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A conditional cytotoxic anti-HIV gene therapy for selectable cell modification

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Gene therapy remains one of the potential strategies to achieve HIV cure. One of the major limitations of anti-HIV gene therapy is recovering adequate number of modified cells to generate an HIV proof immune system. Our study addresses this issue by developing a methodology that can mark conditional vector transformed cells for selection and subsequently target HIV infected cells for elimination via treatment with Ganciclovir (GCV). We utilized the HSV Thymidine Kinase (TK) mutant SR39 that is highly potent at killing cells at low GCV concentrations. This gene was cloned into a conditional HIV vector pNL-GFPRRESA that expresses the gene of interest as well as GFP in the presence of HIV Tat protein. We show here that TK-SR39 was more potent than TK-WT at eliminating infected cells at lower concentration of GCV. As the vector expresses GFP in the presence of Tat, transient expression of Tat either via tat RNA transfection or transduction via a non-integrating lentiviral (NIL) vector marked the cells with GFP for selection. In cells selected by this strategy, TK-SR39 was more potent at limiting virus replication than TK-WT. Finally, in Jurkat cells modified and selected with this approach, infection with CXCR4 tropic Lai virus could be suppressed via treatment with GCV. GCV treatment limited the number of HIV infected cells, virus production as well as virus induced cytopathic effects in this model. We provide proof of principle that TK-SR39 in a conditional HIV vector can provide a safe and effective anti-HIV strategy.

Biography

Anjali Joshi is an Assistant Professor in the Department of Biomedical Science at Texas Tech University Health Sciences Center. She pursued her PhD in Feline Immunodeficiency Virus from North Carolina State University, Raleigh. Immediately after completing her PhD, she received four years of Post-doctoral training at the National Cancer Institute, Frederick on Retrovirus Assembly and Release. Her research interests include virus assembly and release, HIV pathogenesis and anti-HIV gene therapy.

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