ALTERATIONS ON MEGAKARYOCYTE PROGENITORS DURING YELLOW FEVER VIRUS INFECTION

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Introduction: Yellow Fever Virus (YFV) causes an acute hemorrhagic fever related to hemostasis dysfunction, with thrombocytopenia, both related to the disease severity. Viral infections can lead to metabolic dysfunctions such as in the mitochondrial metabolism. The cell metabolic profile can also be modulated, and high free NADH concentrations correlates with a glycolytic profile and lower concentrations with an oxidative profile. Platelets are the final stage of megakaryoblast differentiation and alterations on megakaryoblasts could be related to the pathogenesis and explain in part the thrombocytopenia.
Aim: Here we aim to investigate the processes by which YFV infection leads to thrombocytopenia, studying the interaction between YFV and megakaryoblasts.
Materials and Methods: We infected MEG-01 cells (Human Megakaryoblastic cell line) with YFV 17DD in a multiplicity of infection of 1 and followed infection by plaque assays and fluorescence confocal microscopy. Mitochondrial physiology was analyzed in intact cells through high-resolution respirometry and the free/bound NADH ratio by fluorescence lifetime microscopy.
Results: We confirmed that YFV infects MEG-01 cells, with increasing production of infectious particles until 96 hours post-infection, followed by a decrease. We observed increased cell death in YFV-infected cells from 120 hours post-infection as compared to control. We also observed increased apoptosis from 120 hours post-infection on infected cells by TUNEL assay. Through high-resolution respirometry, we observed decreased routine, ATP synthesis-coupled oxygen consumption and maximum capacity of infected cells electron transport system 144 hours post-infection. By analyzing the free/bound NADH ratio, we observed that since 72 hours post-infection, infection induces a lower free NADH fraction than in control cells, indicating an oxidative profile.
Conclusion: Our data show for the first time that YFV infects and replicates in MEG-01 cells, inducing cell death and apoptosis from 120 hours post-infection. We also observed that YFV infection modulates MEG-01 metabolism by modulating mitochondrial physiology with decreased respiration and a shift to oxidative profile.

Keywords: Yellow Fever, Megakaryocyte, Platelet, Apoptosis
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