Tata Institute of Fundamental Research
Survey No. 36/P, Gopanpally Village, Serilingampally, Ranga Reddy Dist., Hyderabad – 500 046

Seminar

Vaccinia Virus as a Model for Phosphotyrosine Signalling

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Vaccinia virus exiting from host cells activates Src/Abl kinases to phosphorylate A36, an integral membrane viral protein with an unstructured intracellular region. Phosphorylated tyrosine motifs in A36 bind the SH2-SH3 adaptors Nck and Grb2, which locally activates Arp2/3-driven actin polymerisation via N-WASP. This drives the motility of the virus and boosts viral spread. The Vaccinia network strongly resembles signalling events in human physiology such as those activated by growth factors and immune receptors. We demonstrate that the organisation of phosphotyrosine signalling motifs in unstructured regions of A36, is critical for the downstream output of virus motility and spread. By replacing A36 with p14 from the unrelated Orthoreovirus, we highlight the importance of motif positioning in divergent proteins. This work shows that multivalent signalling complexes do not operate by stochastic assembly of components but instead involve well-defined spatial constraints. Further, we used fluorescent molecule counting approaches in live cells to quantify absolute numbers of viral and host proteins at the Vaccinia signalling site. This approach reveals that the number of A36 molecules in the viral membrane is not fixed but varies with host cell type. Secondly, the speed of Vaccinia virus motility is not determined merely by the levels of the Arp2/3 activator N-WASP, but the numbers of Nck molecules at the site play a critical role. Collectively, these results illustrate the power of Vaccinia virus as a model to understand phosphotyrosine signalling. In the future, I plan to harness this tool to investigate functional roles of tyrosine phosphatases.

Monday, Mar 20th 2023

4:00 PM (Tea / Coffee 3.45 PM)

Auditorium, TIFR-H