Medical Xpress

New paradigm for cell-specific gene delivery

June 23 2008

Researchers from Northwestern University and Texas A & M University have discovered a new way to limit gene transfer and expression to specific tissues in animals. In studies to determine how plasmids enter the nuclei of non-dividing cells, the group previously identified a region of a smooth muscle cell-specific promoter that was able to mediate nuclear targeting of any plasmid carrying this sequence uniquely in cultured smooth muscle cells but in no other cell type.

In their current study to appear in the July 08 issue of *Experimental Biology and Medicine*, the team, led by Drs. David Dean and Jennifer Young from the Department of Medicine at Northwestern University, in collaboration with Warren Zimmer from Texas A & M University, now demonstrate that such restriction of nuclear entry using this specific DNA sequence can be used in blood vessels of living animals to direct gene transfer and expression specifically to smooth muscle cells. They have also developed a novel gene delivery approach for the vasculature that uses an electric field to transiently permeabilize the plasma membrane of cells to allow entry of DNA. Thus, this work establishes the control of nuclear entry of gene therapy vectors as a novel approach to target genes and gene expression to desired cell types in the body.

Vascular smooth muscle proliferative diseases, including atherosclerosis and restenosis, are among the leading causes of morbidity and mortality in the US. Gene therapy may represent an important alternative for the treatment and prevention of these proliferative diseases of the vasculature. It can be highly cell-specific, mimic or restore normal in vivo function, and can be permanent or transient depending on vector

design. Currently, a number of gene delivery systems for use on the arterial wall are being studied, but as yet their low efficiency in gene transfer and lack of cell-specific targeting and expression are major limitations. According to Dr. David Dean, "The benefit of our newly described approach is that it can target specific cell types. One of the most commonly envisioned treatments for these proliferative disorders is to deliver genes that kill or inhibit the dividing smooth muscle cells, but we need to target only these muscle cells and not any other cell in the vessel wall and this approach will enable us to do just that".

The goal of the team is to design more effective gene therapy vectors for use in the vasculature by understanding the molecular mechanisms by which DNA and DNA-protein complexes are actively transported into the nucleus. Dr. Warren Zimmer states "these results set the stage for our future use of this technology to deliver therapeutic genes to lessen the severity of restenosis which is the most common issue following angioplasty and placement of stents". Dr. Dean continues, "Now that we have demonstrated proof of principle for this approach we can look for DNA sequences that act in other tissues and develop cell-specific treatments for any number of organs". Dr. Steven R. Goodman, Editor-in-Chief of Experimental Biology and Medicine, stated "The exciting studies reported here are the first to demonstrate that non-viral gene delivery can be made cell-specific by controlling the nuclear entry of plasmid DNA, and as such, establishes a new paradigm for cell-selective gene delivery. Drs. Dean, Young, and Zimmer are to be congratulated on this ground-breaking study".

Source: Society for Experimental Biology and Medicine