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Systemic delivery of thiol-specific antioxidant hPRDX6 gene by AAV8 inhibits atherogenesis in LDLR KO mice on HCD

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Abstract

Atherosclerosis is an inflammatory disorder of arteries and reactive oxygen species (ROS) have been implicated as a major etiologic cause. Various anti-ROS genes, such as superoxide dismutates and catalase, have been studied by gene transfer for their abilities to limit a variety of ROS-related cardiovascular injuries such as ischemia-reperfusion and atherosclerosis. However the thiol-ROS compartment has never been explored by gene therapy for therapeutic intervention. Here, we delivered the thiol-specific anti-oxidant human peroxiredoxin 6 (hPRDX6, AOL2) gene by systemic adeno-associated virus type 8 (AAV8) gene transfer into low density lipoprotein receptor knockout mice on high cholesterol diet (LDLR KO HCD). It was found that AAV8/PRDX6 gene delivery inhibited systolic blood velocity, aortic cross sectional area, and aortic wall thickness compared to Neo-HCD control, consistent with reduced atherosclerosis. Markers of macrophages/foam cells, CD68, ITGAM, EMR, were also lower in the AAV8/PRDX6-HCD-treated animals compared to Neo-HCD controls by either quantitative reverse transcriptase polymerase chain reaction amplification or by immuno-histochemistry, or both, again, consistent with reduced atherosclerosis. Analysis of alterations of the immune state of the aortas (Th1 or Th2, etc.) were unclear, with only IL-10 expression being lower in PRDX6-treated animals. This study, for the first time, demonstrates that PRDX6 gene delivery gives therapeutic benefit against atherosclerosis and suggests further studies of PRDX6, and related anti-thiol-ROS approaches, is warranted.

Biography

Paul L. Hermonat completed his Ph.D. at the University of Florida in 1984, and postdoctoral studies at the National Institutes of Health. He is a professor of Internal Medicine and OB/GYN at the University of Arkansas for Medical Sciences and a Research Career Scientist at the Central Arkansas Veterans Healthcare System. He was the first to generate recombinant adeno-assocociated virus (AAV/NeoR) and to transfer genes into cells via this method. He has over 140 manuscripts published, mostly on the topic of AAV molecular biology and gene transfer.