15.3J: Serine Proteases

The serine proteases are a family of enzymes that cut certain peptide bonds in other proteins. This activity depends on a set of amino acid residues in the active site of the enzyme — one of which is always a serine (thus accounting for their name). In mammals, serine proteases perform many important functions, especially in digestion, blood clotting, and the complement system.

Digestive Enzymes

Three protein-digesting enzymes secreted by the pancreas are serine proteases: chymotrypsin, trypsin and elastase. These three share closely-similar structures (tertiary as well as primary). In fact, their active serine residue is at the same position (Ser-195) in all three. Despite their similarities, they have different substrate specificities; that is, they cleave different peptide bonds during protein digestion.

Clotting Factors

Several activated clotting factors are serine proteases, including Factors 10 (X), 11 (XI), and 12 (XII), Thrombin. and Plasmin.

Complement Factors

Several proteins involved in the complement cascade are serine proteases, including

- C1r and C1s
- the C3 convertases
Serpins

Serpins are Serine Protease Inhibitors. Here is a list of a few important serine proteases and the serpins that control them.

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<th>Serpin</th>
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<td>Chymotrypsin</td>
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<td>Clotting factor 10 (X)</td>
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<tr>
<td>Thrombin</td>
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<td>Plasmin</td>
<td>alpha-2-antiplasmin</td>
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<td>Trypsin</td>
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How Serpins Work

The serpins inhibit the action of their respective serine protease by mimicking the three-dimensional structure of the normal substrate of the protease. The serine protease binds the serpin instead of its normal substrate. This alone would block any further activity by the protease. But the serpin has another trick to play. The protease makes a cut in the serpin leading to the formation of a covalent bond linking the two molecules, a massive allosteric change in the tertiary structure of the serpin, which moves the attached protease to a site where it can be destroyed.

Importance of Serpins

Almost 20% of the proteins found in blood plasma are serpins. Their abundance reflects their importance: putting a stop to proteolytic activity when the need for it is over. This is especially important for the clotting and complement systems where a tiny initial activating event leads to a rapidly amplifying cascade of activity.

Serpin Deficiencies

A number of inherited human diseases are caused by a deficiency of a particular serpin. The deficiency usually results from a mutation in the gene encoding the serpin.
Alpha-1-antitrypsin deficiency

Alpha-1-antitrypsin inactivates the elastase secreted by neutrophils. When the lungs become inflamed, neutrophils secrete elastase as a defensive measure. However, it is important to inactivate this elastase as soon as its job is done. That is the function of alpha-1-antitrypsin. Its name, alpha-1-antitrypsin, suggests that it attacks the digestive enzyme, trypsin. In vitro, it does, but in the body, alpha-1-antitrypsin is found in the blood, not the intestine. Inactivation of trypsin in the intestine is the function of another serpin, pancreatic trypsin inhibitor. People with an inherited deficiency of alpha-1-antitrypsin (they are homozygous for a point mutation in its gene) are prone to emphysema. An effective treatment is on the horizon now that genetic engineering has produced goats that secrete human alpha-1-antitrypsin in their milk.

Alpha-1-antitrypsin deficiency can also lead to liver damage. Alpha-1-antitrypsin is synthesized in the liver. However, some mutant versions of the molecule form insoluble aggregates within the liver cells. This mechanism is similar to that of the prion diseases where protein aggregates destroy neurons in the brain. A drug that enhances autophagy protects mice from the liver damage caused by aggregates of mutant alpha-1-antitrypsin.

C1INH deficiency

A deficiency of C1INH produces hereditary angioedema (HAE). In addition to C1r and C1s, C1INH also inhibits several other serine proteases including kallikrein, the enzyme responsible for forming the potent vasodilator bradykinin. Hence, a deficiency of C1INH can trigger a dangerous swelling (edema) of the airways, as well as of the skin and intestine.

Antiplasmin deficiency

A deficiency in antiplasmin puts the person at risk of uncontrollable bleeding.

Antithrombin deficiency

A deficiency in antithrombin puts the person at risk of spontaneous blood clots, which can lead to a heart attack or stroke. In January 2009, an advisory committee of the U.S. FDA decided that a recombinant human antithrombin (ATryn®) secreted into the milk of transgenic goats was safe for use in therapy.

The Evolution of the Serine Proteases

The close sequence similarity of the various mammalian serine proteases suggests that each is the product of a gene descended by repeated gene duplication from a single ancestral gene.

Other Serine Proteases

Serine proteases and molecules similar to them are found elsewhere in nature.

Subtilisin

Subtilisin is a serine protease secreted by the bacterium Bacillus subtilis. Although it has the same mechanism of action
as the serine proteases of mammals, its primary structure and tertiary structure are entirely different. An example at the molecular level of convergent evolution: two molecules acquiring the same function (analogous) but having evolved from different genes.

**Acetylcholinesterase**

This enzyme is built like and acts like the other serine proteases, but its substrate is the neurotransmitter acetylcholine, not a protein. It is found at several types of synapses as well as at the neuromuscular junction — the specialized synapse that triggers the contraction of skeletal muscle. The organophosphate compounds used as insecticides (e.g., parathion) and nerve gases (e.g. Sarin) bind to the serine at the active site of acetylcholinesterase blocking its action.

**Serpinlike Molecules**

**Angiotensinogen**

This peptide is the precursor of angiotensin II — a major factor in maintaining blood pressure.

**Chicken Ovalbumin**

This is the major protein in the "white" of the egg (and a favorite antigen in immunological research).

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