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Abstract

Identification of a Novel Yellow Fever Virus Cellular Restriction Factor †

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Abstract: Background: We previously identified a yellow fever virus (YFV) genome-derived, short noncoding RNA (vsRNA) generated during infection that targets the 3′ untranslated region (UTR) of a Src-kinase regulatory phosphatase (PTPRE), reducing PTPRE translation. By contrast, a related flavivirus (Zika) did not regulate PTPRE. We assessed the role of PTPRE in YFV and Zika replication. **Methods:** Human PTPRE with a β -Globulin 3′UTR to remove the 3′UTR sequence targeted by the YFV vsRNA was stably expressed in Jurkat and Huh7D cells using a tetracycline-regulated promoter. YFV (17D strain) and Zika (PR strain) were used to infect the different cell lines, and viral replication was measured by viral RNA and infectivity. Attempts to knock out PTPRE by CRISPR were unsuccessful, suggesting that PTPRE may be required for cell survival. **Results:** The expression of PTPRE with nontargeted 3′UTR led to a 100-fold reduction in infectious virus released from Jurkat and Huh7D cells by infectivity and a 3–10-fold reduction in viral RNA levels. Infectivity was restored in cells grown in doxycycline. By contrast, nontargeted PTPRE expression had no effect on the release of infectious Zika virus. PTPRE expression did not alter YFV attachment or entry. Despite reduced infectivity of the supernatant virus produced by PTPRE-nontargeted cells, YFV envelope content in culture supernatants was similar to that released by cells not expressing nontargeted PTPRE. Electron microscopy demonstrated large, empty-appearing viral particles in YFV-infected cells expressing nontargeted PTPRE that were not present in cells not expressing nontargeted PTPRE. **Conclusions:** PTPRE is a novel YFV restriction factor that appears to increase the proportion of defective YFV particles released into cell culture media, potentially by preventing YFV RNA encapsidation. PTPRE's effects on viral replication are not conserved among flaviviruses, as Zika replication was not altered by PTPRE overexpression. Understanding how PTPRE inhibits YFV may provide insight into YFV assembly and release and potentially help to identify novel drug targets.

Keywords: noncoding RNA; yellow fever virus; PTPRE; restriction factor