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New insights into neuroblastoma tumor suppressor may provide clues for improved treatment

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Loss of a gene required for stem cells in the brain to turn into neurons may underlie the most severe forms of neuroblastoma, a deadly childhood cancer of the nervous system, according to a Ludwig Cancer Research study. Published in *Developmental Cell* today, the findings also provide clues about how to improve the treatment of this often-incurable tumor.

Neuroblastoma can appear in nervous tissue in the abdomen, chest and spine, among other regions of the body, and can spawn body-wracking metastasis. The most severe tumors respond poorly to treatment, and the disease accounts for 15 percent of cancer deaths in children.

Johan Holmberg, PhD, at the Ludwig Institute for Cancer Research Stockholm took a close look at the role of the CHD5 tumor suppressor during normal nervous system development. Previous studies had shown that the gene *CHD5* is often inactivated in the most severe forms of neuroblastoma, but little was known about its function in healthy tissue or how it operates. The study, which was conducted in close collaboration with colleagues at Trinity College, Dublin, Ireland, addressed these two key issues.

The researchers found that CHD5 is required for the cellular transition from a stem cell to a mature neuron. In one experiment, the researchers knocked down the CHD5 gene by injecting a small RNA into the brains

of fetal mice while in the womb.

"The result was a complete absence of neurons," says Ludwig researcher Holmberg who is based at the Karolinska Institutet. "Instead of becoming neurons, the cells with CHD5 knocked down stayed in a limbo-like state between an actively-dividing stem cell and a mature nerve cell. It was a very robust effect," added Holmberg.

The researchers also dissected how CHD5 operates, showing that it sticks to certain modifications of histone proteins. These modifications help control how genes are turned on and off. In the absence of CHD5, key stem cell genes are not turned off, and genes required for neuronal maturation are not turned on. The findings highlight how the failure of a cell to properly mature into its terminal state can underlie cancer, a relatively understudied area of research.

"It is necessary for cells in the healthy nervous tissue to be able to go from stem cells to neurons," explains Holmberg. "If you lose this capacity, these cells become locked in an immature state, which might yield quite dangerous tumor cells, especially in combination with additional cancer-promoting cellular events."

The research could also lead to new ways to treat neuroblastoma, perhaps using currently approved drugs. One component of neuroblastoma treatment is retinoic acid, a drug that can drive neuronal maturation. Holmberg and his colleagues found that knocking down the expression of CHD5 in more benign neuroblastoma cells blocked their capacity to mature in response to retinoic acid treatment. "These cells were completely insensitive to treatment, no matter how much we gave them, mirroring the same unresponsiveness to retinoic acid in the more malignant CHD5-negative neuroblastoma cells," says Holmberg.

The results of these cell-based experiments are consistent with clinical

findings that retinoic acid is often unsuccessful in patients with severe forms of the disease. Holmberg reasons that if CHD5 could be re-activated in such hard-to-treat patients, it might increase responsiveness to retinoic acid. The findings may also have relevance for other types of tumors. For instance, CHD5 is often inactivated in glioblastoma multiforme, the most common and most aggressive form of brain cancer in adults.

More information: Egan et al., CHD5 Is Required for Neurogenesis and Has a Dual Role in Facilitating Gene Expression and Polycomb Gene Repression, *Developmental Cell* (2013), dx.doi.org/10.1016/j.devcel.2013.07.008

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