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ID 2990. Mitochondrial Dysfunction Driven by SARS-CoV-2 ORF7a: Unveiling Metabolic Mechanisms in COVID-19 Pathogenesis

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Introducción y Objetivo/Background and objectives

SARS-CoV-2, the causative agent of COVID-19, is among the most significant public health threats stemming from zoonotic spillover events in recent history. Originating from animal reservoirs, it exemplifies how emerging zoonotic viruses can disrupt global health systems. SARS-CoV-2 exploits diverse strategies to manipulate host cell metabolism, enhancing viral replication and evading immune responses. While accessory proteins encoded by SARS-CoV-2 are known to play essential roles in these processes, the specific contribution of ORF7a remains poorly understood. This study aims to investigate the impact of SARS-CoV-2 ORF7a on host cell metabolism, emphasizing mitochondrial function and glycolysis. Understanding these mechanisms could reveal metabolic vulnerabilities induced by zoonotic viruses and guide future therapeutic strategies for emerging infections.

Métodos/Methods

Human bronchoalveolar epithelial (A549), endothelial (HUVEC), and monocyte (THP-1) cells were transduced with lentivirus expressing ORF7a. Transcriptomic and proteomic analyses identified dysregulated pathways in A549 cells. Metabolic flux was assessed using a Seahorse Analyzer to evaluate mitochondrial function. Mitochondrial membrane potential and ROS production were measured by cytometry. Key metabolic regulators, such as PDK4 and PDHC, were analysed by qPCR and Western-Blot.

Resultados/Results

Expression of ORF7a disrupted mitochondrial metabolism, including alterations in glycolysis, fatty acid metabolism, and oxidative phosphorylation. Metabolic flux analysis revealed reduced basal and maximal respiration, loss of mitochondrial membrane potential, and elevated ROS production in ORF7a-expressing cells. Increased PDK4 expression and enhanced PDHC phosphorylation, a key regulator of acetyl-CoA formation, were observed across all cell types. These findings suggest that ORF7a impairs glucose utilization and lipid metabolism, compromising mitochondrial respiratory capacity through PDK4-mediated PDHC inactivation.

Conclusión y Relevancia/Conclusions and relevance

This study highlights the significant impact of SARS-CoV-2 ORF7a on metabolic dysfunction across multiple cell types. Our findings provide new insights into the metabolic reprogramming induced by viral proteins and underscore the potential of targeting metabolic pathways as a therapeutic strategy for managing COVID-19 and other emerging zoonotic infections.