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Selective killing of virus-transduced or cancer cells using a RNA *trans*-splicing based suicide gene therapy approachz

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Statement of the Problem: Acquired and inherited genetic disorders are characterized by the cellular expression of aberrant transcripts and proteins. Viruses such as the human papillomaviruses (HPV) or the human immunodeficiency virus type 1 (HIV-1) integrate their DNA into the genome of the infected host cell and there is no way to get rid of the viral DNA anymore. Similarly, many cancers are characterized by oncogene expression.

Methodology & Theoretical Orientation: We explored a Herpes simplex virus thymidine kinase (HSVtk)/ganciclovir (GCV) suicide gene therapy approach for selective killing of virus-transduced or cancer cells. First we studied the highly efficient mechanism of *trans*-splicing among transcripts of the simian virus 40 (SV40). Then we employed molecular features of SV40 RNA *trans*-splicing and computational RNA structure design to improve both on-target activity and specificity of the *trans*-splicing RNA (tsRNA). As molecular targets we selected the-fetoprotein (AFP), a marker of hepatocellular carcinoma (HCC), human papillomavirus type 16 (HPV-16), or human immunodeficiency virus type 1 (HIV-1) pre-mRNA.

Findings: While unstructured mismatched target binding domains significantly improved 3' exon replacement, 5' exon replacement correlated with the thermodynamic stability of the tsRNA 3' end. Alternative on-target *trans*-splicing was found to be a prevalent event. The specificity of *trans*-splicing with the intended target splice site was improved 10-fold by designing tsRNA harbouring multiple target binding domains shielding alternative on-target and blinding non-target splicing events. Rationally designed tsRNAs efficiently and selectively triggered death of HPV-16, HIV-1 or AFP-positive cells. Dual-targeting tsRNA simultaneously targeting AFP and a second HCC biomarker triggered enhanced cell death at 10-fold lower GCV doses.

Conclusion & Significance: Our observations suggest RNA *trans*-splicing represents a promising approach to suicide gene therapy targeting viral infection, cancer or other diseases characterized by the expression of disease-specific pre-mRNA biomarkers.

Biography

Volker Patzel, chemist, received his Ph.D. from the Ruprecht Karls University in Heidelberg and his MBA from the Steinbeis University in Berlin. He worked as postdoc at the German Cancer Research Centre in Heidelberg and then as research group leader at the Max Planck Institute for Infection Biology in Berlin. Currently he holds a dual appointment as Assistant Professor at the National University of Singapore and Assistant Director of Research at the University of Cambridge. He is founder and director of the Steinbeis Transfer Centre for Nucleic Acids Design. His research focuses on the design and delivery of ribonucleic acids for enhancement, inhibition or repair of gene expression towards diagnostic and therapeutic applications.

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