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Abstract

Yellow Fever Virus Vaccine Reduces T Cell Receptor Signaling and the Levels of Phosphatase PTPRE In Vivo †

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Abstract: Background: A Src kinase-activating phosphatase (PTPRE) is targeted by a genome-derived yellow fever virus (YFV) short noncoding RNA (vsRNA) in vitro. The vsRNA reduces PTPRE translation, which leads to reduced TCR signaling. vsRNA point mutations restore PTPRE expression and T cell function. We examined TCR signaling and PTPRE levels in individuals before and after YFV vaccination (YFVax). **Methods:** Fourteen individuals receiving YFVax ($10^{4.7–5.6}$) IM for travel prophylaxis provided written informed consent for these studies. Blood was obtained once before vaccination and four times after vaccination (days 3 to 28). Serum and PBMCs were purified and YFV was quantified by RNA and infectivity. PBMCs were assessed for activation following anti-CD3 stimulation by measuring phospho-tyrosine-394-Lck and IL-2 release. PBMC PTPRE levels were determined by immunoblot analyses (normalized to actin). A YFV-neutralizing antibody was determined by PRNT. **Results:** YFVax was administered alone (six out of 14 subjects) or in combination with other vaccines (eight out of 14). All subjects demonstrated reduced resting PBMC PTPRE levels and post-TCR stimulation had reduced IL-2 release between days 4 and 21 compared to pre- and day 28 samples. Phospho-Lck was reduced in all but two subjects on the same days, and both of these subjects also received an influenza vaccine. Low-level viremia was detected in 10/14 subjects, with infectious titers of 100/mL. Viremia was not detected in four out of 14 subjects. All recipients developed neutralizing antibodies by day 21. **Conclusion:** YFV vaccination regulates PBMC PTPRE levels 4–21 days after infection, despite the low to absent infectious YFV detected in serum, suggesting that enough YFV vsRNA is produced and released from cells to have a functional (and measurable) effect on T cell function. Studies are underway to determine if this is mediated by exosomes or defective particles containing the vsRNA that targets PTPRE. Furthermore, the association between PTPRE and TCR signaling confirms a role for PTPRE in TCR function.

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