Persistent gene therapy in muscle may not require immunosuppression

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Successful gene therapy is based on the effective delivery and maintained expression of healthy copies of a gene into tissues of individuals with a disease-associated genetic mutation. Recombinant adeno-associated virus (rAAV) vectors have shown promise in early clinical trials as effective therapies for several genetic diseases, including Leber congenital amaurosis, Parkinson disease, and hemophilia.

Unfortunately, delivery of rAAV vectors to tissues other than the retina and CNS often results in development of an immune response against the viral capsid. The development of a neutralizing response against the rAAV vector prevents sustained expression of the healthy gene in the absence of immunosuppression.

In this issue of the *Journal of Clinical Investigation*, Christian Mueller and colleagues at the University of Massachusetts Medical School evaluated the persistence of rAAV-mediated expression the gene encoding M-type ?-1 antitrypsin (M-AAT) in patients that were AAT deficient. Patients received multiple intramuscular doses without immunosuppression, and M-ATT expression was evaluated in muscle biopsies. The authors determined that subjects sustained M-ATT expression in muscle tissue for at least one year, despite an initial influx of immune cells. Further evaluation of muscle fibers revealed a substantial population of regulatory T cells in patients with persistent M-ATT expression.

Together, the results from this study suggests that delivery of an M-ATT-encoding rAAV vector promotes a regulatory immune response that allows for long term gene expression that does not require immune suppression.

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