

The DDX family RNA helicases and SARS-COV-2: targeting host-virus interactions

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DDX3X is an ATPase/RNA helicase of the DEAD-box family and one of the most multifaceted helicases known up to date, acting in RNA metabolism, cell cycle control, apoptosis, stress response and innate immunity. Depending on the virus or the viral cycle stage, DDX3X can act either in a proviral fashion or as an antiviral factor. We have demonstrated that small molecule inhibitors targeting different binding pockets of DDX3X can block the replication of HIV-1, HCV, Dengue virus, West Nile virus, with no toxicity in cultured human cells or animal models (1-5). A first series of anti-helicase compounds have been tested against SARS-CoV-2 infections, unfortunately proving not to be effective.

Based on the available proteomic and crystallographic studies, we have started to investigate the network of interactions of DDX3X and other DDX helicases (DDX1/DDX5) with SARS-CoV-2 proteins, in particular the nucleocapsid N. Molecular modelling allowed us to identify possible protein-protein interaction interfaces. Experiments are ongoing to validate these data through proteomics and to set up functional assays to develop specific inhibitors of these interactions.

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