# A Crystallographic Snapshot of SARS-CoV-2 Main Protease Maturation Process

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SARS-CoV-2 is the causative agent of COVID-19. The dimeric form of the viral Mpro is responsible for the cleavage of the viral polyprotein in 11 sites, including its own N and C – terminus. The lack of structural information for intermediary forms of Mpro is a setback for the understanding of this process. Herein, we used X-ray crystallography to characterize an immature form of the main protease, which revealed major conformational changes in the positioning of domain-three over the active site, hampering the dimerization and diminishing its activity. We propose that this form preludes the cis-cleavage of N-terminal residues. Using fragment screening, we probe new cavities in this form which can be used to guide therapeutic development. Furthermore, we characterized a serine site-directed mutant of the Mpro bound to its endogenous N and C-terminal residues during the formation of the tetramer. We suggest this form is a transitional state during the C-terminal trans-cleavage. This data sheds light in the structural modifications of the SARS-CoV-2 main protease during maturation, which can guide the development of new inhibitors.

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