PROTAC-based approach to develop broad-spectrum antiviral agents triggering the proteolysis of the major viral protease

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In 2020, with the spread of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection, the PROteolysis TArgeting Chimeras (PROTACs) strategy to defeat coronaviruses (CoV) disease was also investigated (1). Indeed, PROTAC degraders acting against the major viral protease 3-chymotrypsin-like protease ($3CL^{Pro}$) were hypothesized to be next-generation anti-CoV drugs (2,3).
$3CL^{Pro}$ (also named nsp5 or main protease) is shared by all coronavirus genera as well as by members of the large genus Enterovirus in the Picornavirus family (4). Combining NMR spectroscopy and X-ray crystallography, we characterize the interaction between the α, β-unsaturated peptidomimetic-based PROTAC (FT235) with $3CL^{Pro}$ from SARS-COV-2 and $3C^{Pro}$ from Coxsackievirus B3 (CVB3), the latter being a cardiotropic virus belonging to enterovirus genus (5). The results are compared with those obtained with the precursor molecule (FT234). We demonstrate that PROTAC molecule bind to the active site of both enzymes and the residues involved in the interaction are identified by solution NMR experiments. Furthermore, the crystal structures of SARS-CoV-2 $3CL^{Pro}$ in complex with both FT234 and FT235 molecules are obtained. For both ligands the Cβ carbon of the α, β-unsaturated amide moiety forms a covalent bond with the catalytic Cys145. Moreover, we obtain the crystal structure of $3C^{Pro}$ from CVB3 in complex with FT234 molecule, relieving the covalent binding with Cys147. Finally, preliminary cellular studies show that the synthetized PROTAC molecule drastically reduces protein levels of SARS-CoV-2 $3CL^{Pro}$ in cultured cells. From this work it therefore appears that PROTAC technology is a promising strategy and it opens up new possibilities for creating cutting-edge antiviral treatments.

References:
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