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EndopeptidasesProteases Enzymes in Proteins

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Introduction

Till date about one third of the proteases are serine proteases. Serine proteases have serine group present at their active site. Serine proteases actively participate at neutral pH and play a significant role in proteolysis. These proteinases include leukocyte serine proteinases, neutrophil elastase, proteinase-3, plasminogen activators, and digestive enzymes like trypsin. These serine proteinases are involved in the killing of bacteria fungi, activation of platelets, cell secretion and production of cytokines.

General properties

The serine proteases have similar properties in sequence and structure as compared to other proteases. Barett and his colleagues developed a classification system according to which proteases are further divided into unique clans and families, serine proteases are categorized into 13 clans and 40 families. The family name depicts the nucleophilic serine in the enzyme site; nucleophilicity of the serine is dependent on the catalytic activity of the aspartic, serine and histidine residues. Four of the protein folds results in the catalytic traid activity namely subtilisin, trypsin, prolyl oligopeptidase, and ClpP peptidase. In most of the proteins this triad is simplified where lysine or histidine is coupled with catalytic activity of serine. Some serine proteases can mediate the binding of histidine residues with nucleophilic serine [1-4]. Mostly serine proteases occur in viral genomes and distributed in nature abundantly. They have specific clan for example, clan PA proteases occur in eukaryotes while absent in prokaryotes. Serine proteases are usually endoproteases, but some exoproteases have also been discovered. These exoproteases can remove the amino acids from large protein molecules [5-8]. In man, there are about 699 proteases out of which 178 belongs to serine family. Among these 178 serine proteases, 138 belong to S1 protease family. The trypsin folds of S1 endonuclease represent the efficient binding of catalyst, specificity of substrate, protein folding regulation mechanism. The summary of catalytic site of serine proteases Table 1.

Table 1. Illustration of Serine Proteinases and their specific Inhibitors.

Families	Clan	Catalytic residues	Representative member	Primary specificity
1	SS	Ser, Glu,His	L, D carboxypeptidase	K
12	PA	Ser, Asp,His	trypsin	A,F, E, Q,R, Y, W
1	SR	Lys, Ser	Lectoferrin	K, R
5	ST	Ser, His	Rhomboid	D, E
2	SK	Ser, His, Asp	Clp peptidase	A
1	SJ	Ser, Lys	Lon peptidase	K, L,M, R, S
2	SC	Ser, His, Asp	Prolyl oligopeptidase	G,P
2	SB	His, Asp, Ser	subtilisin	F, Y, W

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Clan pa proteases

Clan PA proteases with the trypsin fold is among the largest family of serine proteases. The trypsin enzyme is used to cleave the polypeptide chain at positively charged amino acid residues while chymotrypsin cleaves the polypeptide chain at large hydrophobic residues. Mostly clan PA proteases have trypsin specific substrate and arginine or lysine chains are promoted at position P1 of substrate. Many biological processes are dependent on the clan PA proteases, like immune response and blood coagulation which involves the series of zymogen activation [9] Table 2.

Table 2. Main sources available for different kinds of Proteinase.

Proteinase	Inhibiotrs	Source
Granzymes	P1-9	Lymphocytes
Proteinase 3	α1 Macroglobulin Elafin neutrophil	Hepatocytes Epithelial cells Inflamatory cells
Neutrophil elastases	α1proteinases inhibitor	Hepatocytes

The family S1 of clan PA proteases is further divided into S1A and S1B sub-families, the former are trypsins that mediate extracellular functions, they are rarely found in plants and bacteria. The S1B is involved in cellular reactions and involved in intracellular turnover of proteins. The S1A in humans are categorized into six functions, namely Digestion is mediated by large number of exproteases, blood coagulation is done by endoproteases which converts the larger proteins into smaller subunits, Tryptases are involved in the secretion of mast cells granules, Matriptases are membrane bounded proteases having trypsin like specificity, Granzymes are involved in the defense and viral mechanisms. These are significant enzymes having specificity for acidic moieties [10].

