# Jordan University of Science and Technology

## Respiratory syncytial virus nonstructural proteins decrease levels of multiple members of the cellular interferon pathways

**Authors:** Swedan S, Musiyenko A, Barik S

**Abstract:** Viruses of the Paramyxoviridae family, such as the respiratory syncytial virus (RSV), suppress cellular innate immunity represented by type I interferon (IFN) for optimal growth in their hosts. The two unique nonstructural (NS) proteins, NS1 and NS2, of RSV suppress IFN synthesis, as well as IFN function, but their exact targets are still uncharacterized. Here, we investigate if either or both of the NS proteins affect the steady-state levels of key members of the IFN pathway. We found that both NS1 and NS2 decreased the levels of TRAF3, a strategic integrator of multiple IFN-inducing signals, although NS1 was more efficient. Only NS1 reduced IKKepsilon, a key protein kinase that specifically phosphorylates and activates IFN regulatory factor 3. Loss of the TRAF3 and IKKepsilon proteins appeared to involve a nonproteasomal mechanism. Interestingly, NS2 modestly increased IKKepsilon levels. In the IFN response pathway, NS2 decreased the levels of STAT2, the essential transcription factor for IFN-inducible antiviral genes. Preliminary mapping revealed that the C-terminal 10 residues of NS1 were essential for reducing IKKepsilon levels and the C-terminal 10 residues of NS2 were essential for increasing and reducing IKKepsilon and STAT2, respectively. In contrast, deletion of up to 20 residues of the C termini of NS1 and NS2 did not diminish their TRAF3-reducing activity. Coimmunoprecipitation studies revealed that NS1 and NS2 form a heterodimer. Clearly, the NS proteins of RSV, working individually and together, regulate key signaling molecules of both the IFN activation and response pathways.