

P005 Influenza A virus NS1 protein binds p85-beta and activates PI3K/Akt signalling

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Influenza A viruses are globally important human and animal respiratory pathogens that are responsible for both seasonal 'flu' outbreaks, and periodic world-wide pandemics. The multifunctional NS1 protein of influenza A is widely regarded as a virulence factor, and contributes significantly to disease pathogenesis by modulating a number of host-cell processes. Here, we report that NS1 binds directly to the p85-beta regulatory subunit of phosphatidylinositol-3-kinase (PI3K), but not to the related p85-alpha subunit. Activation of PI3K in influenza virus-infected cells was dependent upon genome replication, and showed kinetics that correlated with NS1 expression. Additionally, it was found that expression of NS1 alone was sufficient to constitutively activate PI3K, causing the phosphorylation of a downstream mediator of PI3K signal transduction, Akt. Mutational analysis of a potential SH2-binding motif within NS1 indicated that the highly conserved tyrosine at residue 89 is important for both the interaction with p85-beta, and the activation of PI3K/Akt. A mutant influenza A virus expressing NS1 with the Y89F amino-acid substitution exhibited a small-plaque phenotype, and grew more slowly in tissue culture than wild-type virus. These data suggest that activation of PI3K/Akt signalling in influenza A virus-infected cells is important for efficient virus replication.