In vivo siRNA delivery to tumor cells and its application to cancer gene therapy

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RNA interference (RNAi) is a post-transcriptional gene silencing event in which short double-stranded RNA (siRNA) degrades target mRNA. Silencing oncogenes or other genes contributing to tumor progression by RNAi can be a therapeutic strategy for cancer. Delivery of RNAi effector to tumor cells is one of the key factors determining the efficacy, because the gene silencing is limited in cells reached by RNAi effector. In this study, we developed a tumor cell line stably expressing reporter genes to sensitively and quantitatively evaluate RNAi effect in tumor cells in vivo. Genetically labeled tumor cells were inoculated into the footpad or via the portal vein of mice to establish primary and metastatic tumor models, respectively. Intratumoral injection of either naked siRNA or naked short-hairpin RNA (shRNA)-expressing plasmid DNA followed by electroporation was effective in suppressing the expression of the target gene in tumor cells. Intravenous injection of naked RNAi effectors by the hydrodynamics-based procedure inhibited the gene expression in tumor cells colonizing in the liver. Then, shRNA-expressing plasmid DNA targeting β-catenin or hypoxia inducible factor-1α (HIF-1α) was delivered to tumor cells in order to inhibit tumor growth in vivo. In the primary tumor model, delivery of shRNA-expressing plasmid DNA targeting β-catenin or HIF-1α was effective in inhibiting tumor growth, whereas only shRNA-expressing pDNA targeting HIF-1α was effective in the hepatic metastasis model. We also found that HIF1 expression in liver cells is elevated by inoculation of tumor cells into the portal vein, and the silencing of the expression in normal liver cells is also effective in inhibiting tumor metastasis to the liver.