The ABC of Hand, Foot and Mouth Disease (HFMD): From clinical manifestations, host-virus interactions to antiviral strategies

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Abstract
Hand, foot and mouth disease (HFMD) is a prevalent contagious childhood disease typically associated with fever, oral lesions and limb exanthema. A 5 year (2013-2017) molecular epidemiological study on human enteroviruses causing HFMD in patients admitted to KK Women’s and Children’s Hospital as well as children in childcare centers in Singapore was conducted. Virus isolation coupled with NGS and phylogenetic analysis of virus genomes revealed the predominant human enteroviruses circulating in Singapore and their relationship with outbreaks in the Asia-Pacific countries will be discussed. In addition, the immunological cytokine and chemokine profile of HFMD patients was investigated and these immunological profiles have provided an insight to the clinical manifestation of HFMD including onychomadesis (shedding of nails) which is observed in recent outbreaks.

Given the compact genome of human enterovirus A71 (EV-A71), many cellular proteins are likely to be required for its successful replication. Here we report the identification of host susceptibility (HSF) and resistance factors (HRF) affecting EV-A71 infection from a human genome-wide gene silencing screen coupled with human miRNAome and proteome profiling. The involvement of both HSF and HRF in a plethora of infection processes including transcription regulation, cell cycle, calcium signaling, translation initiation and membrane biogenesis provides a comprehensive map of cellular components involved in EV-A71 replication. To address the urgent need for treatment options, we have performed high throughput screens of small molecule compound libraries for potential antivirals against EV-A71. We have identified a highly potent and non-cytotoxic antiviral flavonoid (MARVAS-Flavon) found in citrus fruit peels for human enteroviruses causing HFMD. MARVAS-Flavon is shown to disrupt viral protein and RNA synthesis. Extensive HEVA71 passaging with MARVAS-Flavon yielded HEVA71-resistant mutants, in which 5 mutations were mapped to the viral IRES region. Furthermore, MARVAS-Flavon effectively impeded HEVA71-associated clinical symptoms and mortality in HEVA71-infected BALB/c mice. These discoveries establish MARVAS-Flavon as a suitable clinical candidate for further development into a HEVA71 therapeutic agent.

Selected Relevant Publications for Reference