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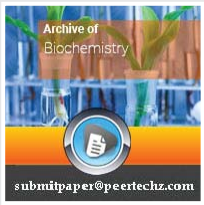

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Review Article

Serum Albumin as a Probable Extracellular Chaperone

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Abstract

Serum albumin has been known for its function as a carrier protein. Recently there have been several studies that reflect the potential role of serum albumin as an extracellular chaperone. Depletion of serum albumin from the plasma has been linked to impaired cognitive function and the potential risk of developing neurodegenerative diseases. Being irreversible in nature, neurodegenerative diseases pose a serious health risk to society. Analyzing the nature of the insult and deficiency in extracellular proteostasis that could predispose the extracellular environment to these misfolding and aggregation-related disorders is very significant. Being a major protein in the plasma, serum albumin holds great potential to serve as an extracellular chaperone.

Introduction

Molecular chaperones help the protein prevent non-native interactions and enter the aggregation phase [1]. The capacity of the cell to maintain the proteasis network decreases as it ages. This leads to the development of diseases that are caused due to protein misfolding and aggregation, like the progression of various cancers, neurodegenerative disorders like AD & PD, and type II diabetes. Depending on the molecular chaperones, they may or may not require ATP for proper functioning. Gro EL and Gro ES molecular chaperone system, which is present in bacteria and is one of the most studied and crucial molecular chaperone systems, requires ATP for their functioning [2,3]. However, Hde A and Hde B, tiny acidic chaperones, work without ATP [4]. Molecular chaperones work in either way to prevent protein misfolding. Either they restore correct conformation of the misfolded or aggregated protein, or they help in the solubilization of aggregates or amyloid fibrils that are insoluble and tend to deposit in the intracellularly or extracellularly like Hsp70-ClpB/ Hsp104. They may direct these misfolded proteins toward the degradation by Clp/Hsp 100 [5]. On the basis of the cellular location, they may be classified as extracellular and intracellular chaperones.

Extracellular spaces remain under surveillance for misfolded and aggregated proteins. They play an essential role in protecting the cell and the tissues against any stress or disruptive effects on the cellular membrane by clearing the misfolded and aggregated proteins, thus helping maintain the integrity of the intercellular spaces. Although the mechanism involved in oligomer toxicity remains elusive, common structural epitopes and exposed hydrophobicity are believed to relate to their toxicity. There is no specific mechanism for oligomer toxicity [6,7]. Misfolded protein, which has high hydrophobicity, may interact with cell surface receptors, which may lead to changes in intracellular cascades and potentially lead the cell toward death [8], or they may directly interact with the cell membrane and cause the disruption of the cell membrane, resulting in toxicity [9]. Irrespective of the extensive research on drug development for neurodegenerative drugs, no promising drug inhibits or suppresses amyloid-induced neurodegeneration. One drug, lecanemab, has been

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approved by the FDA to treat the early stages of AD [10]. It is a humanized monoclonal IgG1 antibody that specifically targets and binds soluble Aβ soluble oligomers, thus inhibiting the very first steps of the aggregation Aβ protein. The best treatment for protein aggregation is to inhibit or suppress the aggregation formation of proteins in the cells in their early stages. For this, studies need to help us understand the mechanism operating in the natural course to combat protein aggregation and protect the cell from cell death.

Extracellular proteostasis

Extracellular chaperones play a pivotal role in maintaining the extracellular proteostasis. They help the clearance of the misfolded proteins prone to get aggregated by keeping them in a soluble state. The extracellular environment is highly oxidizing, and also, due to blood and fluid circulation in the body, the proteins secreted in the extracellular space experience shear stress. With time these proteins, due to continuous shear force, tend to misfold and need restoration. Extracellular chaperones help in the recognition and degradation of the misfolded proteins relatively at a higher pace than their native folded precursors reflecting the importance of the EC proteostasis in protecting the organism from the potential disorders that may arise due to misfolded or aggregated proteins in the extracellular space [11].

The extracellular environment is oxidizing in nature, which is different from the intracellular environment. Also, the concentration of ATP, a primary source of energy for the intracellular chaperones, is much lower in the extracellular space reflecting the low efficiency of the chaperone-assisted machinery to operate the refolding or repair of the misfolded proteins [1,12,13]. Some examples of extracellular chaperones include clusterin, haptoglobin, α_2 macroglobulin, and caseins. Table 1 summarizes the disease associated with extracellular chaperones.

