Are Kinases Double-Agents?: Host Kinase Overexpression as a Guide for Antiviral Drug Development

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Many highly infectious viral diseases such as SARS-CoV-2 currently lack effective antiviral therapies, leading to lasting disability or even death. A new approach to antiviral drug development is to target abnormally expressed host proteins, not viral proteins, as has been the focus in the past. Kinases are a superfamily of host proteins that control important cellular processes involved in cell proliferation, differentiation, and death, and have been implicated as possible antiviral drug targets. When they infect cells, viruses can regulate specific kinases, changing their expression or activity to enhance virus replication. There is limited knowledge on how altering the expression of these virally regulated kinases would affect virus replication. In this study, we examined the kinome expression profile of cells infected with human cytomegalovirus (HCMV), then extracted and curated data from open-source chemical databases to identify the most promising inhibitors of the kinases induced by infection. This process resulted in the identification of nine hits. Compound hit validation was performed by comparing the identified compounds to compounds found in known kinase inhibitor datasets (PKIS1 and PKIS2) and existing antiviral drugs. A fluorescent reporter virus was used for experimental validation, and identified two compounds with inhibitory activity toward HCMV replication and one potent inducer of HCMV replication. We conclude that the computational method we developed to identify possible antiviral drug candidates is effective but non-directional, identifying both inducers and inhibitors of virus replication, both of which will be useful in later mechanistic studies to elucidate the pathways involved in virus replication.