ID der Kurzfassung : **50**

IAV-NS1 inhibits global transcription of the host cell and is associated with nuclear Chromatin/DNA

Inhalt

To study the function of NS1 independent of an IAV infection, we expressed a NS1 estrogen receptor (ERT) fusion-protein that is inducible by tamoxifen. Incubation of NS1ERT expressing cells with tamoxifen at least partially complements the attenuated replication of IAVs lacking NS1 suggesting that a functionally active NS1 is induced. Addition of tamoxifen to cells expressing NS1ERT from diverse IAV subtypes (apart from IAV Puerto Rico/8/34) induces a cytopathic phenotype, the activation of JNK and apoptosis. A NS1 deletion mutant demonstrates that apoptosis induction is solely a function of the C-terminal effector domain of NS1. The transfection of reporter constructs indicates that NS1 inhibits the expression host genes. The analysis of nascent RNA by click-it chemistry shows that upon 4-hydroxy-tamoxifen (OHT) addition to NSERT expressing cells global transcription is attenuated, most efficiently by the C-terminal domain of NS1 alone suggesting that transcriptional inhibition lastly leads to apoptosis in tamoxifen induced, NS1ERT expressing cells. We further show that NS1 is closely associated with the chromatin fraction of the host nucleus. Nuclear localization of NS1 is independent of its interaction with CPSF4. Overexpression of CPSF4 suggests that it counteracts the inhibition of expression by NS1. We speculate that NS1 association to host chromatin enables NS1 to interact with CPSF4 which results in global transcriptional inhibition of host genes.

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