New Role for Muscle Gene as a Tumor Suppressor in Brain Cancer

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VA Morris

Medulloblastoma is the most common brain tumor in children, with 500 new diagnoses in the United States each year. The majority of genetic changes that lead to formation of this brain tumor are largely unknown aside from changes in a few key developmental pathways. Former graduate student Dr. Joyoti Dey, working in the laboratory of Dr. James Olson (Clinical Research Division), found a surprising new player in brain tumor formation with a long history of research at Fred Hutchinson Cancer Research Center. "MyoD was discovered here at the Hutch by Dr. Hal Weintraub's team. It's known as a master regulator of muscle differentiation," according to Dr. Olson. "Who would have imagined that it plays a role in normal brain development and in suppressing the formation of medulloblastoma brain tumors?"

To find novel players in brain tumor formation, collaborator Dr. Michael Taylor's research team at The Hospital for Sick Children in Toronto, Canada took a mouse model of medulloblastoma and introduced a genetic tool called a*Sleeping Beauty* transposon, so named because the system was resurrected from an extinct transposon. Transposons are small pieces of DNA that can jump from one site in DNA to another in a cut-and-paste fashion with the aid of the enzyme transposase. The DNA transposons insert almost randomly throughout the genome when introduced into cells, and these insertions can disrupt the expression of genes, allowing researchers to infer the functions of their encoded proteins. Dey *et al*. found that loss of one copy of*MyoD* accelerated tumor formation in the Sonic Hedgehog (Shh)-driven mouse model of brain cancer.

To confirm their findings, the researchers then looked at *MyoD* genetic changes in human medulloblastomas. No DNA mutations were observed in 310 sequenced tumors; however, the chromosomal region encoding *MyoD* was deleted in 6% of tumors across molecular subtypes. Human medulloblastoma tumors are classified in four subtypes, based on the disruption of two developmental pathways, the Shh pathway and the WNT pathway, or two other poorly characterized subtypes. Previously, the Olson lab created two mouse models of medulloblastoma with two different activating mutations in the Smoothened gene,*SmoA1* and *SmoA2*, which in turn activate the Shh pathway (Dey *et al*., 2012). Deleting one copy of *MyoD* in these mice accelerated tumor formation and decreased survival (see figure), supporting a role for MyoD as a tumor suppressor in brain tumors.

Importantly, the researchers discovered that MyoD protein was also present in the developing normal mouse brain, specifically in cells of the cerebellum that are thought to be precursors to Shh-driven tumors (see figure). MyoD expression is silenced in normal differentiated cerebellar cells, but MyoD expression was increased in the immature proliferating tumor cells in both*SmoA1* and *SmoA2* medulloblastoma mouse models. The expression of *MyoD* in brain tumor cells occurred as a result of tumorigenesis, since expression was not increased in the non-tumor cells of the *SmoA1* and *SmoA2* mice. Expression of some tumor suppressors is decreased in cancer cells, while expression is increased for others in rapidly growing cancer cells in an attempt, albeit unsuccessfully, to control growth or differentiation of cells. The latter seemed to be the case for MyoD in the mouse tumors. However, the fact that a single molecule in a complex neoplastic network involving a plethora of disrupted pathways can hinder tumorigenesis by itself is fascinating. Rarely, human medulloblastoma cells have shown acquisition of features of non-neuronal tissues, including the expression of genes associated with muscle. Dey *et al.* found 36% of human tumors showed *MyoD* expression.

Exactly how MyoD functions as a tumor suppressor has yet to be determined, though it is not through controlling genes involved in muscle differentiation. MyoD can also regulate the cell cycle, and as a transcription factor it regulates the expression of thousands of different genes that could be influencing tumor development. Intriguingly, expression of MyoD is silenced in other solid tumors, such as prostate and colon cancer, yet no function had been described for this gene in cancer formation until this exciting study revealed its tumor suppressor function.

Dey J, Dubuc AM, Pedro KD, Thirstrup D, Mecham BH, Northcott P, Wu X, Shih DJ, Tapscott SJ, Leblanc ML, Taylor MD, Olson JM. 2013. MyoD is a tumor suppressor gene in medulloblastoma. *Cancer Res* Epub ahead of publication, doi: 10.1158/0008-5472.CAN-13-0730-T.

See also: Dey J, Ditzler S, Knoblaugh SE, Hatton BA, Schelter JM, Cleary MA, Mecham B, Rorke-Adams LB, Olson JM. 2012. A distinct Smoothened mutation causes severe cerebellar developmental defects and medulloblastoma in a novel transgenic mouse model. *Mol Cell Biol* 32:4104-4115.

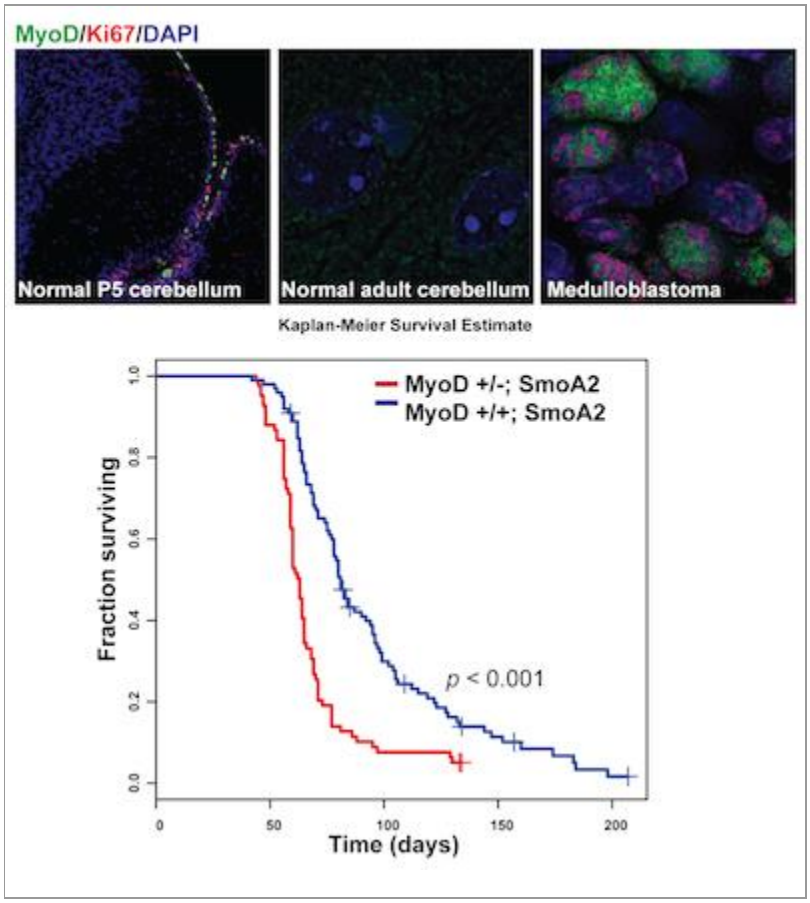

Image provided by Dr. Joyoti Dey

MyoD (green color in top images) is expressed in the developing mouse cerebellum, silenced in the normal adult brain, and highly expressed in medulloblastoma tumors. Genetic loss of MyoD in mouse models of medulloblastoma leads to accelerated tumorigenesis, establishing its function as a tumor suppressor.