June 2000: HIV–1 Protease

A Target for AIDS Therapy

Drugs that attack HIV–1 protease are one of the triumphs of modern medicine. The AIDS epidemic started a few short decades ago-- before that, HIV was unknown. These drugs demonstrate the powerful tools that medical science has to combat a new disease. Already, researchers have discovered a panel of effective drugs which slow the growth of the virus to a standstill. Important problems still remain, however. In particular, an effective vaccine against HIV is not available. But today, HIV–infected individuals have potent options for treatment.
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Attacking HIV

HIV–1 protease performs an essential step in the life cycle of HIV. Like many viruses, HIV makes many of its proteins in one long piece, with several proteins strung together. HIV–1 protease has the job of cutting this long 'polyprotein' into the proper protein–sized pieces. The timing of this step is critical. The intact polyprotein is necessary early in the life cycle, when it assembles the immature form of the virus. Then, the polyprotein must be cut into the proper pieces to form the mature virus, which can then infect a new cell. The cleavage reactions must be timed perfectly, allowing the immature virus to assemble properly before the polyprotein is broken. Because of its sensitive and essential function, HIV–1 protease is an excellent target for drug therapy. Drugs bind tightly to the protease, blocking its action, and the virus perishes because it is unable to mature into its infectious form.

An Enzyme Under Scrutiny

The atomic structure of HIV–1 protease has made much of this work possible. The first structures were reported in 1989. A decade later, over one hundred structures are available in the PDB, including several genetic strains of the enzyme, complexes of the enzyme with many different drugs and inhibitors, and dozens of mutant enzymes. Hundreds more are stored in the proprietary databases of pharmaceutical companies, where they are used to test and refine new drug candidates. Overall, HIV–1 protease is now one of the best–studied enzymes known to medicine. It is an enigmatic enzyme, however, that still hides many of its secrets.

A Small But Effective Enzyme

HIV–1 protease is a small enzyme, composed of two identical protein chains, each only 99 amino acids long. The two chains assemble to form a long tunnel, seen here from the side, covered by two flexible protein "flaps." The flaps open up and the enzyme wraps around a protein chain, closing and holding it tightly in the tunnel.
The active site is at the center of the tunnel, where a water molecule is used to break the protein chain. This illustration shows the enzyme from the top (the PDB accession code for this structure is 7hvp). In the two illustrations on the right, the flaps have been removed to show the active site. The center illustration shows the location of an inhibitor (green) which is similar to the position occupied by a protein chain. (There are no structures of a protein bound to the active form of HIV–1 protease, because the chain would be cleaved before the structure could be solved! So, we need to look at how inhibitors bind to imagine how the enzyme binds to protein chains.) Notice how the inhibitor chain is stretched straight through the active site. In the right illustration, the inhibitor has been removed so that we can see the active site. Two aspartate amino acids, shown with asterisks, do all of the work, attacking the protein chain at the very middle.
Exploring the Structure

Four drugs that attack HIV–1 protease are currently being used to treat people infected with the virus. Structures of all four of these drugs bound to HIV–1 protease are available at the PDB. In the illustration, the enzyme is displayed as a ribbon that follows the two protein chains and the drugs are shown as spacefilling models. The view is from the top—notice how the flaps cover the top of the drug molecules. From left to right, the drugs are Indinavir (PDB entry 1hsg), Saquinavir (PDB entry 1hxb), Ritonavir (PDB entry 1hxw), and Nelfinavir (PDB entry 1ohr). Notice how similar these drugs are. They all have carbon–rich groups arrayed along either side, interacting with the sides of the active site tunnel. They each have two oxygen atoms at the center, pointing towards us in the illustration, that interact with a special water molecule that is normally trapped under the flaps (not shown here). The drugs all mimic a protein chain, binding to the enzyme like protein chains do. But they are more stable than a protein chain. HIV–1 protease cannot cleave them, so they stay lodged in the active site, blocking the normal function of the enzyme.