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No danger of cancer through gene therapy virus

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In fall 2012, the European Medicines Agency (EMA) approved the modified adeno-associated virus AAV-LPL S447X as the first ever gene therapy for clinical use in the Western world. uniQure, a Dutch biotech company, had developed AAV-LPL S447X for the treatment of a rare inherited metabolic disease called lipoprotein lipase deficiency (LPLD) which affects approximately one or two out of one million people. The disease causes severe, life-threatening inflammations of the pancreas. Afflicted individuals carry a defect in the gene coding for the lipoprotein lipase enzyme which is necessary for breakdown of fatty acids. AAV-LPLS447X shall be used as a viral vector to deliver an intact gene copy to affected cells.

The viruses modified for gene therapy cannot integrate their DNA into the host cell genome, because they lack a particular enzyme needed for this. Nevertheless, integration may happen occasionally. "We had to exclude that AAV-LPLS447X tends to integrate at sites in the genome where this integration might activate cancer-promoting genes. This is exactly what had been observed with a virus used for gene therapy," says Dr. Manfred Schmidt, a molecular biologist. Schmidt leads a research group at NCT Heidelberg and DKFZ that studies the safety of gene-therapeutic methods.

In collaboration with scientists from uniQure, the Heidelberg researchers analyzed the genome of five LPLD patients who had been treated with AAV-LPLS447X . In addition, they also studied mice following intramuscular or intravenous administration of the therapeutic virus.

The analysis of 15 million individual genomes of five treated patients showed, as expected, that AAV-LPLS447X rarely integrates into the genome of the host cells (fewer than 1 out of 1,000 AAV-LPLS447X particles). In most cases, the viral genome persists in the cytoplasm as a separate structure. If it is integrated, this happens at random sites. The researchers did not find any tendency for integration at particular sites in the genome.

Christine Kaeppel and Raffaele Fronza, first authors of the article, were very surprised to discover the AAV-LPLS447X genome in the so-called mitochondrial genome. Mitochondria are tiny membrane-enclosed structures that generate energy for the cell. They are the only cellular component aside from the nucleus containing DNA. "An adeno-associated virus has never before been observed to integrate into the mitochondrial genome on its own," reported the scientists.

"For the first time, we have thoroughly analyzed in AAV-treated patients whether and where the viral genome integrates. Now we can regard AAV-LPLS447X as safe. Those few cases where we have observed integration of viral DNA in muscle cells are barely relevant in view of all the reconstructions and rearrangements that are permanently taking place in our DNA anyway," says study director Schmidt.

AAV-LPLS447X is considered to be a prototype vector for gene therapy. "If AAV-LPLS447X stands the test, other gene therapies against more common diseases such as Huntington's disease or Parkinson's might also become possible," says Schmidt. In addition, a growing number of diseases have been found to be linked to alterations in mitochondrial genes. The newly discovered property of the AAV vector might also prove useful for correcting genetic defects in human mitochondrial DNA.

More information: Christine Kaeppel, Stuart G Beattie, Raffaele

Fronza, Richard van Logtenstein, Florence Salmon, Sabine Schmidt, Stephan Wolf, Ali Nowrouzi, Hanno Glimm, Christof von Kalle, Harald Petry, Daniel Gaudet, Manfred Schmidt: A largely random AAV integration profile after LPLD gene therapy. *Nature Medicine* 2013, DOI: 10.1038/nm.3230