School of Medicine
and Public Health
UNIVERSITY OF WISCONSIN–MADISON

Hijacking host kinases to regulate the balance between mRNA & genomic RNA synthesis during influenza virus infection

Arindam Mondal, PhD

Department of Medical Microbiology & Immunology,
University of Wisconsin Madison

11th August 2016, 3:00pm

Influenza virus infections cause one of the most widely spread diseases, resulting in significant health and economic burdens to the world population on an annual basis. These viruses assemble their RNA synthesis machinery in the form of ribonucleoprotein (RNP) complexes that contain negative-sense genomic RNA enwrapped by oligomers of viral nucleoprotein (NP), and the heterotrimeric RNA polymerase (see Figure). RNPs from incoming virions first produce viral mRNAs early in infection, followed by a subsequent transition that drives genome replication through synthesizing additional RNPs. Proper regulation of RNP function between these processes is imperative for successful infection, but the signal(s) that triggers these transitions is poorly understood. Moreover, understanding these crucial regulatory events is key to developing new antiviral strategies. My work demonstrated that the viral RNP is regulated by phosphorylation. Specifically, the influenza polymerase hijacks human protein kinase C (PKC)-δ to control RNP assembly and coordinate the transition from transcription to replication. Polymerase-associated PKCδ phosphorylates NP at its homotypic interface, controlling its assembly into oligomeric NP-RNA complexes within RNPs. CRISPR/Cas9-mediated knockout of PKCδ in human lung cells decreases NP phosphorylation as determined by quantitative mass spectrometric analysis. Formation of nascent RNPs is essential for genome replication, and my results show that knockout of PKCδ selectively decreases genome replication, but does not affect primary transcription from pre-formed RNPs. Furthermore, replication of multiple virus strains is severely impaired in the absence of PKCδ. Together, these data demonstrate that influenza virus exploits host PKCs to regulate the balance between transcription and replication to ensure proper progression through the viral life cycle. Building on these findings, I will present potential strategies to target this virus-host interaction to develop novel anti-viral therapies and expand these observations to create a universal phospho-regulatory scheme for the larger family of RNA viruses.

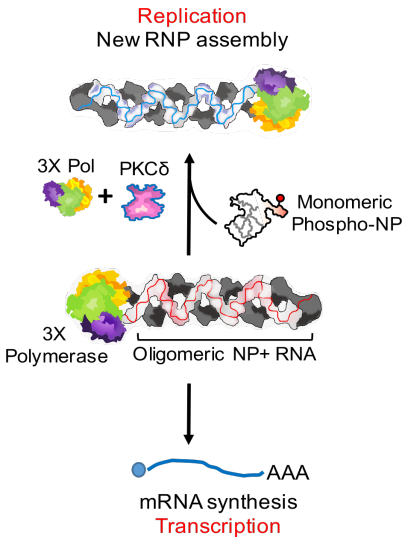

Figure legend: RNP associated polymerase performs transcription, whereas free polymerase performs replication with continuous assembly of monomeric NP into the new RNPs. Free polymerase associated PKCδ regulates NP oligomerization and RNP formation.