

**SPHINGOSINE 1-PHOSPHATE-METABOLIZING ENZYMES CONTROL
INFLUENZA VIRUS AMPLIFICATION AND THE VIRAL CYTO-
PATHOGENICITY**

Young-Jin Seo (Postdoctoral Fellow)

(Bumsuk Hahm, PhD)

Celeste Blake

School of Medicine, Departments of Surgery and
Molecular Microbiology & Immunology

Stephen Alexander, PhD

College of Arts and Science, Division of Biological Sciences

Sphingosine 1-phosphate (S1P) is regulated by cellular catalytic enzymes and has diverse biological functions. However, the effects that S1P-catalyzing enzymes have on host defense and immunity to invading viruses remain unknown. In this study, we investigated the role of S1P-metabolizing enzymes in modulating cellular responses to influenza virus infection. Over-expression of S1P lyase (SPL), which induces degradation of S1P on cells (SPL-cells), interfered with the propagation of influenza virus. Accordingly, SPL-cells were much more resistant to the cytopathic effects caused by influenza virus infection than the control cells. SPL-mediated inhibition of cellular death was supported by impairment of the upregulation of a pro-apoptotic protein Bax, a critical factor for influenza viral cyto-pathogenicity. Importantly, the virus-infected SPL-cells induced early activation of STAT1 and STAT2 that are representative proteins for the anti-viral type I IFN signaling. These results suggest that SPL suppresses influenza virus replication via rapid activation of host innate immunity. In contrast to the SPL, the over-expression of S1P-producing sphingosine kinase 1 heightened the cells' susceptibility to influenza viral infection with suppressed STAT1 activation, representing opposed enzymatic activity. These findings suggest that the modulation of S1P-metabolizing enzymes is crucial for controlling host innate immunity and resultant host defense against influenza viral infection. Thus, S1P-metabolizing enzymes are novel potential targets to treat diseases caused by influenza virus infection.