COMBATTING FUTURE BIOLOGICAL THREATS – HOST-DIRECTED INTERVENTIONS TO EMERGING THREATS FOR RAPID RESPONSE

Identifying Host Responses To Predict Viral Pathogenesis And To Uncover Molecular Targets For Medical Countermeasures

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Infectious diseases threaten military readiness, operational success, and troop morale. Military troops often operate in environments with increased risk of exposure to emerging, vector borne, and exotic diseases. Advances in genetic engineering and accessibility of bioengineering tools also increases the risk of exposure to intentionally designed pathogens. At present we lack the ability to predict and treat the effects of novel agents based on genome sequence alone, and the potential for essentially infinite variation in genome sequence through evolution or deliberate manipulation makes such predictions even more daunting.
In contrast to microbial variability, the human host has a large but finite number of ways it can respond during infection. Because disease sequelae are predicated by the timing, quality, and magnitude of the host response, we hypothesize that if we can characterize molecular host responses to a sufficient number of pathogens, we can define patterns of response that will allow us to make predictions about a novel threat agent based on the host response it generates. By comparing, for example, host responses to agents that cause severe respiratory disease versus those that cause mild disease, we can build tools to recognize and effectively respond when a new respiratory pathogen presents a severe threat.

Toward this objective and to develop a new method for detecting host responses, we analyzed samples from human primary lung cultures infected with SARS-CoV-2 and two strains of measles viruses. Proteomic data was generated using liquid chromatography mass spectrometry, and transcriptomics was performed using RNA-sequencing. Network topological analysis revealed molecular pathways, genes, and proteins differentially perturbed during infection compared to mock-infected cultures. A significant feature of this work is that one set of samples was processed using a conventional approach that does not separate infected and uninfected cells in samples, while a second set was processed by separating infected and bystander cells (uninfected cells in the virus-exposed cultures) by flow cytometry prior to analysis. This work leveraged PNNL's capabilities in nanoscale quantitative proteomics, enabling analysis of small biomass samples. Our approach not only substantially increased the omics signals in the infected cells (by decreasing background noise from uninfected cells), but it also allowed us to independently analyze the bystander population. Our data revealed molecules that are uniquely induced or repressed in bystanders as compared to infected and mock-infected cells. Differentially regulated pathways included those involved in host defense responses to virus, with molecules identified to make cells less permissive to infection.

Our work demonstrates differential expression of molecular features from host responses during infection with three respiratory viruses and demonstrates the value of independently analyzing infected versus uninfected cells. These methods could be used to build models for predicting pathogenesis and for making informed decisions about potential medical countermeasures to novel agents. Moreover, our results reveal differential host responses between bystander and infected cells that will be valuable towards developing medical countermeasures that could stimulate antiviral host responses prior to exposure or early during infection.

We would like to thank the University of Washington Department of Comparative Medicine for access to laboratory facilities and for outstanding support of our work. This research was sponsored by The Defense Threat Reduction Agency under Department of Energy (DOE) Contract Number DE-AC05 -76RL01830 for the management and operation of the Pacific Northwest National Laboratory (PNNL). Part of the research was performed using the Environmental Molecular Sciences Laboratory (EMSL), a national scientific user facility sponsored by the DOE's Office of Biological and Environmental Research and located at PNNL.