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Virus widely used in gene therapy research yields important clues to genomic instability

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Genomic instability—the rearrangement of chromosomes or an abnormal number of chromosomes—is a hallmark of many human cancers. Although the source of genomic instability has been established for many inherited human cancers, the processes and genes involved in cancers that that are not inherited but arise sporadically remain largely unknown. Now, researchers at the University of Pittsburgh School of Medicine say they have the ability to study the potential cause of genomic instability in sporadic cancers using a recombinant adeno-associated virus, the same virus that many researchers around the world use for gene therapy experiments. The results of their work are being presented at the 10th annual meeting of the American Society of Gene Therapy, which is being held May 30 to June 3 at the Washington State Convention & Trade Center, Seattle.

Recombinant adeno-associated virus (rAAV) is a powerful vehicle to deliver genes into various tissues in cells and animals, and these viruses, or vectors, are of great interest not only in the field of human gene therapy but also as a tool to express genes of interest in target cells for research on various human diseases. It is now possible to express a gene of interest in 100 percent of target cells in organs in mice, including liver, skeletal muscle and heart, by a single injection of a rAAV vector into a peripheral vein.

Recent research has demonstrated that rAAV can only insert itself into host chromosomes at sites that are prone to DNA breaks. The research team, led by Hiroyuki Nakai, M.D., Ph.D., assistant professor of

molecular genetics and biochemistry, University of Pittsburgh School of Medicine, recently established a novel method to isolate rAAV integration sites in non-dividing cells on a large scale. They have used this method to identify approximately 1,000 integration sites in mouse liver, skeletal muscle and heart. Furthermore, of 945 rAAV integration sites mapped to the mouse genome, Dr. Nakai and his collaborators found that up to 30 percent of the integration events occurred in DNA palindromes—a sequence of base pairs in DNA that reads the same backwards and forwards across the double strands. A series of bioinformatic and statistical analyses revealed that these breakage-prone palindromes can be found throughout the genome, but only a subset of palindromes of a particular size are susceptible to breakage.

According to Dr. Nakai, the discovery that rAAV can selectively identify breakage-prone palindromes provides an unprecedented opportunity to study these naturally occurring DNA sequences on a whole genome scale in various tissues in living animals and human cells.

"Our findings demonstrate that DNA palindromes of a modest size are a prevalent and significant source of DNA breaks, which may threaten the integrity of the mammalian genome. More importantly, they can contribute significantly to our understanding of the possible contributions to cancer and aging," he explains.

Source: University of Pittsburgh Schools of the Health Sciences