Researchers develop model for better testing, targeting of malignant peripheral nerve sheath tumors

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University of Minnesota Medical School researchers from the Masonic Cancer Center, University of Minnesota, in partnership with the University's Brain Tumor Program, have developed a new mouse model of malignant peripheral nerve sheath tumors (MPNST) that allow them to discover new genes and gene pathways driving this type of cancer.

The research was published this week in the journal *Nature Genetics*.

Utilizing the Sleeping Beauty transposon method, researchers in the lab of David Largaespada, Ph.D., professor in the Medical School and College of Biological Sciences, were able to use an unbiased approach to generate mouse models of MPNST development that lead to the identification of genes related to this tumor's development.

MPNST is a genetically diverse, aggressive form of sarcoma impacting connective tissue surrounding nerves that occurs sporadically or in association with Neurofibromatosis Type 1 (NF1) syndrome. The exact cause of MPNST is not known, but symptoms include swelling in the arms and legs, soreness and stiffness at the site of the tumor. MPNSTs are the most common malignancy in adults with NF1 syndrome and leading cause of NF1-related mortality.

Due to the invasive nature and high incidence of metastasis of MPNSTs, surgical resection, radiotherapy and chemotherapeutic treatments have

proven to be ineffective for long-term treatment, resulting in 5-year survival rates of less than 25 percent with metastatic disease.

One of the most surprising findings in this research showed the gene FOXR2 is intrinsically linked to the growth of MPNSTs. This gene has not been heavily studied as researchers had not identified a clear function of this gene.

"By using an unbiased approach, it helped us identify FOXR2 as an important gene in MPNST development and develop experiments to pinpoint the role FOXR2 plays in maintaining the aggressive nature of these tumors," said Eric Rahrmann, Ph.D., the paper's lead author and a postdoctoral fellow in the Largaespada lab. "When we turn off FOXR2, the growth ability of these MPNSTs drastically decreases."

Other findings showed interesting evidence of pathways that could be viable targets for therapeutics. The activation of the Wnt signaling pathway was shown to drive MPNSTs. This pathway has been highly implicated in colon cancer but not previously linked to MPNSTs.

Researchers also found many of the MPNSTs have dual loss of the genes called NF1 and PTEN. This pairing of lost genes causes MPNST formation. Both of these genes have previously been shown as pathways related to MPNSTs but it wasn't clear the extent to which they work together.

Now, researchers are applying these findings to the testing of therapeutics currently on the market for other drugs. This research is continuing both in the mouse model and within primary tumor settings of human cell lines.

"We want to know if these drugs, which are not currently directed at MPNSTs, could be repurposed to provide alternate therapies for

patients," said Largaespada.

Researchers are also looking into more direct ways to target tumors through the Wnt pathway and paired NF1 and PTEN pathways, utilizing mouse models and human cell lines in the lab setting.

Provided by University of Minnesota