Crystal Structures of SARS Coronavirus Proteins

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Since the 2003 SARS outbreak, which has now subsided, our laboratory has worked to obtain a series of important results in SARS basic research. These results can be summarized as follows:

We successfully determined the structure of the SARS coronavirus main proteinase (M^{pro} or $3CL^{pro}$) and its complex with an inhibitor in 2003. This was the first structure of any protein from the SARS coronavirus to be determined in the world. The SARS-CoV M^{pro}, which is a 33.8-kDa protease (also called the 3C-like protease), plays a pivotal role in mediating viral replication and transcription and is therefore an important target for the design of anti-SARS drugs. We have used the SARS M^{pro} structure to design a series of inhibitors that are effective against four kinds of coronavirus. We have also analyzed the structures of the SARS M^{pro} and the porcine transmissible gastroenteritis virus (TGEV) M^{pro} in complex with the above inhibitors. This series of crystal structures, together with biochemical data, provide an important structural basis for rational drug design.

The second crystal structure to be determined from our laboratory is the SARS-CoV membrane fusion protein. The coronavirus spike (S) protein, an enveloped glycoprotein essential for viral entry, belongs to the class I fusion proteins and is characterized by the presence of two heptad repeat (HR) regions, HR1 and HR2. These two regions are understood to form a fusion-active conformation similar to those of other typical viral fusion proteins. The crystal structure of the SARS-CoV fusion core protein is a six-helix bundle with three HR2 helices packed against the hydrophobic grooves on the surface of a central coiled coil formed by three parallel HR1 helices in an oblique antiparallel manner. We have also determined the mouse hepatitis virus (MHV) S protein fusion core and proposed a conserved molecular mechanism by which the S protein mediates the coronavirus membrane fusion and subsequent viral entry. This work provides a new avenue for the design of anti-SARS therapeutics via strategies aimed at inhibiting viral entry by blocking hairpin formation.

Recently, a third structure has been solved in our laboratory. The complex structure between two non-structural proteins reveals exciting new functional insights into the SARS coronavirus.

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