American Society of Gene & Cell Therapy
Poster Presentation
May 13, 2020
5:30 p.m. ET

Role of Terminal Galactose In Cellular Uptake, Intracellular Trafficking, and Tissue Tropism Using Adeno-Associated Viruses Isolated From Human Stem Cells (AAVHSCs)

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AAVHSCs are a class of hematopoietic stem cell (HSC)-derived Clade F adeno-associated viruses (AAVs). AAVHSCs have been shown to transduce a variety of disease-relevant tissues. Here we report efforts to characterize their mechanism and kinetics of cellular entry. Many viruses bind glycosylated proteins or lipids on the cell surface for attachment and entry in order to invade the host cell. Thus far, AAV9 (Clade F) is the only AAV reported to bind galactose, making it unique among the AAVs that have been studied. Using mutant CHO cell lines expressing different terminal glycans, we now show that AAVHSCs also utilize terminal galactose as a primary receptor for efficient cellular binding and entry. By treating cells with neuraminidase, which exposes additional surface galactose, we were able to improve transduction efficiency with a self-complementary GFP vector by up to 100-fold. Increased expression correlated to an increase in total vector genomes and nuclear vector genomes. In this study, we sought to determine whether naturally occurring subtle mutations in capsid protein sequence can alter the binding affinity. Here we show that capsids containing the 505R residue in VP3 also possess differences in galactose binding and kinetics of nuclear accumulation following neuraminidase treatment. In addition, we identify that one of the naturally derived Clade F AAVs, AAVHSC16, does not bind to galactose in vitro and has reduced transduction efficiency in the liver *in vivo*. This study demonstrates that AAVHSC binding to surface galactose increases transduction efficiency, and that differences among the family of AAVHSCs demonstrate varying levels of tropism for the liver.