proceedings

Abstract

Rotaviruses as Neonatal Vaccine Expression Vectors against Other Enteric Pathogens †

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† Presented at Viruses 2020—Novel Concepts in Virology, Barcelona, Spain, 5–7 February 2020.

Published: 15 June 2020

Abstract: Although the incidence of rotavirus diarrheal disease has been reduced by the introduction of neonatal rotavirus vaccines, other enteric viruses—including norovirus, hepatitis E virus (HEV), and astrovirus—remain significant causes of illness. In this study, we investigated the possibility of generating recombinant rotaviruses that express the capsid proteins of other enteric viruses as an approach for creating neonatal multitarget vaccines. As a first step, we examined whether the segmented dsRNA genome of rotavirus could be engineered to express a separate foreign protein through the use of a 2A translational "self-cleavage" element. These attempts were successful, allowing for the recovery of recombinant rotaviruses with modified-segment-7 RNAs that contained a single open reading frame (ORF) encoding a NSP3-2A-fluorescent protein (FP) cassette. By varying the FP introduced into the cassette, genetically-stable rotaviruses were generated which grew efficiently and directed the robust expression of FP as an independent product (e.g., UnaG (green), mRuby (red), mKate (orange), TagBFP (blue), and (YFP) yellow). Subsequently, attempts were made to recover recombinant rotaviruses with modified-segment-7 RNAs that contained a single ORF encoding NSP3-2A fused to the capsid-protein gene of norovirus (VP1, P, or P2), HEV (ORF2), or astrovirus (VP70 or VP90). These attempts resulted in the generation of recombinant viruses that efficiently expressed capsid proteins of other enteric viruses, despite the required addition of up to 2.5 kB of foreign sequence to the 18.5 kB rotavirus genome. Our findings support the idea that rotaviruses can be engineered as plug-and-play expression vectors to create next-generation neonatal vaccines that can induce immunological protection against not only rotavirus, but other enteric pathogens also.

Keywords: rotavirus; reverse genetics; vaccines; enteric virus; expression vector