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

NRF2 Signaling As A Central, Broad-spectrum Host Defense And Response Strategy Against (re)emerging Viral Pathogens

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The warfighter and civilian population face significant challenges from (re)emerging viral pathogens and associated variants in which available countermeasures are either non-existent or suboptimal at best. In the context of newly emerging and or future viral threats, there exists a critical need for the development of a multi-layered, host-directed and agent agnostic response strategy which enables preparedness and rapid responsiveness against biological threats of unknown origins. In this regard, an important strategic readiness strategy includes identifying key host factors that exhibit critical antiviral functionalities across a broad spectrum of acutely infectious viruses. One such key host factor is the nuclear factor erythroid 2-related factor 2 (NRF2) transcription factor which is primarily known for regulating genes that contain Antioxidant Response Elements (ARE) in response to oxidative stress. In recent years however, NRF2 regulated pathways have been well-documented to be involved in the context of several acutely infectious viral agents including but not limited to Dengue virus (DENV), Zika virus (ZIKV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and influenza A virus (IAV). NRF2 has further been implicated in the modulation of the innate immune response through a variety of different mechanisms including the regulation of the nuclear factor kappa B (NF-kB) and type I interferon response pathways. Thus, NRF2 stands as a potential host-directed target for an agent agnostic strategy that can provide multiple layers of protection to the warfighter through both antiviral and anti-inflammatory mechanisms. Our ongoing research with the FDA-approved small molecule NRF2 activator Omaveloxolone (OMA) has demonstrated the ability of OMA to exert a significant and broadly effective therapeutic effect under alphavirus, bunyavirus, and flavivirus infection. OMA treatment has been shown to differentially regulate several host signaling events as identified by both proteomics and transcriptomic studies in the context of infected endothelial cells. Further studies on NRF2 depletion during alphavirus infection have demonstrated that the silencing of NRF2 results in increased viral loads. These outcomes have led us to hypothesize that NRF2 signaling plays a critical role in the maintenance of endothelial integrity and function across a variety multiple acutely infectious viruses. Thus, the maintenance of NRF2 functionality potentially offers a broad-spectrum and layered defense against newly (re)emerging pathogens. Current studies involve the analysis of transcriptomic changes that occur during alphavirus infection of human brain microvascular endothelial cells (HBMECs) as well as bunyavirus infection of human umbilical vein endothelial cells (HUVECs) under OMA treatment in hopes of identifying common host events that correlate with the rescue of endothelial function and integrity. Analysis of such transcriptomic studies will involve the use of sophisticated and exhaustive machine learning strategies that will help underline the subtle gene expression changes that occur during infection. Proposed and ongoing studies include both an in vitro NRF2 knockout model and an in vivo NRF2 knockout mouse model to further study the role of NRF2 during infection, in hopes of determining the potential role of NRF2 as a host-directed target that can exhibit a broad spectrum and agent agnostic layered protection for the warfighter.