Gene therapy strategy found effective in mouse model of hereditary disease TSC

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Patients with tuberous sclerosis complex, a genetic disorder characterized by the growth of noncancerous tumors in multiple organs of the body, have limited treatment options. A team led by investigators at Massachusetts General Hospital (MGH) has now shown that gene therapy can effectively treat mice that express one of the mutated genes that cause the disease. The research is published in *Science Advances*.

The gene, called TSC2, codes for tuberin, a protein that acts to inhibit cell growth and proliferation. When mutations occur in TSC2, resulting in a lack of tuberin in cells, the cells enlarge and multiply, leading to the formation of tumors.

To restore the function of TSC2 and tuberin in a mouse model of tuberous sclerosis complex, researchers developed a form of gene therapy using an adeno-associated virus vector carrying the DNA that codes for a condensed form of tuberin (which fits within the vector's carrying capacity) and functions like the normal full-length tuberin protein. Mice with tuberous sclerosis complex had a shortened life span of about 58 days on average, and they showed signs of brain abnormalities consistent with those that are often seen in patients with the disease. When the mice were injected intravenously with the gene therapy treatment, however, their average survival was extended to 462 days, and their brains showed reduced signs of damage.

"Current treatments for tuberous sclerosis complex include surgery and/or lifelong treatment with drugs that cause immune suppression and potentially compromise early brain development. Therefore, there is a clear need to identify other therapeutic approaches for this disease," says co-lead author Shilpa Prabhakar, an investigator in the MGH

departments of Neurology and Radiology. "Adeno-associated virus vectors have been used widely in clinical trials for many hereditary diseases with little to no toxicity, long-term action in nondividing cells, and improvement in symptoms," adds Prabhakar. She notes that benefits can be seen after a single injection, and some forms of the viral vector can efficiently enter the brain and peripheral organs after intravenous injection.

The U.S. Food and Drug Administration has approved a limited number of gene therapy products for use in humans, and the results from this study suggest that clinical trials are warranted to test the strategy's potential in patients with tuberous sclerosis complex.

More information: Pike-See Cheah et al, Gene therapy for tuberous sclerosis complex type 2 in a mouse model by delivery of AAV9 encoding a condensed form of tuberin, *Science Advances* (2021). DOI: 10.1126/sciadv.abb1703

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