Invited Talk

Proteins of SARS coronavirus - experimental and theoretical studies

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All protein functions required for SARS coronavirus replication are encoded by the replicase gene of the virus. This gene encodes two overlapping polyproteins (pp1a and pp1ab), from which the functional proteins are released by extensive proteolytic processing. This is primarily achieved by the 33-kDa main proteinase (Mpro), which is frequently also called 3C-like proteinase (3CLpro) to indicate a similarity in substrate specificity with the 3C proteinase of picornaviruses. Because of its important role in the viral life cycle, the SARS-CoV Mpro is an attractive target for antiviral drug design. The structure of the enzyme has first been modelled on the basis of crystal structures of homologous proteinases from other coronaviruses (1,2), and then determined by X-ray crystallography itself (3-5). Inhibitors have been identified by virtual screening and by conventional structure-based design (2,6-8). The experimentally observed, pH-dependent conformational changes of the enzyme have been reproduced by extended molecular dynamics (MD) simulations (4). In addition to the main proteinase, the coronaviral replicase gene codes for at least 15 additional non-structural proteins (Nsps), the functions of which are not known in many cases. Experimental results on Nsp1, 3, 7, 8, 9, 10 and 12 of SARS-CoV, HCoV-229E, and HCoV-NL63 will be presented, as well as modelling studies on Nsp12 and the SARS-unique domain of Nsp3. It will be shown that the applied combination of X-ray crystallography and structural bioinformatics has great potential in suggesting possible biological functions for the Nsps, which can then be subjected to experimental testing.

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