cancer cell lines.

Cancer cells show alterations in gene expression related to modifications in the state of their chromatin, the "package" containing the genes in the cell nucleus. A group of enzymes called histone deacetylases (HDACs) helps to organize DNA within the cell nucleus by keeping chromatin in a more condensed state, thus inhibiting gene expression. The HDAC system is one component in the set of epigenetic mechanisms that regulate gene readout. There is growing interest in investigating compounds that inhibit HDACs, thereby allowing chromatin relaxation and increased gene expression, as candidate anticancer drugs.

Medulloblastoma is the most common type of childhood brain cancer. Although cure rates have improved, about 30% of patients with medulloblastoma tumors still have a low chance of being cured and survivors often experience long-term neurocognitive and neuroendocrine impairments.

In a study published in the December 2013 issue of the journal *Molecular Neurobiology*, Carolina Nör and colleagues – namely, study leader Rafael Roesler, ICI-RS researchers Caroline Brunetto de Farias, Ana Lucia Abujamra, and Algemir Lunardi Brunetto, and UFRGS and HCPA researchers Gilberto Schwartsmann, Felipe A. Sassi, and Guido Lenz - showed that sodium butyrate, a drug that acts on epigenetic

regulation by inhibiting HDACs, reduces the survival of cultured medulloblastoma cells as well as formation of neurospheres in the cell cultures, which may indicate inhibition of cancer stem cell proliferation. In addition, cells treated with sodium butyrate showed enhanced mRNA expression of a marker of differentiation towards a mature neuronal phenotype. Finally, sodium butyrate enhanced the anticancer effect of the chemotherapeutic drug etoposide. These findings support and extend previous evidence indicating that HDAC inhibitors can reduce brain tumor growth by allowing genes involved in the promotion of cell death and maturation to be expressed.

"The use of HDAC inhibitors is currently the most important pharmacological approach to manipulate the epigenome. We are using cultured human brain tumor cell lines to identify novel effects of HDAC inhibitors. Although these findings need to be confirmed by in vivo experiments as well as by studies using cancer cells obtained directly from patients, our results support the view that these agents can allow the expression of genes related to cell death, or those involved in differentiation of tumor cells into mature brain cell types, hence having anticancer effects", says Roesler.

In addition to public research funding organizations, including the National Council for Scientific and Technological Development (CNPq) and the National Institute for Translational Medicine (INCT-TM), major support for the study was provided by the Rafael Koff Acordi Project, a research fund created by the Koff Acordi family in partnership with ICI-RS. "It is still uncommon to see basic cancer research being supported by private donations in Brazil, and we are working to promote this type of initiative", says Remi Acordi. "Our goal is to increasingly engage in basic research informed by clinical needs", says Algemir Brunetto, President of ICI-RS, a non-profit private organization focused on pediatric cancer treatment and research.

More information: Carolina Nör, Felipe A. Sassi, Caroline B. de Farias, Gilberto Schwartsmann, Ana Lucia Abujamra, Guido Lenz, Algemir L. Brunetto, Rafael Roesler. The histone deacetylase inhibitor sodium butyrate promotes cell death and differentiation and reduces neurosphere formation in human medulloblastoma cells. *Molecular Neurobiology* 2013, 48: 533-543.