

Understanding Virus-Host Interactions

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Viruses have been long known to exploit host cellular factors to facilitate various steps of their replication cycle. While viruses like HIV have available, although expensive therapies, others like Influenza virus are rapidly developing drug-resistance and yet others like the *Filoviridae* family of Ebola and Marburg viruses, have no effective drugs or licensed vaccines currently available. My primary research interest is to understand the interactions of such globally dangerous viruses with their host cells and design effective strategies to block these interactions.

Using dendritic cells from wild type and TAM triple knockout mice, our studies have uncovered a novel mechanism by which viruses can engage and activate a family of receptor tyrosine kinases called the TAM (**T**yro3, **A**xl and **M**er) family to inhibit Interferon-alpha 4, Interferon-beta, Tumor Necrosis Factor-alpha and Interferon regulatory factors 3, 5 and 7 (IRF-3, 5, and 7). Furthermore, viruses also engage TAM receptors to induce suppressors of cytokine signaling proteins 1 and 3 (SOCS1 and 3). Taken together, these factors are all major components of the cellular Type I Interferon response. Also, Immunoblotting analysis revealed that virions coated with TAM ligands trigger TAM receptor autophosphorylation and hyperactivation, suggesting that viruses activate TAM receptors during entry. Since the Type I Interferon response is the most potent cellular innate immune response against viral infections, our results demonstrate how viruses can evade this major cellular defense mechanism to facilitate their replication cycle. Therefore, our studies offer an exciting new possibility of using TAM kinase inhibitors to block viral infection by restoring the cellular Type I interferon response against these viruses.

Additionally, using multiple approaches in the form of chemical inhibitors, dominant-negative proteins and RNAi, we have also examined the role of the clathrin endocytic pathway in Ebola and Marburg glycoprotein (GP) mediated viral entry. To monitor virus infection, we employed reporter viruses encoding either the green fluorescent protein (GFP) or the Renilla luciferase gene and expression of these genes was examined as a marker for viral entry. These studies have revealed an important role for the clathrin endocytic pathway in filovirus GP mediated entry and have shown that Ebola and Marburg GP have differential requirements for key components of this pathway. Furthermore, our studies have uncovered a novel beta-arrestin 1 (ARRB1) and adaptor-related protein complex 1 (AP-1) dependent pathway in the clathrin-mediated entry of Influenza virus. Our results also indicate that the requirements for Marburg GP mediated entry are strikingly similar to Influenza virus entry suggesting that further characterization of the ARRB1 and AP-1 dependent clathrin pathway could reveal a major pathogen entry mechanism.