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REVIEW

A critical review on serine protease: Key immune manipulator and pathology mediator

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Abstract Proteolytic activity is fundamental to survival, so it is not surprising that all living organisms have proteases, especially seine protease. This enzyme in its numerous isoforms and homologues, constitutes the quintessential offence and defence factors, in the form of surface proteins, secreted molecules, gut digestive enzymes, venom in specialised glands or plant latex, among other manifestations. Occurring as trypsin, chymotrypsin, elastase, collagenase, thrombin, subtilisin etc., it mediates a diverse array of functions, including pathological roles as inflammatory, coagulatory to haemorrhagic. This review emphasizes that despite the superficial differences in mechanisms, most health issues, be they infectious, allergic, metabolic, or neural have a common conduit. This enzyme, in its various glycosylated forms leads to signal misinterpretations, wreaking havoc. However, organisms are endowed with serine protease inhibitors which might restrain this ubiquitous yet deleterious enzyme. Hence, serine proteases-driven pathogenesis and antagonising role of inhibitors is the focal point of this critical review.

Introduction

Mankind is afflicted with a number of health issues, infectious, allergic, metabolic, neural, among others. Unfortunately, with rising pollution, excessive reliance on drugs and increased incorporation of chemicals in diet and day-to-day consumables, health concerns are soaring.[1] Cutting-edge studies are unravelling the hidden mechanisms of diseases, and drugs are being developed, yet morbidity and untimely mortality continues. Killer virus, bacteria, protozoa, and fungi claim millions of lives every year, more so in developing countries.[2] Allergies and cancers are more prevalent in developed countries, where irritants exceed.[3] Although the disparity is largely getting fuzzy, and both forms of pathogenesis converge in exacerbating the immune system.[4] The complexity and diversity of pathological mechanisms render it difficult to track the precise pathways exploited by the pathogens, allergens or mutagens. A myriad of factors have been attributed to the maladies. Proteins, in particular enzymes, are pivotal in signal processing and resultant pathologies. Proteases are fundamental to survival

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across all living organisms, evident from their 2 to 4% share from the entire proteome.[5] Proteases have been involved in almost all health risks, which can be classified roughly into six categories such as serine proteases, cysteine proteases, aspartate proteases, threonine proteases, glutamic acid proteases, and metalloproteases.[6] Out of which, specifically serine protease is particularly crucial as it is widely present, from virus to human. This review hypothesises serine protease as a quintessential player in majority of human morbidities and analyses the literature to find pertinent evidence. The scope of recruiting serine protease inhibitors to bridle the enzyme has been discussed. Overall, this review examines this ancient and diverse enzyme family in a new light, which is believed to be of therapeutic concern.

Serine proteases

Serine protease (EC 3.4.21) is an endopeptidase that cleaves peptide bonds like any other protease; however, the serine residues in the active site (serine as a nucleophile) can coordinate many other critical functions, via protein hydrolysis.[7] The functions are vast, some of which are important such as protein metabolism, digestion, blood coagulation, apoptosis, immunity regulation of development, and fertilisation.[8,9] Although its role is too pervasive and intricate, cleavage of protease-activated receptors (PARs), the G-protein-coupled receptors on epithelial, vascular, neural and immune cells is the first step in proteolysis.[10,11] For its key roles, it is quintessentially present across all living beings, virus to human, including plants.[12]

