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Effective herpes simplex virus vector retargeting by combined engineering of three viral envelope glycoproteins gD, gB and gH

Joseph C. Glorioso

University of Pittsburgh School of Medicine, USA

Herpes simplex virus (HSV) vectors are promising agents for oncolytic virotherapy. Here we report the establishment of HSV retargeting systems that rely on the combination of three engineered viral glycoproteins, gD (receptor binding function), gB and gH (virus entry function). For virus retargeting to cells bearing tumorassociated antigens, such as the epidermal growth factor receptor (EGFR) or carcinoembryonic antigen (CEA), we mutated or deleted gD residues essential for binding to the natural entry receptors nectin-1a and the herpes virus entry receptor (HVEM). The natural receptor binding function was replaced by a single-chain antibody to provide alternate vector receptor recognition. Moreover, mutant forms of gB and gH were introduced into the vector backbone that facilitated virus infectivity and spread of retargeted receptors. One of the EGFR-retargeted viruses efficiently killed a panel of EGFR-expressing human tumor lines in vitro and reduced the growth of human tumors in nude mice. Toxicity experiments involving intracranial virus inoculation demonstrated symptom-free animal survival at a 100,000-fold higher dose than a dose of wild-type virus that is fatal. Our results show receptor specificity without marked loss of lytic activity and indicate the adaptability of our system to different targeting ligands Further development of this platform may provide a new generation of broadly applicable and effective oncolytic HSV vectors.

Biography

Dr. Glorioso was Professor of Microbiology and Immunology at the University of Michigan School of Medicine and Professor and Chair of the Dept of Microbiology and Molecular Genetics at the University of Pittsburgh School of Medicine. He was president of the American Society of Gene and Cell Therapy and founding Editor of the Journal Gene Therapy. He serves on the National Gene Vector Labs and Repository steering committee. He is best known for his research on the development of HSV gene vectors for the treatment of cancer, neurodegenerative diseases and chronic pain. He has published more than 350 peer reviewed papers and reviews.