Catching the flu: control of host range and pathogenesis by the influenza virus replication machinery

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Friday, February 27
2:15PM
1400 Centennial Hall

Abstract
During viral infection, a struggle exists between cells, which contain anti-viral factors that selectively target and inhibit viral proteins and nucleic acids, and viruses, which neutralize these inhibitors and co-opt other cellular factors important for replication. My lab studies this battle during influenza virus infection. We focus on the influenza virus polymerase, the heart of the viral replication machinery. The polymerase is essential for viral replication mediating transcription of viral genes and replication of the viral genome. The polymerase is also a major determinant of the pathogenic potential of emerging influenza viruses and a key regulator of cross-species transmission as viruses move from birds into humans. In general, polymerases derived from avian viral isolates function very poorly in human cells, although the mechanism of this restriction is not known. Our data suggest that this restriction is caused by a potent and selective inhibitor in humans that disables avian-derived polymerases. We have characterized strategies used by the virus, including seasonal influenza viruses and the 2009 H1N1 pandemic virus, to escape this inhibitor and adapt to replication in human cells. In addition, we have identified new approaches that the virus might exploit. Ongoing work in the lab uses biochemical, structural and genetic techniques to identify the viral and host factors that control polymerase function, with a particular emphasis on those that regulate cross-species transmission. Ultimately, it is hoped that our work will help predict, and possibly prevent, the cross-species transmission of influenza virus and provide new avenues for the development of antiviral therapies.