Mouse model could help identify viral vectors that may cause tumors

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Investigators at Nationwide Children's Hospital have identified a mouse model that could help evaluate the risk that viral vectors used in gene therapy might promote tumor formation as a side-effect. The study appears in *Molecular Therapy*.

Modified viruses used to deliver genetic material into cells, known as viral vectors, have become the go-to delivery capsule in gene therapy. Capitalizing on their viral nature, investigators use viral vectors to efficiently target certain cells and deliver genetic material into the cell nucleus where native genes reside.

Viral vectors from recombinant adeno-associated virus (rAAV) are favored gene transfer systems for human clinical trials because of their safe track record in human clinical trials. In fact, the first gene therapy drug, approved in Europe, treats a rare disease that disrupts fat production in the body and is based on the recombinant adeno-associated virus platform. Still, a few reports have surfaced suggested that some rAAV vectors may cause DNA mutations in a host, with results showing excess liver tumors in mice.

"While preclinical studies have overwhelmingly supported the safety of rAAV treatment in numerous different tissues and animal models, even a small fraction of vector integration in a tissue as large as a human liver could create many tumor-promoting mutations," says Douglas M. McCarty, PhD principal investigator in the Center for Gene Therapy at The Research Institute at Nationwide Children's Hospital and lead study author. "The studies in mice that showed genotoxicity suggest that specific features of certain rAAV vector constructs may encourage liver tumor formation rather than rAAV vector treatments in general."

To help identify which vector constructs may be more prone to causing harmful mutations and what factors contribute to these changes, Dr. McCarty's team compared a conventional rAAV vector with one designed to be more apt to activate cellular genes. They tested the vector in both a normal mouse model and a tumor-prone mouse model.

Results showed that excess tumors were observed in tumor-prone mice after 10 months of age. The tumors were a result of gene insertions in specific sets of proto-oncogenes (a normal gene that when mutated, can become cancerous) and shared common pathways or common juxtapositions relative to the gene.

"We took specific steps to increase the likelihood of tumor promotion, so our study clearly does not reflect therapeutic conditions in humans nor does it represent the majority of animal models that have been used in rAAV preclinical studies," says Dr. McCarty, also an associate professor of Pediatrics at The Ohio State University College of Medicine. "However, this sensitive mouse model may be a valuable tool for determining the relative risk between different rAAV vector constructs and may help identify potential tumor-promoting elements within these vectors. With these tumor samples in hand, we can understand how the oncogenes got activated and use that to design safer rAAV vectors"

More information: Rosas LE, Grieves JL, Zaraspe K, La Perle KM, Fu H, McCarty DM. Patterns of scAAV Vector Insertion Associated With Oncogenic Events in a Mouse Model for Genotoxicity. *Mol Ther*. 2012 Sep 18. doi: 10.1038/mt.2012.197.

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