Substrate specificity

The serine proteases are distinguished from each other on the basis of the distinctive structure consisting of two beta domains on the catalytic site. These enzymes have different substrate specificity like,

Trypsin-like: These enzymes are used to cleave the peptide bonds of positive amino acids like lysine and arginine.

Chymotrypsin-like: The proteases are more hydrophobic and cleave the peptide bonds of amino acids like tyrosine and tryptophan.

Thrombin-like: These proteases include the thrombin which is tissue activating plasminogen and plasmin. They are involved in blood coagulation process.

Elastase-like: These proteases have smaller cleft and the amino acids they cleave includes alanine, valine and glycine.

Subtilisin-like: It is a present in prokaryotes, having same catalytic mechanism like nucleophilic serine.

Primary specificity

In trypsin folds, the catalytic residues are distributed equally in the polypeptide chains. Two six stranded β-barrels are arranged in such a way that they form a catalytic traid. H57 and D102 belong to the N terminal β-barrelsand the oxyanion hole, with the C terminal β-barrel. The differences in the amino acid

residues are 10Å deep inside the active site and at the bottom are the trypsin residues having D189 and chymotrypsin having S189. Recent advances have shown that the S189 replacement in chymotrypsin results in the trypsin specificity, moreover a structural and functional relationship is required for the proper molecular functioning of serine proteases [11-12].

The E* form

A serine protease for blood coagulation, thrombin showed some changes in the trypsin folds. Thrombin exists in three forms as sodium free form the Enzyme and the sodium-bounded form E: Na are the highest and lowest activity conformations of the enzymes another third form, E* is an inactive state and in equilibrium with the enzyme. The E* cannot bind to the sodium ions directly until converted to active from. There are small differences in the enzyme and enzyme bounded sodium ions form which can lead to the genetic changes in the active and ground states of the enzyme is shown in the Figures 1-2.

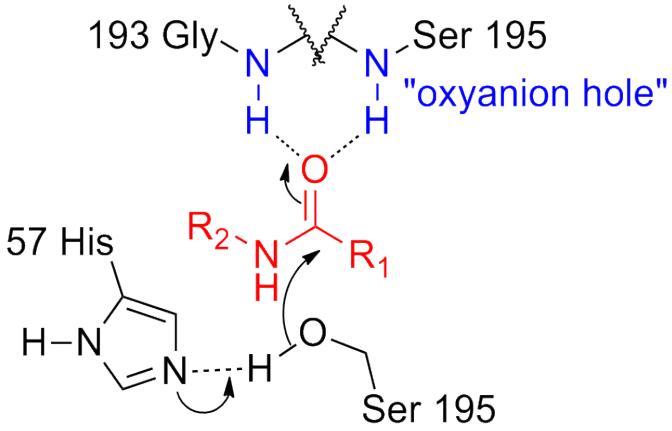

Figure 1. Structure of protein Proteases.

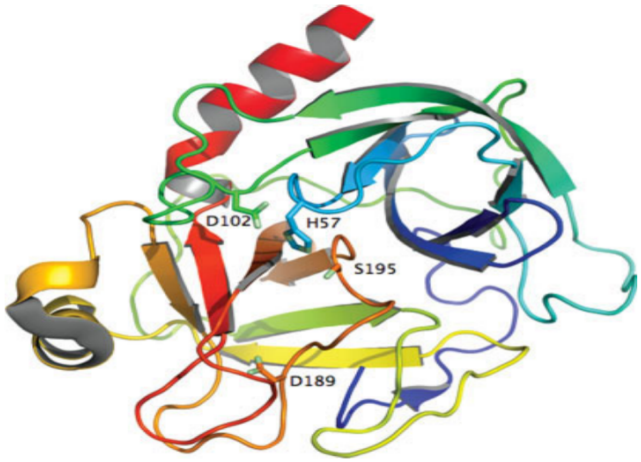

Figure 2. Structure of serine protease representing the primary structure of enzyme.

