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Meeting abstract

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Capability of the viral NS1 proteins to bind to the cellular adaptor proteins Crk and CrkL determines sensitivity of influenza viruses to Crk/CrkL expression

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The non-structural protein 1 (A/NS1) of influenza A viruses harbors several src homology domain (SH)-binding motifs that are required for interaction with cellular proteins, such as the p85 beta subunit of PI3-kinase. Besides the A/NS1 interaction with p85 beta it could be shown, that the SH3-binding motif 2 (aa 212–217 [PPLPPK]) within A/NS1 is essential for binding to the cellular adaptor proteins Crk and CrkL. Both regulate diverse pathways in the cell including activation of the MAP kinase JNK, that was previously shown by us to mediate antiviral responses [1,2]. To elucidate Crk/CrkL functions in the infected cell we knocked-down expression of the adaptor proteins by a siRNA approach. We could demonstrate that only those influenza A viruses that encode a A/NS1-protein harboring the Crk/CrkL SH3-binding motif 2 PPLPPK are attenuated upon downregulation of Crk/CrkL. It could also be observed that the PPLPPK site-harboring candidate strains exhibit a stronger viral activation of the JNK/ATF-2 signaling module compared to other strains and that knock-down of the adaptor proteins resulted in an even stronger activation of this virus-induced antiviral acting pathway. Consistent with this observation, overexpression of Crk or CrkL resulted in a reduced virus-induced JNK activation. Further analysis revealed that the localization of the A/NS1 is altered in Crk overexpressing cells and that the CrkL-phosphorylation pattern is changed upon binding to A/NS1. The data so far suggest that A/NS1 binding to Crk or CrkL contributes to the suppression of the antiviral acting JNK/-ATF-2 pathway. The Crk/CrkL binding capability may have only evolved in virus strains that over-induce this antiviral signaling module to suppress its detrimental action.

References

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