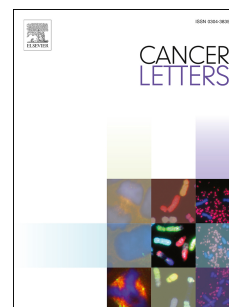


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Cancer-type organic anion transporting polypeptide 1B3 is a target for cancer suicide gene therapy using RNA *trans*-splicing technology

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Abstract

Cancer-type organic anion transporting polypeptide 1B3 (Ct-OATP1B3) has been identified as a cancer-specific transcript in various solid cancers, including colorectal cancer. Given its excellent cancer-specific expression profile, we hypothesized that Ct-OATP1B3 could represent a promising target for cancer-specific expression of the suicide gene, herpes simplex virus 1 thymidine kinase (HSV-*tk*), via a spliceosome-mediated RNA *trans*-splicing (SMaRT) approach. SMaRT technology used to recombine two RNA molecules to generate a chimeric transcript. In this study, we engineered an RNA *trans*-splicing molecule carrying a translation-defective HSV-*tk* sequence (RTM44), which was capable of inducing its own *trans*-splicing to the desired Ct-OATP1B3 pre-mRNA target. RTM44 expression in LS180 cells resulted in generation of Ct-OATP1B3/HSV-*tk* fusion mRNA. A functional translation start site contributed by the target pre-mRNA restored HSV-*tk* protein expression, rendering LS180 cells sensitive to ganciclovir treatment *in vitro* and in xenografted mice. The observed effects are ascribed to accurate and efficient *trans*-splicing, as they were absent in cells carrying a splicing-deficient mutant of RTM44. Collectively, our data highlights Ct-OATP1B3 as an ideal target for the HSV-*tk* SMaRT suicide system, which opens up new translational avenues for Ct-OATP1B3-targeted cancer therapy.

Keywords: Organic anion transporting polypeptide 1B3, spliceosome-mediated RNA *trans*-splicing, herpes simplex virus 1 thymidine kinase, colorectal cancer, suicide gene therapy

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