Defining MARCO-virus Interactions Important for Chikungunya Virus Clearance from the Circulation

Arboviruses, such as mosquito-borne alphaviruses, are major public health concerns, and the capacity of an arbovirus to be transmitted in a human-mosquito-human transmission cycle has fueled explosive outbreaks worldwide. Major determinants of arbovirus transmission, geographic spread and pathogenesis are the magnitude and duration of viremia in the vertebrate host. Previously, we determined that multiple arthritogenic alphaviruses, including chikungunya (CHIKV) and Ross River (RRV) viruses, are cleared efficiently from murine circulation by scavenger receptor A6 (MARCO) expressed on liver macrophages. Here, we find that MARCO-dependent clearance of CHIKV is contingent on the presence of specific biochemical features of the virion surface E2 and E1 glycoproteins: a lysine (K) residue at E2-200 (K200), a negative charge at E2-208, and a positive charge at E1-61. Utilizing an *in vitro* cell culture system, we uncovered that ectopic expression of murine MARCO promoted binding and internalization of CHIKV particles via the scavenger receptor cysteine-rich (SRCR) domain, which has a distinct electrostatic distribution and can support ionic interactions with the critical charged surface residues identified on CHIKV. In addition, we observed that the SRCR domain of MARCO from vertebrate species reported to develop low to no viremia supported CHIKV internalization whereas those from known amplification hosts (i.e., humans, nonhuman primates) did not. Furthermore, lack of CHIKV-MARCO interactions resulted in more efficient viral dissemination and greater viral burden in hosts. Collectively, these findings suggest a role of MARCO in CHIKV pathogenesis and transmission cycle, where CHIKV-MARCO interactions influence disease severity and determine whether a vertebrate serves as an amplification or dead-end host.