Differential Proteome Analysis of Chikungunya Virus Infection on Host Cells

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Abstract

Background: Chikungunya virus (CHIKV) is an emerging mosquito-borne alphavirus that has caused multiple unprecedented and re-emerging outbreaks in both tropical and temperate countries. Despite ongoing research efforts, the underlying factors involved in facilitating CHIKV replication during early infection remains ill-characterized. The present study serves to identify host proteins modulated in response to early CHIKV infection using a proteomics approach.

Methodology and Principal Findings: The whole cell proteome profiles of CHIKV-infected and mock control WRL-68 cells were compared and analyzed using two-dimensional gel electrophoresis (2-DGE). Fifty-three spots were found to be differentially modulated and 50 were successfully identified by MALDI-TOF/TOF. Eight were significantly up-regulated and 42 were down-regulated. The mRNA expressions of 15 genes were also found to correlate with the corresponding protein expression. STRING network analysis identified several biological processes to be affected, including mRNA processing, translation, energy production and cellular metabolism, ubiquitin-proteasome pathway (UPP) and cell cycle regulation.

Conclusion/Significance: This study constitutes a first attempt to investigate alteration of the host cellular proteome during early CHIKV infection. Our proteomics data showed that during early infection, CHIKV affected the expression of proteins that are involved in mRNA processing, host metabolic machinery, UPP, and cyclin-dependent kinase 1 (CDK1) regulation (in favour of virus survival, replication and transmission). While results from this study complement the proteomics results obtained from previous late host response studies, functional characterization of these host proteins is warranted to reinforce our understanding of their roles during early CHIKV infection in humans.

Introduction

Chikungunya (CHIK) is a long-neglected disease that only recently began to garner attention from the scientific community following devastating outbreaks that struck India and the Indian Ocean Islands from 2004 to 2007. This disease causes substantial morbidity and an estimated death rate of 1 in 1,000 [1]. Despite being perceived as a tropical disease, recent CHIK cases and sporadic outbreaks were documented in temperate regions, suggesting that this infectious disease is no longer geographically restricted to tropical countries [2]. In Malaysia, three separate outbreaks have been reported over the past 15 years [3,4,5].

The causative agent for CHIK infection is the chikungunya virus (CHIKV), an alphavirus belonging to the family Togaviridae [6]. CHIKV is transmitted by the mosquito Aedes aegypti and Aedes albopictus. CHIKV can be genotypically classified into the East Central South African, West African and Asian genotypes [7]. Upon infection, CHIKV causes an acute illness characterized by the classical triad of symptoms of fever, rash and debilitating arthralgia which can persist for years. However, cases from recent outbreaks saw an increasing occurrence of atypical clinical manifestations such as neurological and cardiovascular complications [8]. As there is currently no effective vaccine or antiviral regimen to combat this disease, treatment is solely palliative. All things considered, it is not surprising that CHIK is now regarded as a potential health problem in need of a solution.

Recent research efforts have focused on understanding the viral tropism and mechanisms associated with the pathogenesis of CHIK infection. In vitro studies using a panel of mammalian cell lines showed rapid induction of cytopathic effects and cell death via apoptosis in most adherent cell lines with the exception of blood-derived cell lines [9]. Autophagic process and apoptosis were also recently shown to facilitate CHIKV dissemination [10,11]. At the molecular level, proteomics studies on CHIKV interaction with vector and mammalian host proteins have unravelled new clues in elucidating the mechanisms involved in viral replication and transmission from vector to host as well as disease progression in host cells [12,13,14]. Despite the extensive