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Multiple functional domains and complexes of the two nonstructural proteins of human respiratory syncytial virus contribute to interferon suppression and cellular location

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Abstract: Human respiratory syncytial virus (RSV), a major cause of severe respiratory diseases, efficiently suppresses cellular innate immunity, represented by type I interferon (IFN), using its two unique nonstructural proteins, NS1 and NS2. In a search for their mechanism, NS1 was previously shown to decrease levels of TRAF3 and IKK?, whereas NS2 interacted with RIG-I and decreased TRAF3 and STAT2. Here, we report on the interaction, cellular localization, and functional domains of these two proteins. We show that recombinant NS1 and NS2, expressed in lung epithelial A549 cells, can form homo- as well as heteromers. Interestingly, when expressed alone, substantial amounts of NS1 and NS2 localized to the nuclei and to the mitochondria, respectively. However, when coexpressed with NS2, as in RSV infection, NS1 could be detected in the mitochondria as well, suggesting that the NS1-NS2 heteromer localizes to the mitochondria. The C-terminal tetrapeptide sequence, DLNP, common to both NS1 and NS2, was required for some functions, but not all, whereas only the NS1 N-terminal region was important for IKK? reduction. Finally, NS1 and NS2 both interacted specifically with host microtubule-associated protein 1B (MAP1B). The contribution of MAP1B in NS1 function was not tested, but in NS2 it was essential for STAT2 destruction, suggesting a role of the novel DLNP motif in protein-protein interaction and IFN suppression.