Pharmaceutically-controlled replication of adenoviruses in mesenchymal stem cell-based cell carriers improves oncolytic virotherapy for advanced human renal cell carcinoma

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Cell-based carriers were recently exploited as a tumor-targeting tool to improve systemic delivery of oncolytic viruses for cancer therapy. However, the slow clearance of carrier cells from normal organs indicates the need for a controllable system which allows viral delivery only when the carrier cells reach the tumor site. In this communication, we sought to develop a pharmaceutically-inducible cell-based oncolytic adenovirus delivery strategy for effective targeting and treatment of renal cell carcinoma (RCC), which is one of the most malignant tumor types with an unfavorable prognosis. Herein, we demonstrated the intrinsic tumor homing property of human bone marrow-derived mesenchymal stem cells (hMSCs) to specifically localize primary and metastatic RCC tumors after systemic administration in a clinically relevant orthotopic animal model. PDGF-AA secreted from RCC was identified as a chemoattractant responsible for the recruitment of hMSCs. Like endogenous osteocalcin whose barely detectable level of expression was dramatically induced by vitamin D_3, the silenced replication of human osteocalcin promoter-directed Ad-hOC-E1 oncolytic adenoviruses loaded in hMSCs was rapidly activated and the released viral progenies sequentially killed co-cultured RCC cells upon vitamin D_3 exposure. Moreover, systemic treatment of RCC tumor-bearing mice with Ad-hOC-E1-loaded hMSCs had very limited effect on tumor growth, but when it combined with vitamin D_3 treatment induced effective viral delivery to RCC tumors and significant tumor regression. Therapeutic effects of hMSC-based Ad-hOC-E1 delivery were confirmed to be significantly greater than those of injection of carrier-free Ad-hOC-E1. Our results presented the first pre-clinical demonstration of a novel controllable cell-based gene delivery strategy that combines the advantages of tumor tropism and vitamin D_3-regulatable human osteocalcin promoter-directed gene expression of hMSCs to improve oncolytic virotherapy for advanced RCC.