New insight into the genetics of brain tumor formation

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In a G&D paper published online ahead of its April 1 print publication date, Dr. William Kaelin (Dana Farber Cancer Institute) and colleagues identify a potential new neuronal tumor suppressor.

“It has been suspected for decades that the short arm of chromosome 1 harbored one or more tumor suppressor genes because this region is deleted in a variety of tumors, including many neural crest-derived tumors. Our work suggests that KIFB{beta} is one such gene,” explains Dr. Kaelin.

Neural crest-derived tumors include neuroblastomas and medulloblastomas, which are the most common malignant pediatric solid tumors, as well as paragangliomas (relatively rare tumors of the sympathetic nervous system) and melanomas, the deadliest form of skin cancer.

Under normal developmental conditions, neural crest cells respond to diminishing growth factor signaling by inducing apoptosis, via a pathway involving the enzyme EglN3. However, the acquisition of mutations that enable cells to avoid apoptosis under low growth factor conditions provide a growth advantage and an effective route to tumorigenesis.

In this issue, Dr. Kaelin and colleagues identify that the protein KIF1B{beta} mediates EglN3-induced neuronal apoptosis, and thus provides a protective effect against the development of neural crest-derived tumors.

Importantly, KIF1B{beta} is positioned on the region of chromosome 1p that is deleted in a number of neural crest-derived tumors. The Kaelin group demonstrated that the supplementation of 1p-deleted neuroblastoma cancer cells with KIF1B{beta} protein is sufficient to restore apoptosis and identified inactivating point mutations in neural crest-derived tumors. They also showed that partial reduction of KIF1B{beta} - but not complete loss - confers protection against apoptosis, perhaps explaining why most 1p deleted tumors still retain the other KIF1B{beta} allele in its normal form.

While further research is needed to delineate the mechanism by which KIF1B{beta} induces apoptosis, this work opens up several avenues for investigation. For example, EglN3 is an oxygen-dependent enzyme that responds to a variety of signals and can be modulated with drug-like molecules. Dr. Kaelin points out that “an intriguing possibility is that an increase in EglN3 activity is responsible for the spontaneous regressions frequently observed in neonates who present with Neuroblastoma (so-called Stage 4S Neuroblastoma). Perhaps, in time, we can mimic this with EglN3 agonists.”

Source: Cold Spring Harbor Laboratory