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

Characterization Of Iron Homeostasis During New World Arenavirus Infection For Therapeutic Drug Design

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Arenaviruses (AV) are enveloped, single-stranded, ambisense, bi-segmented RNA viruses that can be classified into two geographically distinct subgroups – Old World (OWAV) and New World (NWAV). A subset of AV cause hemorrhagic fever in humans; the OWAVs Lassa (LASV) and Lujo (LUJV) and five NWAVs – Junín (JUNV), Machupo (MACV), Chapare (CHAPV), Sabia (SABV), and Guanarito (GTOV). All the AV hemorrhagic fever viruses are CDC and NIAID category A pathogens, CDC select agents, and several are known to have been weaponized, indicating their biothreat potential. Case fatality rates during outbreaks of NWAVs have been reported to be as high as 60%. There are no FDA approved medical countermeasures (MCM) for treatment of AV infection.

NWAVs enter the host cell when NWAV GP1 receptor-binding domains engage host transferrin receptor 1 (TfR1), triggering clathrin-dependent endocytosis. TfR1 is ubiquitously present on erythroblasts and rapidly proliferating cells that complex with transferrin (Tf) or ferritin carrying iron ions to initiate endocytosis and endosome formation in the host cell. These iron ions are then reduced and transported to the cytosol for host cell use. Iron is a critical cofactor and micronutrient that is involved in various metabolic processes and disruption of iron homeostasis may result in unbound iron in serum leading to systemic anemia or organ toxicity.

NWAV receptor engagement of TfR1 occurs at the apex domain, which is distinct from the transferrin-binding domain. Ferritin, however, binds to TfR1 at the same apical binding domain and the relationship between ferritin and NWAV has yet to be explored. It is important to note that non-pathogenic NWAV enter the host cell through an unknown receptor, highlighting the significance of TfR1 as a viral receptor important for human pathogenesis. The downstream effects of receptor endocytosis during iron uptake on NWAV pathogenicity have yet to be fully characterized. The purpose of this study is to elucidate the role of iron homeostasis during NWAV infection to better inform engineering of future host-targeting MCMs for warfighter protection.

Here, using biolayer interferometry for high resolution analysis, we demonstrate the full binding kinetics of NWAV GP1 receptor-binding domains in association with TfR1. We then use replication-competent reporter VSV-chimeric viruses expressing both pathogenic and non-pathogenic NWAV GP1 to interrogate the effect of iron depletion and supplementation on infection efficiency in endothelial cells. TfR1 expression and iron homeostasis signaling pathway modulation by NWAVs is further described by measuring gene and protein expression to enable future MCM engineering efforts targeting TfR1.

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