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Abstract

Pioneering siRNA-Mediated Protection of Mammalian Cells against Zika Virus (MR-766) Infection †

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Abstract: Here, we present empirical data documenting the siRNA-mediated protection of cells after Zika virus (ZIKV) infection. siRNAs were designed to target well-conserved sequences across the ZIKV genome. Several delivery technologies were utilized. After the electroporation of 100 nM siRNA into human hepatocyte-derived carcinoma (Huh7) cells, the Feron Zv-2 sequence (specific to the ZIKV NS3 gene) yielded a cell viability of 150.3% ± 7.4% (SEM: n = 4) (p = 0.0004) relative to the cells treated only with the virus (33.9% ± 12%, SEM: n = 4). Furthermore, 100 nM siRNA Feron Zv-4 (specific to ZIKV 3'UTR) resulted in 119.1% ± 11.2% cell viability (SEM: n = 4) relative to the control cells treated with ZIKV (p = 0.0021). The cells were electroporated with siRNA prior to ZIKV infection and viability was monitored four days after this. Additionally, two novel siRNA delivery systems were tested. The first utilized recombinant *Bacillus anthracis* PA83 (octomer-forming mutants), co-incubated with the N-terminal 255 amino acids of *B. anthracis* lethal factor (LFn) fused in-frame with the RNA binding domain for human protein kinase R (LFn-PKR) at a concentration of 50 μg/mL (each). Here, baby hamster kidney (BHK) cells, treated with 100 nM siRNA Feron Zv-1, yielded 79.0% ± 4.0% viability relative to the control (50.2% ± 1.7%, SEM: n = 3) three days after exposure to ZIKV (p = 0.0096). Finally, HeLa exosomes loaded with siRNA Feron-Zv2 were incubated with Huh7 cells prior to ZIKV infection. For the siRNA-exosome treated cells, a viability of 123% ± 46% (SEM: n = 18), relative to 8% ± 16% (SEM: n = 18) for the same concentration of control HeLa exosomes, was recorded (p = 0.0416). In each instance, 0.3 moI was used and cell viability monitored using the Pierce™ Firefly Luciferase Glow Assay Kit by Thermo Scientific™. Here, we show for the first time that siRNA can significantly reduce ZIKV-induced cell killing. Future work will require quantitating ZIKV mRNA in relation to siRNA treatment, as well as testing the siRNAs and delivery systems within more complex models.

Keywords: Zika virus; siRNA; exosome; anthrax toxin