III Jornadas Científicas PTI+ Salud Global

20-22 de noviembre de 2023

Centro de Ciencias Humanas y Sociales (CCHS), CSIC, Madrid

N°10

Metabolic and mitochondria alterations induced by SARS-CoV-2 accessory proteins ORF3a, ORF9b, ORF9c and ORF10

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Antiviral signaling, immune response and cell metabolism in human body are dysregulated by SARS-CoV-2, the causative agent of COVID-19. However, the impacts of individual accessory proteins on host cell metabolic pathways are unknown. Here, SARS-CoV-2 accessory proteins ORF3a, ORF9b, ORF9c and ORF10 were individually transduced into A549 lung carcinoma cells. Furthermore, by combining transcriptomic analysis with functional and metabolic data in accessory protein-specific GSMMs, several alterations were identified that may point to a putative target for investigating novel therapies. In this study, we showed that these accessory proteins induced a significant mitochondrial and metabolic reprogramming in A549 lung epithelial cells. ORF9b, ORF9c and ORF10 induced largely overlapping transcriptomes. In contrast, ORF3a induced a distinct transcriptome, including the downregulation of numerous genes with critical role in mitochondria function and morphology. On the other hand, while all four ORFs altered mitochondrial dynamics and function, only ORF3a and ORF9c induced a marked structural alteration in mitochondrial cristae. Genome-Scale Metabolic Models identified both metabolic flux reprogramming features shared across all accessory proteins and specific ones for each accessory protein. Notably, a downregulated amino acid metabolism was observed in ORF9b, ORF9c and ORF10, while an upregulated lipid metabolism was distinctly induced by ORF3a. Next, qMTA identified gene knock downs (KDs) that would have the potential to revert the metabolic reprogramming induced by each individual accessory protein, especially in ORF3a and ORF10. These findings reveal metabolic dependencies and vulnerabilities prompted by SARS-CoV-2 accessory proteins that may be exploited to identify new targets for intervention.