MECHANISM OF SERINE PROTEASE

Akansha Aggarwal
Msc. Biochemistry

INTRODUCTION

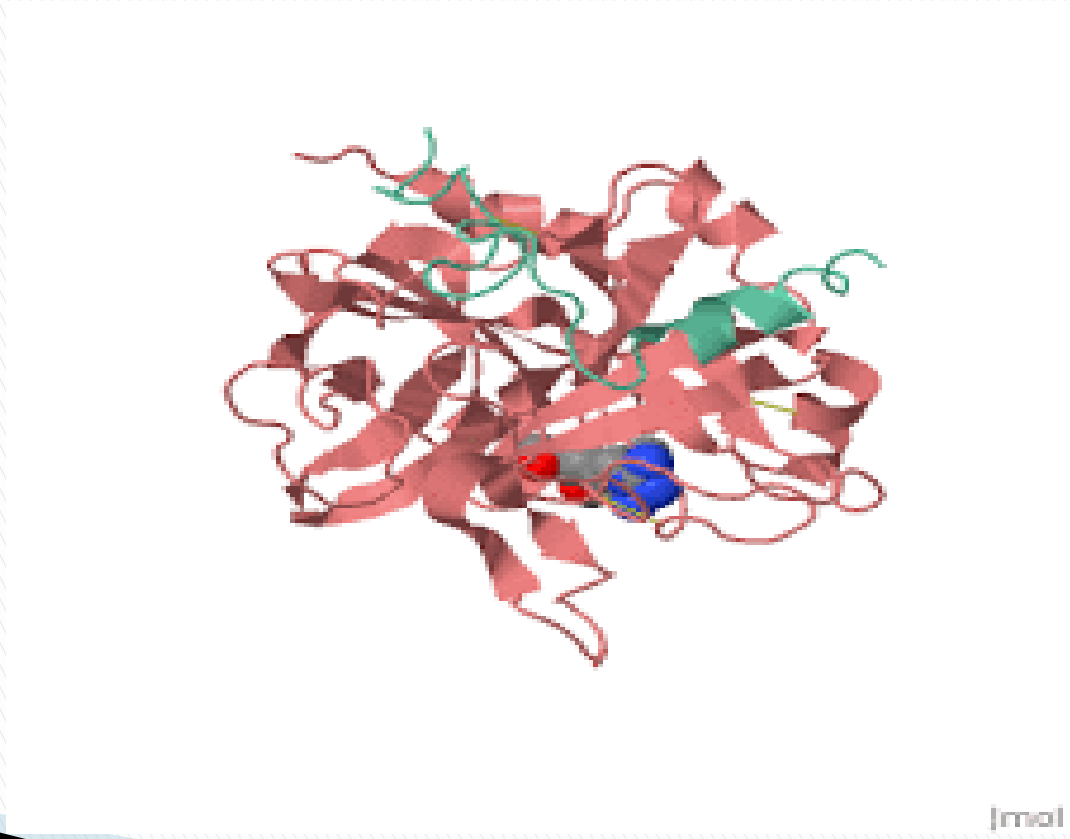
- They are a large family of proteolytic enzymes

- All such have serine residue at their active site which plays a crucial part in the enzymatic activity.

Serine proteases are enzymes that cleave peptide bonds in proteins, in which **serine** serves as the nucleophilic amino acid at the (enzyme's) active site. They are found ubiquitously in both eukaryotes and prokaryotes.

All the mammalian serine proteases have a common 3D structure. They all have the same catalytic mechanism.

Three Dimensional Structure



- Serine proteases include:
- the pancreatic proteases: trypsin, chymotrypsin and elastase,
- *various tissue/intracellular* proteases such as leukocyte elastase
- enzymes of the blood clotting cascade
- some enzymes of complement system
- Many serine proteases are synthesized as inactive precursors (zymogens) which are activated by proteolysis

Classification

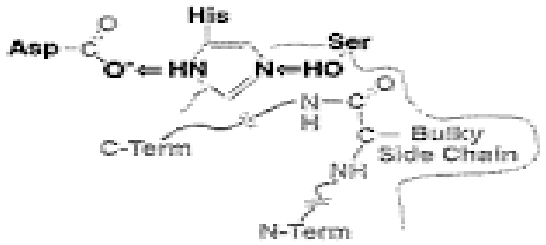
- Trypsin like serine peptidase – if it prefers to cleave peptide bonds of lys & arg
- Chymotrypsin like serine peptidase – if it prefers to cleave aromatic amino acids.
- Elastase like serine peptidase – if it prefers to cleave amino acids with small side chain groups like ala.

