Medical Xpress

Cellular origins of pediatric brain tumors identified

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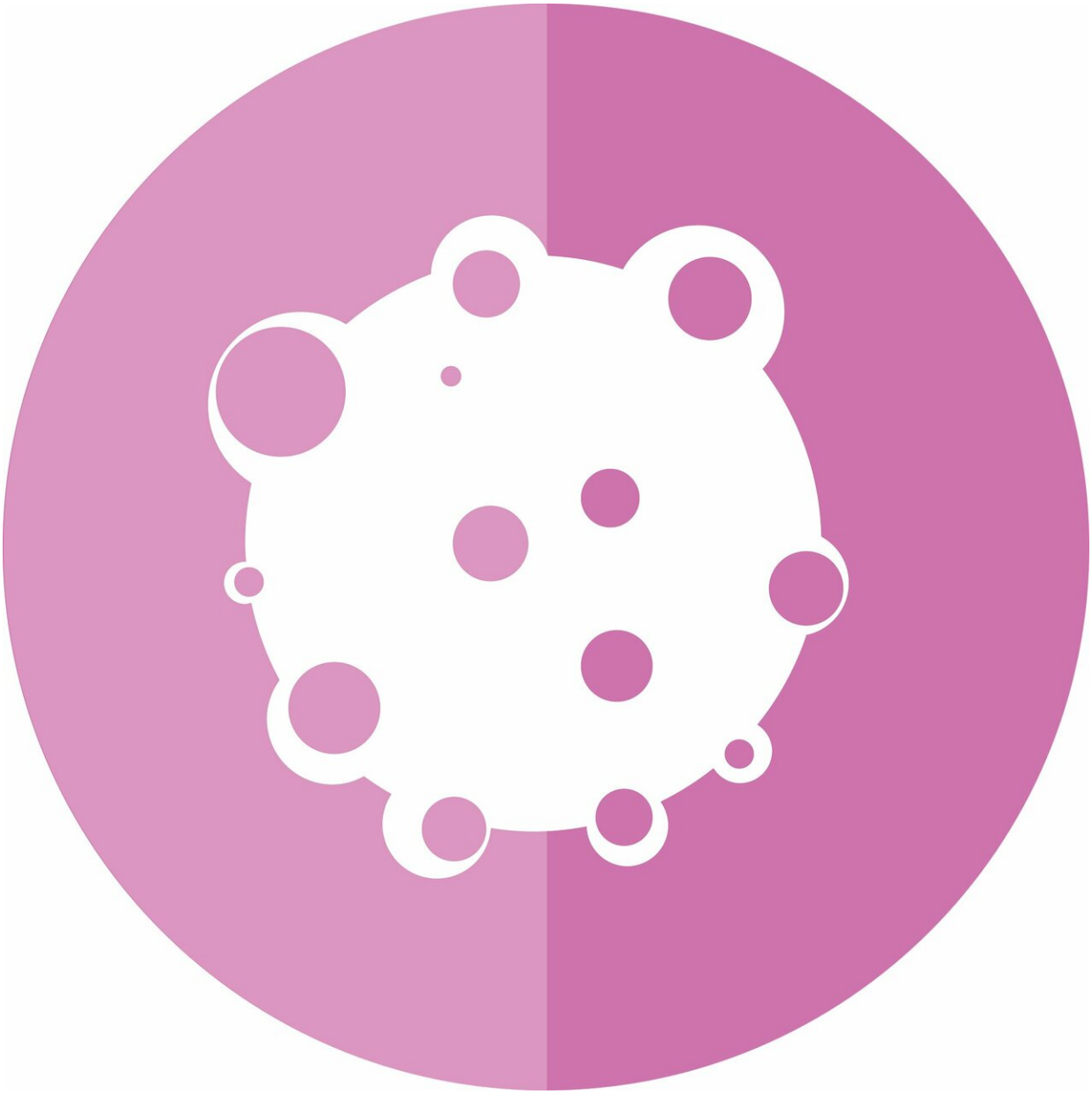

