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Using cystine knot proteins to retarget oncolytic measles virus for tumor-associated integrins

Sangeet Lal, Hong Ma and **CoreyRaffel**
University of California San Francisco, USA

Introduction: Modified measles virus (MV) is an effective oncolytic virus and is currently being investigated in clinical trials for various cancer types. An advantage of using MV is the ease of retargetingthe virus to a receptor of choice. We investigated the use of cystineknot proteins (CKP) to direct MV activity. CKP are short polypeptides that bind their targets with high affinity. A library of these proteins has been made, and a CKP that binds αvβ3 and αvβ5integrins with single digit nanomolar affinity has been isolated. We have used this CKP to target MV to the integrins.

Methods: MV genome was modified to express the integrin-binding CKP at the C-terminus of a mutated H protein that does not bind to its normal receptor CD46. We tested the virus for specificity to integrinsby assessing cell killing and MV replication *in vitro*.

Results: MV-CKP killed and replicated in glioblastoma, medulloblastoma,DIPG and breast cancer cells, which express the target integrins. The virus did not kill and did not replicate in cells in which αvintregrin expression was knocked down with anαv-integrin antisense lentivirus. MV-CKP activity was competitively blocked by echistatin, an integrin binding peptide. When the CKP was cleaved from the virus at an inserted protease site, virus activity was abrogated.

Conclusions: These results indicate that CKP can be used to selectively target MV. Because the integrins of interest are expressed by tumor cells and tumor-associated endothelium and because the CKP used has been shown to localize to tumor when injected IV, MV-CKP may be potentially effective as IV therapy, a major step forward in the use of MV. In addition, the CKP library can be screened for other targeted CKPs of interest. Importantly, the use of CKP to target viruses is applicable to many viruses other than MV.

Biography:

Sangeet Lal is a postdoctoral scholar in the lab of Corey Raffel at UCSF.He has createda modified oncolytic measles virus (MV) targeting tumor-specific receptors and is investigating the efficacy ofMV for the treatment of pediatric brain cancers using immune-competent murine models. At OHSU, he performed research of clinical interest showing that simultaneous expression of αv integrin and HER2, a tyrosine kinase receptor, is required for the invasion of Her2-positive breast cancer cells in brain microenvironment. The interaction between αv integrin and HER2 regulates the localization of HER2 on cell membrane.During Ph.D.,Sangeet studied the role of calpain2 protease in the invasion of glioblastoma tumor cellsand developed a novelin vivoorthotopicxenograftmodel of zebrafish tomonitor invasion of transplanted glioblastoma cells in the brain of living animals. Sangeet has published 6 papers with another 4 in peer-review or preparation stage and presented his research(oral and poster) at international meetings.His long-term goalis to develop as a notable scientist in the field of translational brain cancer research and therapy.