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Gene replacement for TSC effective in mouse model

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Patients with tuberous sclerosis complex (TSC) frequently develop tumors as well as seizures, hydrocephalus, and neurodevelopmental disability. Current treatment options such as rapamycin analogs, however, may compromise early brain development. In a recent study published in *Science Advances* (http://advances.sciencemag.org/content/7/2/eabb1703), Cheah and colleagues report that a novel gene therapy extended lifespan and reduced brain pathology in a mouse model of TSC. Variants in either *TSC1* encoding hamartin or *TSC2* encoding tuberin lead to TSC. Typically, hamartin and tuberin form a complex to inhibit mammalian/mechanistic target of rapamycin complex I (mTORC1) via guanosine triphosphatase (GTPase) activating effects on Rheb, a brain-enriched Ras homolog. Variants in *TSC1* or *TSC2* lead to cellular enlargement and proliferation, and consequent tissue lesions. The researchers generated a condensed tuberin construct (cTuberin) that retained hamartin-binding domain and GTPase-activating protein activity and inserted it into an adeno-associated virus (AAV) vector. Transfecting the construct into cells showed no apparent toxicity despite levels twice as high as those of endogenous tuberin. Coimmunoprecipitation assays demonstrated that cTuberin bound to hamartin and Rheb1 to the same extent as full-length tuberin. Additional cell-based experiments revealed that cTuberin inhibited mTORC1 activity to a similar degree as full-length tuberin. Together the results suggest that cTuberin has high expression but low toxicity and retains critical functions of full-length tuberin, including mTORC1 inhibition. Subsequent experiments in an animal model mirrored cellular results. To assess the preclinical efficacy of cTuberin, the researchers utilized *Tsc2* homozygous floxed mice injected with an AAV-Cre recombinase vector at postnatal day 0 to inactivate *Tsc2* in a subset of brain cells. At postnatal day 21 the mice were injected with either an AAV-cTuberin construct or an AAV-null vector. Control mice that either did not receive an injection or received the null vector survived about 60 days, whereas mice injected with AAV9-cTuberin survived more than 460 days. The researchers also saw regression of ependymal/subependymal overgrowths in mice treated with AAV-cTuberin. Finally, AAV-cTuberin injection lowered signal of a downstream mTORC 1 effector, pS6K, in brain sections of P42 animals and reduced cell size by 23%, indicating reduced mTORC1 activity. The authors conclude that the results support the potential of AAV gene therapy to treat TSC2 lesions, particularly for infants and children in whom pharmaceutical approaches currently envisioned may interfere with early brain development. —*V. L. Dengler, News Editor*

How *GNAO1* variants cause movement disorder

Oscar Wong/Getty

The G protein α subunit o (Gαo) is an abundant brain protein that is critical for nervous system function. Variants in the gene that encodes Gαo, *GNAO1*, cause neurological disorders that influence motor control. How these variants impact Gαo function and manifest as disease, however, remains unknown. In a study recently published in *Cell Reports* (https://doi.org/10.1016/j.celrep.2021.108718), Muntean and colleagues demonstrate that movement control requires Gαo and that dominant negative variants alter Gαo function in a neuron type–specific manner. The researchers first generated mice that lack the protein in the striatum, a major motor control brain structure. The mice displayed marked motor deficits, including hindlimb clasping, ineffective hindlimb use in a ledge test, and impairments in coordination and balance. The researchers then knocked out Gαo in two populations of striatal cells that are thought to coordinate motor programs: direct pathway medium spiny neurons (dMSNs) and indirect pathway medium spiny neurons (iMSNs). Mice lacking Gαo in dMSNs performed as well as wild-type mice in balance and coordination challenges, except the motor learning rotarod test. In contrast, mice lacking Gαo in iMSNs showed no deficits in the rotarod test, but phenocopied striatal knockout mice across the remaining coordination and balance tests. The findings indicate that striatal Gαo is required for motor function via differential programs in dMSNs and iMSNs. To assess how Gαo variants affect signaling in MSNs, the researchers introduced two dominant negative variants, G203R and R209C, into neurons. Dose–response analyses revealed differential effects. The R209C variant exclusively affected iMSN responses, lowering the efficacy of dopamine signaling, whereas the G203R variant lowered efficacy in iMSNs but increased potency of the response in dMSNs. Adenosine responses mirrored these changes, with the R209C variant exclusively affecting dMSNs, diminishing efficacy of adenosine signaling, while the G203R variant lowered efficacy in dMSNs and increased potency of adenosine responses in iMSNs. Together the results indicate that dominant negative Gαo variants interfere with dopamine and adenosine signal processing in a cell type–selective manner. Expression of either of the dominant negative Gαo variants in dMSNs or iMSNs in mice led to significant hindlimb clasping and reduced coordination and balance. Together, the findings indicate that Gαo functions in specific circuits to regulate dopamine and adenosine signals critical for motor control. The authors conclude that the mechanisms they elucidated will inform individualized pharmacotherapies. —*V. L. Dengler, News Editor*

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