

RESEARCH ARTICLE

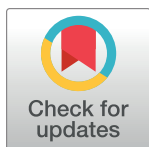
Porcine circovirus type 2 infection promotes the SUMOylation of nucleophosmin-1 to facilitate the viral circular single-stranded DNA replication

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Abstract

The mechanism of genome DNA replication in circular single-stranded DNA viruses is currently a mystery, except for the fact that it undergoes rolling-circle replication. Herein, we identified SUMOylated porcine nucleophosmin-1 (pNPM1), which is previously reported to be an interacting protein of the viral capsid protein, as a key regulator that promotes the genome DNA replication of porcine single-stranded DNA circovirus. Upon porcine circovirus type 2 (PCV2) infection, SUMO2/3 were recruited and conjugated with the K263 site of pNPM1's C-terminal domain to SUMOylate pNPM1, subsequently, the SUMOylated pNPM1 were translocated in nucleoli to promote the replication of PCV2 genome DNA. The mutation of the K263 site reduced the SUMOylation levels of pNPM1 and the nucleolar localization of pNPM1, resulting in a decrease in the level of PCV2 DNA replication. Meanwhile, the mutation of the K263 site prevented the interaction of pNPM1 with PCV2 DNA, but not the interaction of pNPM1 with PCV2 Cap. Mechanistically, PCV2 infection increased the expression levels of Ubc9, the only E2 enzyme involved in SUMOylation, through the Cap-mediated activation of ERK signaling. The upregulation of Ubc9 promoted the interaction between pNPM1 and TRIM24, a potential E3 ligase for SUMOylation, thereby facilitating the SUMOylation of pNPM1. The inhibition of ERK activation could significantly reduce the SUMOylation levels and the nucleolar localization of pNPM1, as well as the PCV2 DNA replication levels. These results provide new insights into the mechanism of circular single-stranded DNA virus replication and highlight NPM1 as a potential target for inhibiting PCV2 replication.