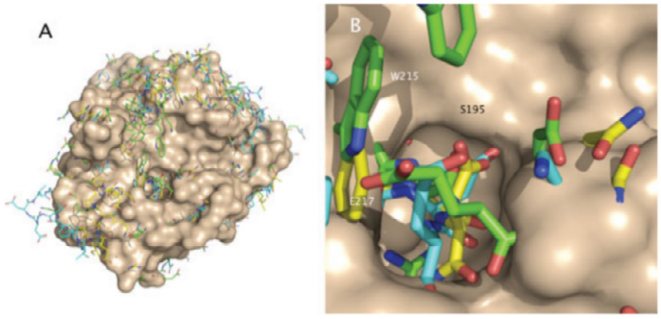

Figure 3. Two forms of allosteric of Serine Proteases.(A) Inactive form of serine protease E and activated serine Protease E* (B) Molecular based allosteric form of Serine Protease.

For example, E* shows a collapse from 215 -217 amino acid residues in the β-barrel of the active site, the oxyanion hole is disturbed due to the changes in the peptide bond between E192 and G193 in the β turn. The changes in the D189 in the sodium free from the enzymatic form also results in the disruption of oxyanion hole.

Catalytic mechanism

The activity of serine proteases requires the catalytic activation of zymogen precursors. The cleavage of protein molecule occurs at the same position in between 15 and 16 residues of the family members. Proteases includes the tissue plasminogen activators has lysine at position no 156 that have ion effect on D194 which is involved in the oxyanion hole and substrate specificity and covert the protein fold into proteolytic cleavage at position no 15. All of the clan PA proteases utilizes the canonical triad and hydrolyzes the peptide bond by the two tetrahedral intermediates. The breakdown of tetrahedral intermediates results in the acyl-enzyme intermediate and N terminus is stabilized during the reaction. The water molecule further displaces the free polypeptide end and reacts with the acyl-enzyme intermediate. The oxyanion hole then stabilizes the tetrahedral intermediate and the breakdown of these two intermediates results in the formation of C terminus in the substrate. The catalytic mechanism shown Figures 3A and 3B.

Inhibitors of serine proteinases

The serine protease inhibitors are usually used to control the activity of serine proteases, comprising about 10% of the total plasma proteins. The major plasma serpins are produced by hepatocytes, endothelial, epithelial and inflammatory cells. Secretory leukocyte proteinase inhibitor (SLPI) is produced by the epithelial cells of respiratory track. PI-9 is an intracellular protease inhibitor found in the cytoplasm of lymphocytes. Human GRZ A, GRZ B are not being inhibited by a1-PI, a1-antichymotrypsin, elafin, or SLPI in Figure 4.

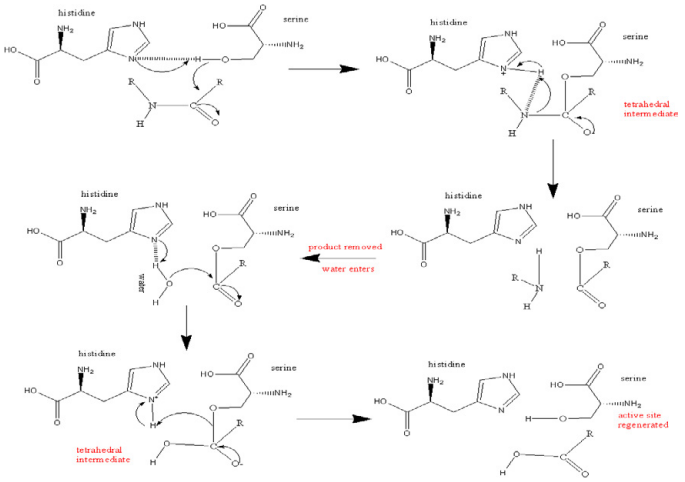

Figure 4: Catalytic mechanism of serine protease.

Conclusion

Proteases are involved in the breakdown of larger protein molecules into smaller proteins or their peptides. This protease enzymes breakdown the peptide bond within the protein molecule by hydrolysis reaction. There are different types of proteases which include the Aspartic proteases, Cysteineproteases, Glutamic proteases, Serine proteases, Threonine proteases and Metalloproteases. Among these proteases, serine proteases mostly play an important role in the treatment of disease, inflammation, viral diseases, bleeding disorders and cancer.

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