ChemBio Seminar Series

Thursday, February 8, 2018, 12:30 pm
Seaver Science Library, Room 150
SSC Auditorium next to the library

Professor Matt Shoulders

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Viral Evolution, the 1918 Spanish Flu, and the Chemical Biology of Proteostasis

Rapidly evolving viruses are renowned for their ability to hijack an array of host cell mechanisms to assist their replication. Beyond transcriptional, translational, and trafficking pathways, these viruses also co-opt host chaperones to assist viral protein folding. We recently reported that these host proteostasis mechanisms are an important force that shapes the mutational trajectories accessible to an evolving influenza population, and that they help to define the pace of viral evolution. The discovery was made possible by a suite of custom-designed chemical genetic methods that allow user-defined control of cellular protein folding mechanisms. We have since used deep mutational scanning on influenza nucleoprotein to systematically and quantitatively evaluate the roles of host chaperones and the heat shock response in defining the fitness of $>10^6$ possible nucleoprotein sequences. We find that the depletion of a select suite of host chaperones using a custom-designed HSF1 inhibitor has striking effects on nucleoprotein mutational fitness at restrictive temperatures that mimic fever, whereas HSF1 inhibition has no effects at permissive temperatures. Of particular note, host chaperone depletion very strongly reduces the fitness of Pro283 in influenza nucleoprotein. Pro283 is a critical nucleoprotein variant that catalyzed the 1918 Flu pandemic by assisting escape from the human MxA viral restriction factor. Our data indicate that specific host chaperones are essential to compensate for the poor protein folding properties of the Pro283 nucleoprotein variant. We conclude that immune escape by the 1918 Spanish Flu relied critically on the activity of host chaperones. The connection between host proteostasis and escape from innate immunity mechanisms has potentially important implications for relevant issues including viral host-switching, vaccine development, and the design of improved antiviral therapeutic strategies.

Hosted by Professor Matthew Pratt

The scientific community is invited