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Nuclear Transport Machinery: from Viral pathogenesis to Antiviral Response

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Nuclear export of mRNAs is a central step in eukaryotic gene expression and is highly regulated by viruses and interferons (IFN). Viruses subvert host cell mechanisms to favor their replication and in the process reveal key steps in host pathways that are critical points for regulating antiviral responses. Influenza A virus, through its NS1 protein, and vesicular stomatitis virus (VSV), through its M protein, each inhibit mRNA nuclear export, down-regulating host gene expression and antiviral responses. Based on the knowledge of NS1 functions in the nucleus as an inhibitor of gene expression, we performed a high throughput screen (HTS) of 200,000 synthetic compounds. We identified novel small molecules that significantly reverted the mRNA export block induced by influenza virus infection and that also inhibited influenza virus replication and cytotoxicity. Among the most potent compounds was a member of the napthalimide family that targeted a specific host factor not previously known to have functions in antiviral response and nucleocytoplasmic trafficking. Since this naphthalimide targeted the host antiviral response and not the virus, it was also effective in inhibiting VSV and Vaccinia Virus replication, which are evolutionary diverse viruses. Thus, this chemical genetics approach led to the identification of novel antiviral factors and of a small molecule that has broad antiviral activity.

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