Mechanism of serine protease catalysis.

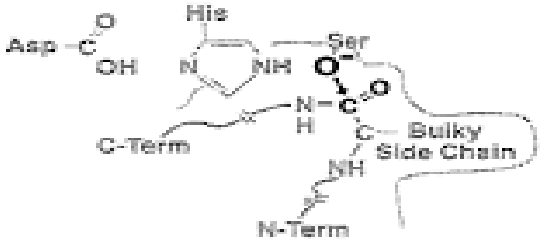
- The three key residues in serine proteases are collectively known as the catalytic triad. Aspartate is the H-bond acceptor, holding histidine in place. Histidine is a general acid/base catalyst, acting on serine, water, and the addition-elimation leaving groups. Serine is the nucleophile which initiates attack using its oxygen atom.

- The reaction proceeds as two addition-elimination steps. The first forms a covalent acyl intermediate, while the second deacylates the serine using water, freeing up the active site. All proton transfers are accounted for using histidine as an acid and a base, and the oxyanion hole stabilises the TI.

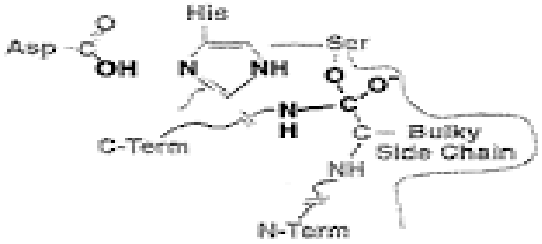
Step 1: H^+ shift generates Ser-O^-



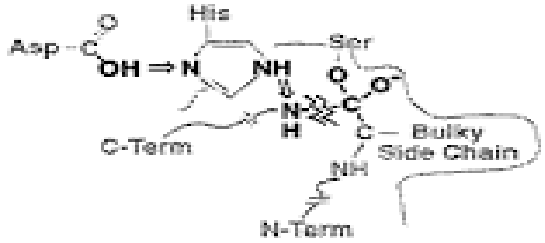
Step 2: Ser-O^- binds to C=O



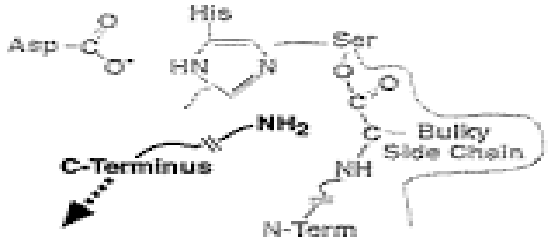
Step 3: Transition State I



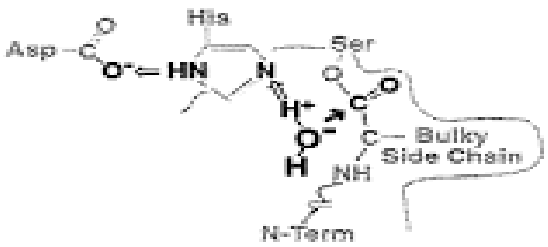
Step 4: Peptide bond breaks



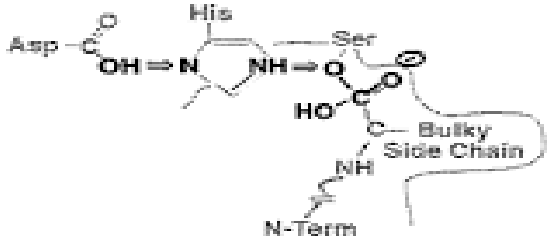
Step 5: C-Terminal peptide leaves



Step 6: Ionization of water



Step 7: Transition State II



Step 8: N-terminal peptide leaves