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AAV8/hB7-H1-gene delivery lowers Th1 response *in vitro* and atherogenesis *in vivo*

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Atherosclerosis is an inflammatory disorder of arteries, yet the immune system is complex and "inflammation" is a very non-specific term. B7-H1 is a co-stimulatory molecule of the B7 family which is usually expressed on antigen presenting cells and some cancers. B7-H1 modulates T cell response, in particular inhibiting Th1 response. To investigate the contribution of activated Th1 T cells in atherogenesis and therapeutic value of their regulation the human (h)B7-H1 gene was delivered using adeno-associated virus type 8 (AAV8). In *ex vivo* human cell experiments, delivery of hB7-H1 gene into dendritic cells resulted in T cell populations with the significant lower antigen-specific, MHC/HLA Class I-restricted Th1 cytotoxic T lymphocyte killing. AAV8/hB7-H1 was then tail vein injected into low density lipoprotein receptor knockout (LDLR KO) mice which were then placed on high cholesterol diet (HCD). hB7-H1 aortic expression was observed and resulted in lower atherosclerosis, displaying lower aortic systolic blood velocity, larger aortic cross-sectional area and thinner wall thickness than Neomycin resistance (Neo)-HCD gene-treated mice. Aortic levels of macrophage markers CD68 and ITGAM were lower in the hB7-H1-treated mice than Neo-treated controls by immuno-histochemistry, as was nitrotyrosine, a marker of reactive oxygen species. Markers of activated Th1 T cells, IFN-γ in the aorta and CD69 in the liver, were also significantly lower in hB7-H1-treated mice than Neo-treated controls by Q-PCR analysis. This is the first report of therapeutic B7-H1 gene delivery, these data suggest that activated Th1 T cells play a significant role in atherogenesis and suggest that B7-H1 gene delivery may be useful clinically to treat this disease.

Biography

Paul Hermonat received his Ph.D. from the University of Florida in 1984. There he mutationally mapped the genes of AAV and carried out the first AAV-based gene transfer experiments. Now at the University of Arkansas for Medical Sciences, he has 141 publications and has helped lay the foundation of knowledge on AAV molecular biology and its use in gene therapy. Presently he studies AAV-based gene therapy for treating cardiovascular disease and cancer, and studies the use of helper genes for AAV production.

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