DEVELOPMENT OF IMMUNE MICROPHYSIOLOGICAL SYSTEMS (IMMUNE SYSTEMS ON A CHIP) FOR MCM TESTING

Applying Machine Learning To Human Microphysiological Systems To Predict Infection And Virulence For New And Emerging Viruses

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DOD personnel are at high risk of exposure to new, emerging and re-emerging viruses for which there are no treatments. Deciphering the interplay between viruses and cells is crucial for the development of new antiviral strategies, particularly for those that target host responses. Traditional in vitro and animal models provide valuable insight into virus-host dynamics, yet they often fail to recapitulate human responses and have proven unreliable in predicting human outcomes. To characterize human tissue responses to infection with greater fidelity, we developed three-dimensional human microphysiological systems (MPS) consisting of primary tissue-specific epithelial cells, tissue-specific stromal cells and vascularized endothelia. Incorporation of epithelial, stromal, and endothelial cell types enhances phenotypic maturation and allow for the study of multicellular responses to infection. After validating the integrity of MPS using functional and molecular methods, acute responses of upper airway, skin, and buccal MPS were evaluated after infection by more than 50 different viruses from 13 respiratory and skin virus families. Time-dependent and dose-dependent responses to infection were characterized using multiomics analyses, biochemical assays, functional assays and whole-mount confocal imaging. Our findings reveal reproducible tissue-specific and virus-specific patterns of host responses to infection. These data reflect the innate antiviral responses that ultimately lead to immune cell activation, providing novel information that cannot be measured in human or animal models. In addition to performing basic bioinformatics comparisons among these data, AI/ML is being applied to discover biomarkers that are predictive of infection and virulence. The initial results are highly promising, identifying constellations of early biomarkers that (a) are signature of viral infection; (b) distinguish among virus types; and (c) discriminate between highly virulent and low virulent strains of the same virus. Our findings underscore the power of combining AI / ML with human MPS in unraveling the complexity of cellular antiviral responses in a tissue-specific context. We anticipate that this approach will provide the basis for an ecosystem of new technologies designed to rapidly identify and assess the virulence of new viral threat agents. In follow-on studies, we will explore the potential of the MPS platform to develop broad-spectrum, host-targeted antiviral therapies, provide novel diagnostics of infection, test the efficacy of medical countermeasures, and evaluate host responses to other pathogens.