Cell Communication and Signaling BioMed Central

Meeting abstract

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Influenza A viruses induce PI3-kinase activation by two interdependent mechanisms late in the infection cycle

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from 12th Joint Meeting of the Signal Transduction Society (STS). Signal Transduction: Receptors, Mediators and Genes
Weimar, Germany. 29–31 October 2008

Published: 26 February 2009

Cell Communication and Signaling 2009, **7**(Suppl 1):A43 doi:10.1186/1478-811X-7-S1-A43

This abstract is available from: http://www.biosignaling.com/content/7/S1/A43

We have previously shown that the cellular PI3K/Akt pathway is strongly activated upon influenza A virus infection in later stages of the infection cycle and that this activation was dependent on the expression of the viral non-structural protein 1 (A/NS1) [1]. Later it was demonstrated by us and others that activation occurs upon direct interaction of the A/NS1 to the regulatory subunits of PI3K, p85 alpha and beta [2,3]. Several reports proposed that two src homology (SH)-binding motifs within A/NS1 (aa 89 [YXXXM] (SH2-binding motif) and aa 164–167 [PXXP] (SH3-binding motif 1)) may mediate binding to p85 beta. Our work confirms that tyrosine 89 within the A/NS1 is required for the interaction of A/NS1 with p85 beta, subsequent PI3K-activation. However, mutant viruses that carry a phenylalanine instead of the tyrosine at position 89 of the NS1 only showed marginal differences to wt viruses with regard to their replication fitness. More detailed analysis revealed that both, wt type and mutant viruses induced similar PI3K activation levels late in infection, suggesting that besides expression of the NS1 there are alternative virus-induced mechanisms to activate the kinase. Here we demonstrate that this additional inducer is viral 5'triphosphate RNA that accumulates late in the infection cycle. Thus, PI3K activity is regulated by a NS1 protein-dependent as well as a vRNA-dependent mechanism, presumably via the RIG-I sensory pathway. Since NS1 is also a negative regulator of RIG-I, we suggest that influenza viruses have developed multiple mechanisms to achieve a well-balanced PI3K activation at later phases of the infection cycle.

References

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