Gene Therapy Approach Raises Questions

Treating patients with gene therapies requires a safe vehicle to ferry in helpful genes, and adeno-associated virus (AAV) is widely regarded as one of the safest. But new research shows that at least some human cancer cells treated with the virus develop abnormal chromosomes, raising concerns about the long-term safety of AAV-based gene therapies.

Some researchers thought AAV was safer for gene therapy than other so-called viral vectors, because infection with AAV is common and causes no known ill effects. AAV-based therapies have also passed muster in several safety trials. Still, it's been unclear exactly how the virus delivers and activates genes inside human cells. Scientists wondered how AAV's DNA jumped into the cell chromosomes and whether it damaged them by doing so.

To find out, geneticist David Russell of the University of Washington, Seattle, and his colleagues studied AAV's impact on genes in a cultured cancer cell line. The researchers used an AAV strain designed to pop out of chromosomes when the cells are treated with a certain drug, carrying nearby pieces of chromosome with it. By then analyzing the DNA sequences of those chromosome pieces, the team could reconstruct how AAV had altered the cell's chromosomes when inserting itself.

As reported in the February issue of Nature Genetics, the cell chromosomes had small pieces missing or added where the virus had inserted itself. In one cell line two different chromosomes had abnormally fused. Despite this link, it's not clear whether the type of cells studied—a line of cancer cells commonly used by researchers—somehow enabled AAV to wreak extra damage. More testing on other kinds of cells is needed, Russell says, to determine whether patients treated with AAV are at higher risk of chromosomal disruption, which can lead to cancer.

The study raises a warning flag. "We're going to have to follow these patients" enrolled in safety trials, says gene therapist Malcolm Brenner of Baylor College of Medicine in Houston, who adds the results suggest that AAV vectors are probably no safer than other viral vectors currently used. Still, Brenner adds, it's far too soon to consider jettisoning AAV, given that other evidence suggests it's safe.

--DAN FERBER

Related sites
Background on gene therapy from U.S. Department of Energy
Questions and answers on gene therapy from the National Cancer Institute
Animated gene therapy primer