Molecular pathology selected abstracts

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Development of brain circuits after gene therapy for Parkinson's disease

Parkinson's disease is caused by a loss of dopamine-producing nerves in the specialized substantia nigra pars compacta area of the brain. As these nerves degenerate, brain metabolism and nerve connections change, which ultimately leads to overactivity in the subthalamic nucleus (STN), resulting in movement dysfunction. A mainstay of therapy for Parkinson's disease is medication such as levodopa, which provides replacement dopamine to the brain, but it loses its effect over time. More recent therapies include deep brain stimulator implants that target the STN, although numerous side effects may occur due to surgery and implantation of the device. To provide better long-term benefit to patients with the disease, a group of scientists is using adeno-associated virus (AAV) to deliver the glutamic acid decarboxylase *(GAD)* gene to reduce substantia nigra overactivity. The resultant GAD protein is an enzyme that catalyzes the production of gamma-aminobutyric acid, an inhibitory neurotransmitter that reduces nerve signaling, from L-glutamic acid. This research builds on work initially published in a phase one study in 2007, which showed that catheter infusion of AAV-*GAD* to the STN was safe and had potential benefits in reducing symptoms. The rationale behind this approach was that *GAD* gene therapy could convert some of these neurons into an inhibitory subtype, thereby reducing STN activity and mitigating symptoms. However, the mechanism underlying the way in which AAV-*GAD* worked remained unclear. To address this issue, the authors of the current study used ^{18}F-fluorodeoxyglucose positron emission tomography (PET) scans to compare brain metabolism between 15 patients with Parkinson's disease who underwent successful delivery of AAV2-*GAD* and completed longitudinal brain imaging and 20 patients who received a sham control during a 12-month period. The authors assessed the Parkinson's disease-related covariance pattern (PDRP), a disease-specific network PET signal that indicates symptom progression. But despite the improvement in symptoms, the authors did not see a difference in PDRP scores between control and treatment groups. Therefore, they returned to the scans and found a new metabolic signature, which they termed *GAD*-related pattern (GADRP). It correlated with reduced metabolism in areas normally overactivated in Parkinson's disease and also increased metabolism in the premotor cortex and supramarginal gyrus. The GADRP signature increased over time in AAV-*GAD*–treated patients and was seen in 14 of 15 AAV-*GAD* patients compared with only one of 20 control patients. This signature corresponded to new connections developed in the brain between the STN and the motor regions of the brain. These new connections were also associated with improved clinical outcomes. The results of this study suggest that viral gene therapy for Parkinson's disease is effective and, while it may not alter the background disease process, can help the brain overcome abnormal activity by making new nerve connections and restructuring how the brain works in the areas affected by Parkinson's disease.

Niethammer M, Tang CC, Vo A, et al. Gene therapy reduces Parkinson's disease symptoms by reorganizing functional brain connectivity. *Sci Transl Med.* 2018;10. http://stm.sciencemag.org. Accessed December 12, 2018.

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Kaplitt MG, Feigin A, Tang C, et al. Safety and tolerability of gene therapy with an adeno-associated virus (AAV) borne *GAD* gene for Parkinson's disease: an open label, phase 1 trial. *Lancet.* 2007;369:2097–2105.

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Use of giant tortoise genomes in the study of longevity and disease

Giant tortoises are unique in their ability to live well beyond 100 years and defy many biological processes, such as cancer and diabetes, that lead to earlier death in other creatures. In an attempt to understand how genomes

contribute to tortoises' longevity, a group of scientists studied the genomes of *Aldabrachelys gigantea* giant tortoises from the Indian Ocean and the genomes of Lonesome George, the last of the *Chelonoidis abingdonii* giant tortoises from the Galapagos Islands of Ecuador. They used supervised and unsupervised clustering to perform comparative analyses of the genomic sequences in these tortoises and other species, including humans. The authors first used homology gene searches with genomic data from humans and tortoises to predict protein families that were expanded during the evolution of the tortoises and to identify potential gene variants proposed to affect human health. Many of the genes identified suggest that exosomes, which are shed cellular contents that signal to neighboring cells, may have been important in the evolution of these tortoises. The authors then identified a set of 43 predicted genes that were positively selected in tortoise evolution, many of which have been implicated in successful human aging (*AHSG* and *FGF19*), immune system regulation (*MVK, IRAK1BP1*, and *IL1R2*), and intracellular vesicle trafficking (*VPS35*). The authors also analyzed a set of 3,000 genes manually selected for their potential impact on human physiology and aging. Although some of these genes appear to serve unique functions in tortoise evolution, such as tooth loss, shell formation, and increased relative size, others appeared relevant to human aging. These genes had diverse functions and included variants involved in glucose regulation and uptake (*MIF* and *GSK3A*), genomic expansion of genes that protect against infection (*APOBEC1* and *CAMP*, among others), and regulation of immune surveillance (*SET* and *PRF1*). In addition, alterations in several cancer-related genes were identified, including duplications in tumor suppressors such as *SMAD4, NF2, PML, PTPN11,* and *P2RY8*, which may partially explain the low cancer rates in giant tortoises. Finally, the authors selected 500 genes directly related to human aging to analyze, and they identified genomic changes that enhanced genome integrity (*NEIL1* and *RMI2*), DNA repair (*XRCC6*), telomere maintenance (*TERF2*), and mitochondrial function (*ALDH2, NLN, GAPDH*), among other benefits. The results of this study indicate that many genes considered important in human disease development and aging are the same ones for which long-lived animals, such as giant tortoises, have shown positive selection throughout their evolution. These factors include maintenance of metabolism, immune mechanisms to enhance surveillance against infections and cancer, telomere maintenance, accentuated tumor suppressor expression, and DNA repair. Additional work to define the role of signaling factors identified in this study may further enhance understanding of the aging process in humans.

Quesada V, Freitas-Rodriguez S, Miller J, et al. Giant tortoise genomes provide insights into longevity and age-related disease. *Nat Ecol Evol.* 2018. doi:10.1038/s41559-018-0733-x.

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