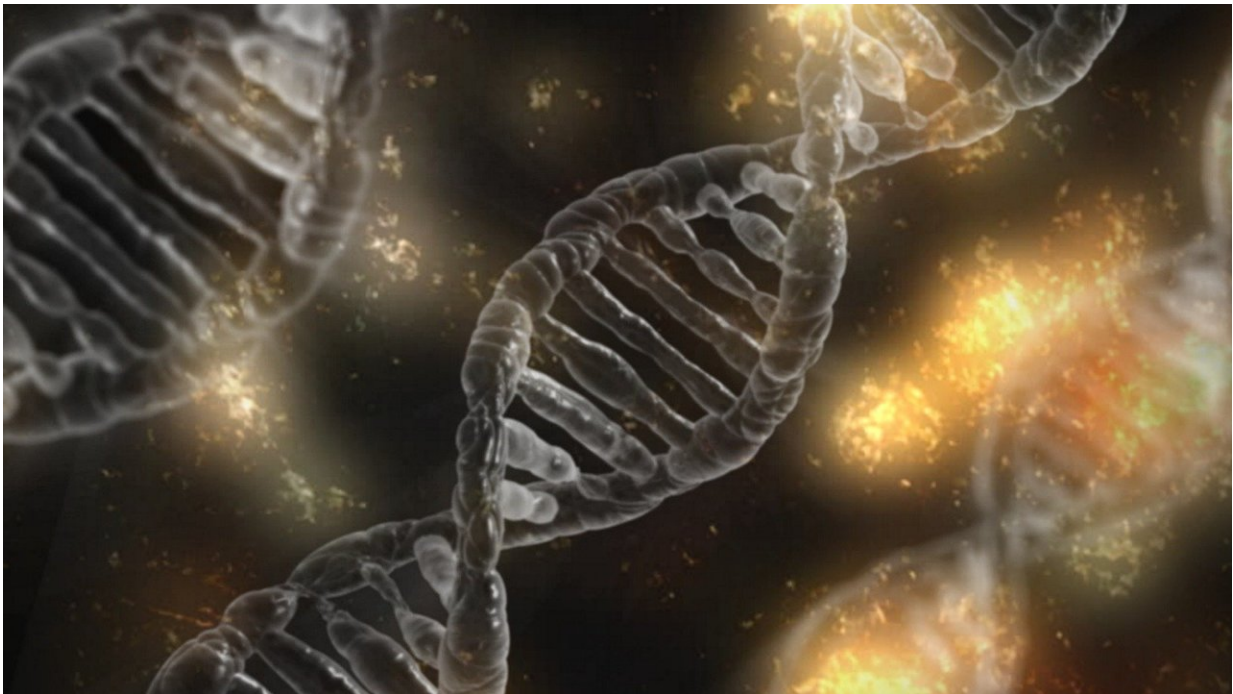


Scientists engineer way to prevent immune response to gene therapy in mice

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Stanford University School of Medicine researchers have demonstrated that gene therapy can be effective without causing a dangerous side effect common to all gene therapy: an autoimmune reaction to the normal protein, which the patient's immune system is encountering for the first time.

The researchers showed this in a mouse model that accurately recapitulates Duchenne muscular dystrophy. One in every 5,000 boys is born with this crippling disease, which leaves patients wheelchair-bound by mid-adolescence and is typically fatal by young adulthood. It stems from a genetic defect that deprives skeletal and cardiac muscles of a working version of a protein called dystrophin.

"Gene therapy is on the cusp of becoming a mainstream approach for treating single-gene disorders," said Lawrence Steinman, MD, professor of neurology and neurological sciences and of pediatrics at Stanford. "But there's a catch: If you give a gene that's a recipe for a normal protein to someone with a faulty version of the gene, whose body never made the normal protein before, that person's immune system will mount a reaction—in some cases, a lethal one—to the normal protein, just as it would to any foreign protein. We think we've solved that problem."

The findings are described in a study to be published online Sept. 3 in the *Proceedings of the National Academy of Sciences*. Steinman, who holds the George A. Zimmermann Professorship, is the study's senior author. The lead author is senior research scientist Peggy Ho, Ph.D.

Going viral

Duchenne muscular dystrophy is the result of a single defective gene, making it an excellent candidate for gene therapy in which a patient's faulty gene is replaced with the correct version. One way to do this is by co-opting viruses, which are simple entities that are adept at infecting cells and then forcing every invaded cell's reproductive machinery to copy their own viral genes. For gene therapy, viruses are modified by ridding them of unwanted [genes](#), retaining the ones necessary for infectivity and adding the therapeutic gene to be delivered to a patient.

The gene encoding dystrophin is far too big for a gene-hauling virus to

take onboard. Fortunately, a mere fraction of the entire gene is enough to generate a reasonably functional version of dystrophin, called microdystrophin. The abridged gene fits snugly into a viral delivery vehicle designed some time ago by Jeffrey Chamberlain, Ph.D., a co-author of the study and a professor of neurology, medicine and biochemistry at the University of Washington.

Inducing tolerance

But there's still that sticky autoimmunity problem. To get around it, Steinman and his colleagues spliced the gene for microdystrophin into a different kind of delivery vehicle called a plasmid.

Plasmids are tiny rings of DNA that bacteria often trade back and forth to disseminate important traits, such as drug resistance, among one another. The particular bacterial plasmid the investigators co-opted ordinarily contains several short DNA sequences, or motifs, that the immune system recognizes as suspicious and to which it mounts a strong response.

But some years ago, Steinman and a few other Stanford scientists—including Ho and study co-author William Robinson, MD, Ph.D., professor of immunology and rheumatology—figured out how to replace those troublesome DNA motifs with another set of DNA sequences that, far from exacerbating the immune response, subdue it. This immune-tolerance-inducing plasmid has been deployed in clinical trials for two different autoimmune conditions, with promising results.

For the new study, the researchers used a one-two punch to deliver gene therapy and protection against autoimmunity to the mice: viral delivery of the microdystrophin gene, followed by the plasmid-assisted induction of tolerance to microdystrophin.

Fifteen 6-week-old mice—an age roughly equivalent to that of a young child—bioengineered to lack functioning dystrophin were injected with the virus carrying microdystrophin. Starting a week later, they were divided into three groups and given weekly injections for 32 weeks of either a dummy solution; the dummy solution plus the tolerance-inducing plasmid absent the microdystrophin gene; or the plasmid with the microdystrophin gene.

At the end of the 32-week period, by which time the mice were the human equivalent of young adults, the ones that got the microdystrophin-loaded plasmid had significantly greater muscular strength and substantially more dystrophin-producing muscle fibers. They had lower levels of key bloodborne signaling chemicals that carry inflammatory messages between immune cells, and they had weakened antibody responses to normally immunogenic portions of microdystrophin.

"It's still early days here—this was, after all, a mouse experiment—but it seems we can induce tolerance to a wide assortment of formerly immunogenic proteins by inserting the gene for the protein of interest into the plasmid," Steinman said. "We've seen this with the insulin precursor, in people who have Type 1 diabetes, and with myelin, in people who have multiple sclerosis. It now looks as if the concept may hold for [gene therapy](#), too."

More information: Peggy P. Ho et al., "Engineered DNA plasmid reduces immunity to dystrophin while improving muscle force in a model of gene therapy of Duchenne dystrophy," *PNAS* (2018).

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