The Role of Phosphodiesterase 3A in Influenza Virus Disease Severity and Viral Replication

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Background/Objective
Cyclic nucleotide phosphodiesterases (PDEs) are key regulators of many physiological processes by modulating the cellular cAMP/cGMP level. Recent evidence showed that various PDEs play a role in the pathogenesis of viral infection. In this study, we sought to investigate the association between severe 2009 pandemic influenza virus (A[H1N1]pdm09 virus) infection and PDE3A genetic polymorphisms, and assess the effect of PDE3A on viral replication.

Method
In the first part of the study, 121 single nucleotide polymorphisms (SNPs) related to PDE genes were compared between 42 patients with severe and 42 patients with mild A(H1N1)pdm09 virus infection who were matched for age, sex and underlying risk factors of infection. In the second part of the study, the effect of PDE3A on the growth kinetics of A(H1N1)pdm09 virus was assessed using siRNA knockdown of PDE3A in human alveolar basal epithelial A549 cells.

Result
Three SNPs related to PDE3A gene were significantly associated with severe A(H1N1)pdm09 virus infection with a P value of <0.001 (rs7314545-T [odds ratio=16.6; P=4.36x10-4], rs6487131-T [odds ratio=16.6; P=4.36x10-4], rs6487132-G [odds ratio=15.64; P=6.77x10-4]. In vitro viral replication study showed that siRNA-mediated knockdown of PDE3A expression in A549 cells significantly enhanced the replication of A(H1N1)pdm09 virus. At 24 hour post infection, the viral titers in the PDE3A knockdown A549 cells were significantly higher than those of A549 cells without PDE3A knockdown (mean viral titer: 4922 [SEM= 321] vs 1978 [SEM= 163] PFU/ml; P=2.32x10-6).

Conclusion
Genetic variations of PDE3A are associated with disease severity of A(H1N1)pdm09 virus infection. Reducing the expression of PDE3A enhanced the replication of A(H1N1)pdm09 virus in vitro.