Albumin as a probable extracellular chaperone

Albumin present in the serum is one of the most abundant proteins in mammals as it constitutes 60% of plasma. The primary function of serum albumin is to transport molecules like free fatty acids, drugs, hormones, and various ligands like ions of copper, calcium, and other hydrophobic molecules [27]. Being the most abundant protein in the circulating plasma it determines the oncotic pressure of the circulating fluid of the body. It is also responsible for the antioxidant potential of plasma and performs the detoxification of the plasma [28]. It interacts with a diverse group of molecules and increases their solubility, thus helping in their transportation. The concentration of BSA is 640 μm and 6 μm in the plasma and cerebrospinal fluid, respectively. Research in the last two decades has shown the potential role of BSA as an extracellular chaperone as it reflects many functional similarities with the bonafide extracellular chaperones. It has been observed that BSA has potentially reduced the heat-induced precipitation, thermal inactivation, and heat-induced aggregation of various client proteins similar to bonafide extracellular chaperones clusterin, haptoglobin, α2 macroglobulin and even more efficiently than α-crystallin (an intracellular chaperone) [29-33]. Like other EC chaperones, it also shows a broad specificity and ubiquitous presence in the extracellular fluids. There is research work that demonstrated binding of BSA and Aβ peptide further inhibits the Aβ induced lysis of erythrocytes and fibrillar aggregation of Aβ peptide, reflecting the potential role of BSA as a molecular chaperone and potential role of BSA in the absence of protein aggregates in the mammalian peripheral tissues [34].

Low serum albumin concentrations in the blood (hypoalbuminemia) may occur in the body due to various pathological conditions like chronic liver disease [35], lack of nutrition, or due to progression of cancers or various infections [36]. Hypoalbuminemia has been shown to have a positive correlation with thrombotic events. Studies have shown that hypoalbuminemia has a direct implication on the progression of acute pulmonary embolism [37]. Patients have also shown a potential risk of developing venous thromboembolism [38]. C-Reactive Protein (CRP) concentrations are also found to be elevated in patients suffering from hypoalbuminemia [39].

Low serum albumin levels have also shown a positive link with the severity of COVID-19 patients. Patients with low serum levels faced unfortunate outcomes [40].

Hypoalbuminemia has been also analyzed with the potential risk of neurodegenerative diseases [41]. Recently there have been many studies that elucidate the possible link between serum albumin and cognitive functions in the human population. These studies show that maintaining albumin at healthier or normal levels in the body leads individuals to better cognitive functions and lowers the risk of dementia [42,43]. Serum albumin has been shown to inhibit secondary nucleation secondary nucleation in the case of amyloid beta-peptide polymerization [44], and HSA can decrease the overall aggregation of TDP-432C [45]. Our studies also reflect the chaperone potential of BSA as it solubilizes the Hb aggregates, effectively inhibits secondary nucleation and aggregation of Hb, and retains the structural integrity of Hb and cyt c at high temperatures [46,47].

Table 1: Some examples of the co-localized extracellular chaperones with the disease associated with aggregated proteins.

Extracellular chaperones found co-localized with disease-specific protein aggregates	Associated disease
Clusterin	Alzheimer's disease [14]. Spongiform encephalopathies [15]. Macular degeneration [16]. Atherosclerosis [17]. Familial British dementia [18]. Familial Danish dementia [19]. Downs' syndrome [20]. Type II diabetes [21] Amyloidotic cardiomyopathy [22]
α_2M	Alzheimer's disease [23]. Atherosclerosis [17]. Hemodialysis-related amyloidosis [24]
Haptoglobin	Alzheimer's disease [25]. Glomerulonephritis [26]

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The plethora of consequences of low serum albumin concentrations reflects the important role of serum albumin in maintaining protein homeostasis. Understanding the extracellular chaperone potential of serum albumin and aggregation dynamics in vivo opens up new research endeavors. How serum albumin affects the general protein homeostasis is hence of great importance in biomedicine and pharmacology. However, additional research is needed in this field because the mechanisms are not completely understood.

Our knowledge of the processes that maintain proteostasis in extracellular bodily fluids is still limited, but it has improved as a result of the identification of a small but expanding family of constitutively released extracellular chaperones. The molecular factors involved in the misfolding of extracellular proteins remain elusive and poorly understood. Possible mechanisms involved in extracellular proteases have been continuously addressed in recent research over the past two decades. Understanding the sequence of events and molecular mechanism of chaperone action of serum albumin helps researchers in prevention and drug development.

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