

IMMUNOBIOLOGY OF WNV-INDUCED NEUROINFLAMMATION

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Neurological complications such as inflammation, compromised blood-brain barrier (BBB), and neuronal death contribute to the mortality and morbidity associated with WNV-induced meningitis. Compromised BBB indicates the ability of the virus to gain entry into the CNS via the BBB. To investigate WNV entry into the CNS, we developed in vitro BBB model comprised of human brain microvascular endothelial (HBMVE) cells and an in vivo mouse model. We demonstrated that cell-free WNV can cross the BBB model, without compromising the BBB integrity. Further we characterized the expression of matrix metalloproteinases (MMP) in WNV-infected HBMVE and human brain cortical astrocytes (HBCA), and their role in BBB disruption. Expression of multiple MMPs was significantly induced in WNV-infected HBCA cells. Naïve HBMVE cells incubated with the supernatant from WNV-infected HBCA cells demonstrated loss of tight junction proteins, which were rescued in the presence of MMP inhibitor, GM6001. Further, supernatant from WNV-infected HBCA cells compromised the in vitro BBB model integrity. Similarly, our in vivo mouse data further implicate role of multiple MMPs in the BBB disruption and strategies to interrupt this process may influence the WNV disease outcome. These data suggest astrocytes as one of the sources of MMP in the brain, which mediates BBB disruption allowing unrestricted entry of immune cells into the brain. Additionally, we provide direct in vitro evidence that WNV-induced COX-2/PGE2 is involved in modulating the expression of multiple neuroinflammatory mediators, thereby linking COX-2 with WNV disease pathogenesis. These findings warrant further investigations in the role of COX-2 in WNV diseases pathogenesis. Because of the unavailability of WNV antivirals and vaccines, use of MMP inhibitors and/or COX-2 inhibitors as an adjunct therapy for clinical management of neuroinflammation associated with WNV encephalitis disease progression is warranted.

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