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Proteomic approaches for identification of critical host responses to infectious pathogens

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Abstract

We have employed different proteomic approaches to begin an elucidation of host signaling events that occur during infection with pathogenic agents. Using complimentary analytical approaches, we performed a detailed proteomic profiling of purified virions of the hemorrhagic fever virus Rift Valley fever virus (RVFV), followed by functional characterization of select hits. The virion-associated host protein complement was thoroughly examined by coupling the Gel LC/MS/MS approach with an alternative technique that preserves protein complexes and has been traditionally used to investigate mitochondria. Over 300 host proteins and multiple macromolecular complexes were identified. Host chaperones were among the over-represented protein families, and siRNA gene silencing and small molecule inhibitors identified several of them as essential viral host factors. Inhibitor time-of-addition studies and real-time analysis of inhibitor effects on intracellular virus demonstrated a role for specific HSPs during the viral replication phase. As some of the inhibitors tested have already completed phase II clinical trials for cancer treatment, the potential of repurposing them to treat RVF is highly appealing. We have also applied a Reverse Phase Protein Microarray (RPMA) platform to studies of host signaling events during infection with *Yersinia pestis*. In order to obtain a an overall picture of host signaling network connections and changes, multiple MOIs, host cell types, and times post infection were compared using 132 validated antibodies that target a variety of signaling pathways. These studies highlight the utility of different proteomic approaches for identifying critical host factors during infectious diseases in order to devise novel therapeutic strategies.

Biography

Hakami completed his Ph.D. in Biochemistry in the laboratory of the Nobel Laureate Professor Har Gobind Khorana at the Massachusetts Institute of Technology. He was then awarded a NRSA fellowship from NIH to complete postdoctoral training at Harvard Medical School and subsequently completed a postdoctoral fellowship at the National Human Genome Research Institute. He is a faculty member at the School of Systems Biology and the National Center for Biodefense and Infectious Diseases at George Mason University. He has published more than 20 peer-reviewed research articles in reputed journals.