A research team led by Dr. Claudia Kleinman, an investigator at the Lady Davis Institute at the Jewish General Hospital, together with Dr. Nada Jabado, of the Research Institute of the McGill University Health Centre (RI-MUHC), and Dr. Michael Taylor, of The Hospital for Sick Children (SickKids), discovered that several types of highly aggressive and, ultimately, fatal pediatric brain tumors originate during brain development. The genetic event that triggers the disease happens in the very earliest phases of cellular development, most likely prenatal. The findings represent a significant advance in understanding these diseases, and are published in *Nature Genetics*.

"We have determined that stalled development of progenitor cells in the pons and forebrain, where a large proportion of high-grade embryonal and pediatric tumors emerge, is responsible for several childhood brain cancers," said Dr. Kleinman, an Assistant Professor of Human Genetics at McGill University. "Rather than developing normally, the cells' progress is arrested and they transform into malignancies. But they retain many features of the original cells, and we could pinpoint the tumor origins among the hundreds of different cell types present in the brain."

"New technologies allowing us to interrogate tumor cells each one at a time points to stalled development at the root of several high grade brain tumors in children," added Dr. Jabado, who is also an hemato-oncologist at the Montreal Children's Hospital of the MUHC and a professor of Pediatrics and Human genetics at McGill University. "We name this the Peter Pan Syndrome as these cells are stuck in time unable to age and this is what causes these tumors. The challenge is now to identify how best to unlock these cells promoting their differentiation, and allowing for normal processes to take over."

Brain tumors are the leading cause of cancer-related deaths in children. For several of these tumors, there are no effective therapies and survival is often less than two years. Indeed, Dr. Kleinman points out, very limited progress has been made in treating afflicted children.

"The cornerstone to fighting these conditions is to identify the biological process at work, which is what our research has achieved," she said. "Once we understand the underlying mechanisms, the search can begin for the means to unblock the arrested development of the cells. The complexity of the brain is astounding, and we now have narrowed down where to search."

Applying sophisticated single cell sequencing techniques and large-scale data analysis, researchers compiled the first comprehensive profile of the normal prenatal pons, a major structure on the upper part of the brainstem that controls breathing, as well as sensations including hearing, taste, and balance.

While Dr. Jabado, and her team in the Child Health and Human Development Program at the RI-MUHC, and Dr. Taylor, Paediatric Neurosurgeon and Senior Scientist in Developmental and Stem Cell Biology at SickKids, undertook much of the clinical research, Dr. Kleinman's team performed the bio-informatics and establishing the molecular identity for cell types in this and other brain regions, as well as the dynamics underlying their differentiation. They created an atlas of more than 65,000 individual cells and defined the developmental dynamics for 191 distinct cell populations. They then mapped patient samples to this atlas, and identified the origins of WNT medulloblastomas, embryonal tumors with multilayered rosettes (ETMRs), and high grade gliomas (HGGs).

This work is the result of extensive international collaborations that include researchers from across Quebec, Canada, the United States, and

France. Summarizing their achievement, the authors of the paper, "Stalled developmental programs at the root of pediatric brain tumors," wrote, "Current evidence thus supports a common etiological model for these tumors, where genetic alterations in vulnerable cell types disrupt developmental gene expression programs, ultimately leading to oncogenesis."

The genesis of the tumors is very early in brain development, which means that there are really no environmental instigators or preventive measures that parents can take," Dr. Kleinman said. "Advancing our understanding of these tumors is important because the effects are so devastating, we want to bring hope to the patients."

More information: Jessa, S. et al. Stalled developmental programs at the root of pediatric brain tumors. *Nat Genet* (2019) DOI: 10.1038/s41588-019-0531-7 , nature.com/articles/s41588-019-0531-7

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