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Mechanism and functional studies on sumoylation of influenza A virus nucleoprotein

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Influenza A virus is a substantial threat to human health. During the replication cycle, viruses take advantage of host post-translational modifications for their own benefit. It was recently reported that influenza A virus proteins interact extensively with the host sumoylation system. Thereby, several viral proteins including NS1 had reported are sumoylated to facilitate viral replication. However, to what extent sumoylation is exploited by influenza A virus and the functional outcomes of viral sumoylation are not well understood. In our study, we found that influenza A virus nucleoprotein (NP)is a target of sumoylation in both NP-transfected cells and virus-infected cells at the two most N-terminal residues, lysine 4 and lysine 7 and that the sumoylation at lysine 7 of NP is highly conserved across different influenzaA subtypes and strains. The NP-sumoylation-defective virus, WSN-NPK4,7R virus, exhibited an early cytoplasmic localization of NP.The growth of the WSN-NPK4,7R virus was highly attenuated compared to that of WSN-WT virus. We evaluated whether members of the PIAS family, the best-characterized E3 ligases could function as an E3 ligase for NP. Among all PIAS homologs, over-expression of PIASxa had the strongest effect on NP sumoylation which resulted in an enhanced virus growth suggesting that PIASxa is the predominant E3 ligase for NP. Thus, sumoylation of influenza A virus NP is essential for intracellular trafficking of NP and for virus growth, illustrating sumoylation as a crucial strategy extensively exploited by influenza A virus for survival in the host.

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T cell mediated immunity to influenza virus infection requires integrated signals from the TGFb receptor and Smad4

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Influenza viruses are a leading cause of respiratory disease-associated morbidity and mortality. Although virus-specific CTLs can provide cross-protection between related viruses, eliciting memory populations with the properties that are required for immunity is a major challenge for vaccination. We have previously shown that optimal protection requires a combination of circulating memory CD8 T cells which use the bloodstream to move around the body, as well as tissue-resident memory CD8 T cells which mount rapid responses to reinfection by remaining near the site of inoculation. The signaling pathways that permit individual memory CD8 T cell subsets to adopt specialized characteristics are poorly defined. We are currently analyzing the molecular pathways that support memory CD8 T cell differentiation. Our data show that Smad4, a signaling-intermediate that acts downstream of the TGFβreceptor, plays an essential role during the differentiation of some circulating virus-specific memory CD8 T cells, while CD103+ tissue-resident memory CD8 T cells are Smad4-independent. Perturbation of these virus-specific CTL populations has important implications for long term immunity.

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