Insights into the SARS-CoV-2 Main Protease obtained using X-ray and Neutron Diffraction

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The main protease from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, is an essential enzyme for viral replication. It plays a pivotal role in mediating viral replication and transcription functions through extensive proteolytic processing of two replicase polyproteins, pp1a and pp1ab. The main protease possesses an unusual catalytic dyad in its active site composed of a histidine and a particularly reactive cysteine residue along with a water molecule that is believed to be important in catalysis. As the enzyme has no human counterpart, it makes for an attractive drug target. Several groups around the world have been studying this cysteine protease using a range of structural, in silico and biochemical techniques. We have used room temperature X-ray and neutron crystallography (1-4) to study this critical enzyme's structure and how interaction with various inhibitors alters the active site's shape and protonation state. During this talk, I will present an overview of our structural and biochemical work to date, along with the most recent developments in the field.

References

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