BROAD-SPECTRUM THERAPEUTICS FOR VIRAL DISEASES: A MEDICAL COUNTERMEASURE PLATFORM FOR EMERGING THREATS

Early Growth Response 1 (egr1): A Potential Therapeutic Target For Encephalitic Viral Infections?

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Although highly trained in combat, the American warfighter still remains at risk of encountering an unsuspecting and deadly enemy: the mosquito. Emerging arboviruses, such as Venezuelan equine encephalitis virus (VEEV), are increasingly important causes of neurological disease in humans. Globalization and climate change have increased the population density and geographic range of competent vectors and as such clinical cases of arboviral infections remain on the rise. Unfortunately, there are no FDA-approved preventative or medical countermeasures available for the vast majority of these encephalitic arboviruses and it is estimated that 50-70% of survivors of encephalitic arboviral infection will develop chronic and debilitating neurological sequelae. Thus, there is an urgent need to identify potential therapeutic targets in order to develop broad-spectrum therapeutics capable of limiting the neuronal insults encountered during these infections. Early growth response 1 (EGR1), an immediate early gene and transcription factor was found to be upregulated, albeit to varying degrees, following infection of human astrocytes with encephalitic viruses including VEEV, eastern equine encephalitis virus (EEEV), chikungunya virus (CHIKV), Zika virus (ZIKV), Sindbis virus (SINV), and Rift Valley fever virus (RVFV). EGR1 is most notably known for its roles in neurological development and neuropsychiatric diseases but is also involved in the regulation of inflammation, apoptosis, and antiviral signaling. Our lab has previously shown that loss of EGR1 results in decreased cell death following infection with VEEV. Furthermore, using a bioinformatic approach we identified genes downstream of EGR1 that are known to induce inflammation, cell death, and/or apoptosis. The inflammatory mediators, CXCL3, CXCL8, CXCL10, TNF, and PTSG2 and transcription factors Fos, Jun, ATF3, KLF4, and EGR1 itself were confirmed to be transcriptionally dependent on EGR1 in virally infected astrocytoma cells. EGR1 -/- mice infected with VEEV displayed a delay in viral replication in the brain with a corresponding delay in clinical symptoms as compared to WT mice infected with VEEV. Select EGR1-dependent genes were targeted using small molecule inhibitors to determine their ability to rescue cells from VEEV-induced cell death. Treatment of VEEV-infected cells with Celecoxib, an FDA-approved NSAID that targets PTGS2, was able to rescue cells from VEEV-induced cell death in a dose-dependent manner. Additionally, treatment of VEEV-infected cells with T-5224, a small molecule inhibitor targeting AP-1, a key complex in apoptotic signaling, was able to rescue cells from VEEV-induced cell death. Ongoing studies in the lab are examining the efficacy of these inhibitors against other encephalitic arboviruses with a particular interest in EEEV due to it having the most EGR1-dependent genes of all of the viruses tested. Additionally, we aim to evaluate the ability of these inhibitors to prevent virally induced neurological sequelae in vivo. The mission of developing and/or repurposing therapeutics for their ability to preserve neuronal integrity during these encephalitic viral infections is of utmost importance as neuronal cell death contributes to the development of life-long neurological sequelae in survivors.

This work was funded through the Defense Threat Reduction Agency (DTRA), grant HDTRA1-21-1-0008 to KKH. Funders do not have any role in the design of the study and collection, analysis, and interpretation of data, nor in the preparation of the work presented here.