PDB-101

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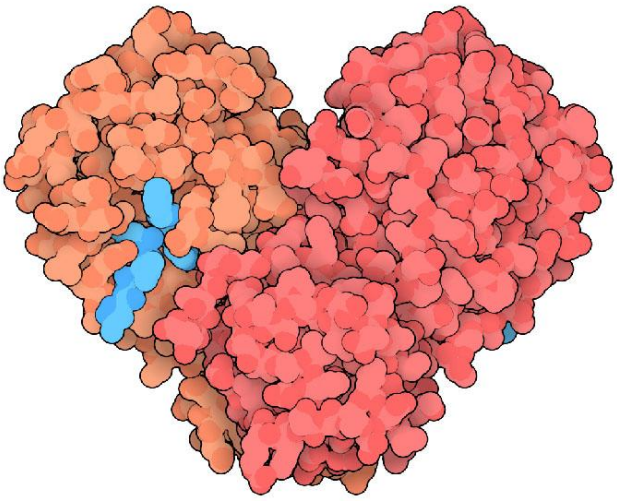
Coronavirus Proteases

Coronavirus proteases are attractive targets for the design of antiviral drugs.

In this world of fast and easy travel, emerging viruses are increasingly becoming a major danger to world health. Coronaviruses are a notable example. Particularly virulent forms have emerged from their natural animal hosts and pose a threat to human communities. In 2003, the SARS virus emerged in China from bat populations, moving to civets and finally to humans. Ten years later, the MERS virus also emerged from bats, transferring in the Middle East to dromedary camels and then to humans. Recently, another coronavirus has emerged in China by way of animals in a live market. Structural biology is helping us understand these dangerous foes, and hopefully will help us develop new ways to fight them.



SARS-CoV-2 (2019-nCoV) coronavirus main protease, with inhibitor in turquoise.

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Coronavirus Code

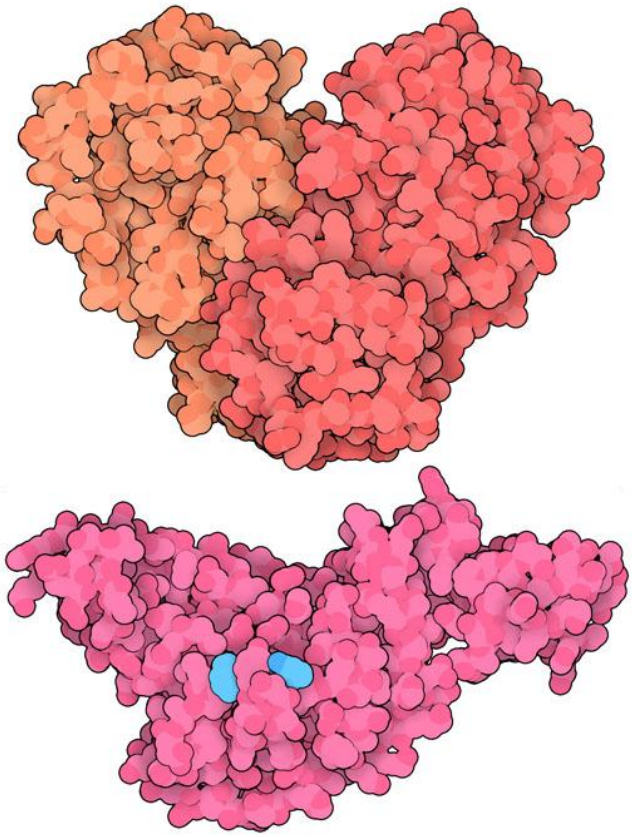
Coronaviruses contain a genome composed of a long RNA strand—one of the largest of all RNA viruses. This genome acts just like a messenger RNA when it infects a cell, and directs the synthesis of two long polyproteins that include the machinery that the virus needs to replicate new viruses. These proteins include a replication/transcription complex that makes more RNA, several structural proteins that construct new virions, and two proteases. The proteases play essential roles in cutting the polyproteins into all of these functional pieces.

Main Protease

The main protease of coronavirus makes most of these cuts. The one shown here (PDB entry 6lu7) is from the SARS-CoV-2 (2019-nCoV) coronavirus that is currently posing dangers in Wuhan. It is a dimer of two identical subunits that together form two active sites. The protein fold is similar to serine proteases like trypsin, but a cysteine amino acid and a nearby histidine perform the protein-cutting reaction and an extra domain stabilizes the dimer. This structure has a peptide-like inhibitor bound in the active site.

SARS Proteases

The two proteases from SARS are shown here. The main protease (PDB entry 1q2w) is similar to the Wuhan one, and cleaves at 11 sites in the polyproteins. The papain-like protease (PDB entry 4ow0) has single subunit and also uses a cysteine in



SARS main protease (top) and papain-like protease (bottom), with inhibitor in turquoise.

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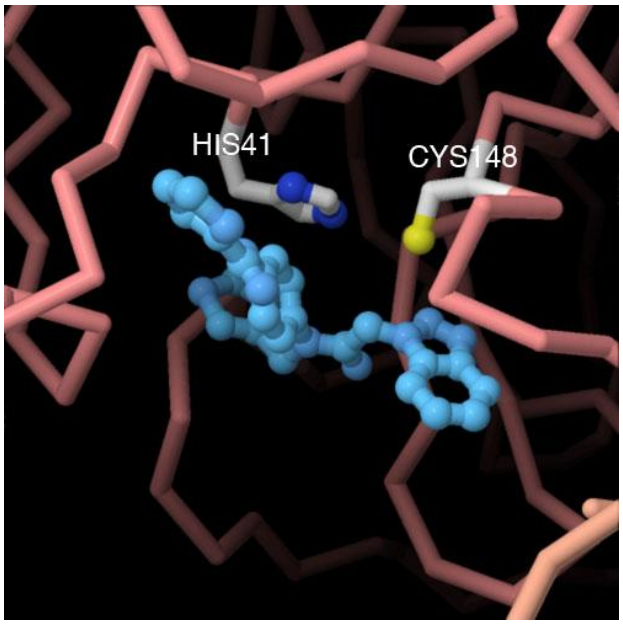
the reaction. It makes three specific cuts in the SARS polyproteins, and also clips several proteins in the infected cell, including removing ubiquitin from ubiquitinated proteins. One of the consequences of this deubiquitination is that it interferes with production of interferons in the innate immune system, short-circuiting some of our defenses against the virus.

Exploring the Structure

Image | JSmol

Bat Coronavirus Main Protease with Inhibitor



Researchers are actively using these structures to search for compounds that block the action of the proteases, for use as antiviral drugs. The diversity of coronaviruses poses a great challenge with this effort: coronaviruses have been classified into four separate genera, and sequence and structural studies have shown that the proteases of these viruses can be very different, so drugs designed to fight one may not be effective against others. One possible way to address this challenge is to try to design a broad-spectrum inhibitor targeted against the progenitor bat coronavirus, such as the one shown here from PDB entry 4yoi, which may then provide a head-start for discovering inhibitors against newly emerging viruses. The active site cysteine and histidine are shown in the illustration,

with an inhibitor in turquoise. To explore this structure in more detail, click on the image for an interactive JSmol.

Topics for Further Discussion

1. An unusual octameric form of the main protease may be involved in its maturation. You can see it in PDB entry 3iwm.
2. You can compare the folds of coronavirus main proteases and serine proteases using the “Structure Align” tool. Try using trypsinogen (PDB entry 1tgs), so that the whole enzyme is one chain for the alignment.

Related PDB-101 Resources

- More about Coronavirus Proteases
- Browse Viruses

References

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