Serine (Ser or S) is a polar amino acid encoded by six codons (UCU, UCC, UCA, UCG, AGU and AGC), the highest number of codons for any amino acid.[13] The human body can synthesise it, and it can be formed from glycine (by hydroxymethylation with the help of vitamin B) and in turn be converted to cysteine/methionine.[14] Non-essentiality status of this amino acid can be attributed to its indispensability for purine and pyrimidine synthesis,[15] antibody synthesis (the effector molecule of immune system), also sphingolipid and folate synthesis. Both L and D-form serine exists in humans, with L-form synthesised in the brain astrocytes, which in turn transforms to D-form by the activity of serine racemase.[16] The dual configuration makes serine a complicated amino acid, as each form has different functions, with D-serine perturbation attributed to neural pathologies.[17,18] Named after its first protein source, the silk protein sericin, serine can be found widely. Serine-rich proteinous foods include meat, dairy products, nuts (almonds, walnuts, peanuts), gluten, sesame seed, and soy beans (surprisingly, those associated with food allergies). Serine is very prone to bindings, thus can lead to deactivation of the protein it is harboured by (insecticides are based on this approach).[19] The secreted proteins of bacteria and fungi have been discovered to contain serine proteases, of which the serine residue is often glycosylated (N glycosylation).[20] Glycosylation (the addition of glycans or oligosaccharides) of serine, makes the protease complex.[21] This posttranslational modification is crucial but stochastic as it largely depends on environment and epistasis between genes.[22,23] Protease glycosylation has been linked to diseases such as diabetes,[24] cancer[25] and an array of neurodegenerative ailments.[26] Phosphorylation of serine/threonine by kinases and dephosphorylation by phosphatases is the hallmark of signalling pathways.[27] Further, the occurrence of serine in both L and D form in humans has been linked to neural diseases like epilepsy, amyotrophic lateral sclerosis (ALS), Alzheimer, schizophrenia.[17] Fig. 1 illustrates features of serine amino acid.

Based on substrate specificity (casein, albumin, haemoglobin, extracellular matrix proteins as fibronectin, fibrinogen, collagen, etc.), serine proteases are ramified into numerous types, prominent of which are trypsin-like, chymotrypsin-like, subtilisin-like, elastase-like, kallikrein, cathepsin, etc.[7] The target of each of these serine proteases seem to be different (gut mucosa, skin epithelial cell, lung mucosa). The enzymes are divided into many clans/superfamilies (further divided into families), based on catalytic site topology. PA is a major superfamily (clan) of serine proteases of which S1 (trypsin-like fold) is a well-studied family.[28] Here, the active site is generally made of three amino acids, Ser, His and Asp (the catalytic triad which works by charge-relay network). Sometimes one or more of these residues are substituted by similar amino acids. The residues play a critical and complementary role, despite their dispersed location in the protein. Trypsin-like proteases cleave peptide bonds at Lys or Arg, variations of the enzyme being tryptase, matriptase, kallikrein and granzymes.[9] Extreme plasticity of this protease fold is conspicuous, and several domains to bind here are apple, CUB (for complement C1r/C1s, Uegf, Bmp1), epidermal growth factor-like (EGF), fibronectin, kringle, sushi, and von Willebrand factor.[8] Its role in digestion, blood coagulation, and immunity (executed through a cascade of sequential zymogen activation) is well-validated.[29] Chymotrypsins cleave the peptides on the carboxyl side of Phe, Tyr and Try (the larger hydrophobic residues). The role of chymotrypsin in impairing cell–cell adhesion has been validated. Elastase-like proteases cleave bonds at the smaller non-polar amino acids Ala, Gly or Val. Fig. 2 shows the polarisation of nucleophile serine by a strategically aligned acid and base residues. Subtilisin-like protease functions by the same mechanisms, leading to a wide array of atopic conditions, although it is phylogenetically different. Overall, the enormous extent of diversification in serine proteases (isoforms, homologues, etc.) has occurred due to convergent evolution, and resultant polymorphism (from the requirement of protection against different attackers). Also, this aspect can be held responsible for the low substrate specificity and subsequent high IgE-reactivity among allergens. A study on phyto-pathogen insects revealed the occurrence of multiple serine protease genes adjacent to each other in the genome, implying frequent gene duplications in this family.[30] Empirical studies on this enzyme have revealed their molecular weight (16–95 kDa) and conformation (monomeric to multimeric) varying widely, due to variable extraction, purification conditions, also, glycosylation and complexation variabilities. However, universally, their N terminal sequence is conserved as it constitutes the signal part.[31]

Serine protease-mediated inflammation

Serine protease is ubiquitous to all living organisms, although niche specialisation and adaptive evolution has

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