Metabolic modeling elucidates phenformin and atpenin A5 as broad-spectrum antiviral drugs against RNA viruses

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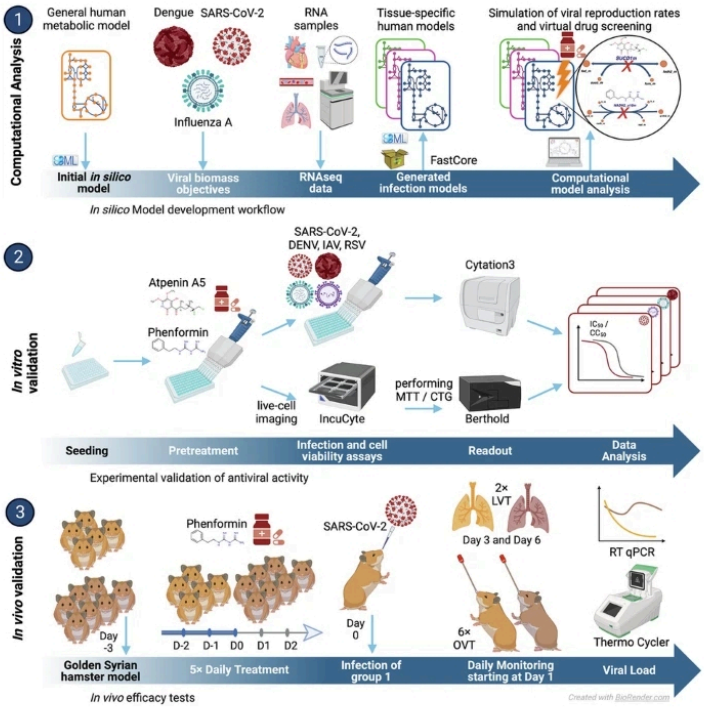
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Abstract

The SARS-CoV-2 pandemic has reemphasized the urgent need for broad-spectrum antiviral therapies. We developed a computational workflow using scRNA-Seq data to assess cellular metabolism during viral infection. With this workflow we predicted the capacity of cells to sustain SARS-CoV-2 virion production in patients and found a tissue-wide induction of metabolic pathways that support viral replication. Expanding our analysis to influenza A and dengue viruses, we identified metabolic targets and inhibitors for potential broad-spectrum antiviral treatment. These targets were highly enriched for known interaction partners of all

analyzed viruses. Indeed, phenformin, an NADH:ubiquinone oxidoreductase inhibitor, suppressed SARS-CoV-2 and dengue virus replication. Atpenin A5, blocking succinate dehydrogenase, inhibited SARS-CoV-2, dengue virus, respiratory syncytial virus, and influenza A virus with high selectivity indices. In vivo, phenformin showed antiviral activity against SARS-CoV-2 in a Syrian hamster model. Our work establishes host metabolism as druggable for broad-spectrum antiviral strategies, providing invaluable tools for pandemic preparedness.