Serum Albumin

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Being one of the most abundant proteins in human and other mammals, albumin plays a crucial role in transporting various endogenous and exogenous molecules and maintaining of colloid osmotic pressure of the blood. It is not only the passive but also the active participant of the pharmacokinetic and toxicokinetic processes possessing a number of enzymatic activities. A free thiol group of the albumin molecule determines the participation of the protein in redox reactions. Its activity is not limited to interaction with other molecules entering the blood: of great physiological importance is its interaction with the cells of blood, blood vessels and also outside the vascular bed. This topic review contains data on the enzymatic, inflammatory and antioxidant properties of serum albumin.

Keywords: albumin ; blood plasma ; enzymatic activities ; oxidative stress

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Albumin is a family of globular proteins, the most common of which are the serum albumins. All the proteins of the albumin family are water-soluble and moderately soluble in concentrated salt solutions. The key qualities of albumin are those of an acidic, highly soluble and very stable protein, able to withstand temperatures of 60 °C for 10 h [1]. Human serum albumin (HSA) has a total of 83 positively charged residues (Arg + Lys) and 98 negatively charged residues (Asp + Glu), with a theoretical pI of 5.12. Albumins are commonly found in blood plasma and differ from other blood proteins in that they are not glycosylated. Several other blood transport proteins are evolutionarily related to serum albumin, including alpha-fetoprotein, vitamin D-binding protein and afamin [2][3]. This family is only found in vertebrates [4]. The four canonical human albumins are arranged on chromosome 4 region 4q13.3 in a tandem manner [5]. The human albumin gene is 16,961 nucleotides long from the putative ‘cap’ site to the first poly(A) addition site. It is split into 15 exons that are symmetrically placed within the three domains thought to have arisen by triplication of a single primordial domain.

Humans are not the only organisms for which serum albumin plays a critical role; albumin has also been characterised in an extensive number of species, including (but not limited to) canines, chickens, several species of frogs, lampreys, pigs and salamanders (an exhaustive list can be found at albumin.org [6]). Albumin-like proteins, which were sequenced from a sea urchin, were found to have a cysteine binding pattern similar to that seen amongst other proteins in the albumin family [7].

The precursor of serum albumin (preproalbumin) has the N-terminal peptide, which is cut off before the protein leaves the rough endoplasmic reticulum. The product of this removal (proalbumin) is transported to the Golgi apparatus. In secretory granules, the limited proteolysis occurs and the mature non-glycosylated albumin is secreted into the extracellular environment [1]. Synthesis occurs in the polysomes of hepatocytes, and in healthy adults, 10–15 g/day of albumin can be produced; this accounts for nearly 10% of total protein synthesis in the liver [8]. While 30% of albumin is maintained in the plasma, the remaining pool is found predominantly in skin and muscle tissue.

The molecule of HSA consists of 585 amino acids forming one polypeptide chain. The length of the primary sequence can be different in albumins of other species; for example, 584 amino acids in bovine serum albumin (BSA) and 583 residues in rat serum albumin (RSA). The amino acid compositions of HSA and RSA are 73.0% identical, of BSA and RSA—69.9%. Molecular weight of HSA based on amino acid composition is 66.439 kDa, BSA—66.267 kDa, RSA—65.871 kDa; however, the values of molecular weight can vary because of post-translational modifications and genetic variants. The secondary structure of the protein contains about 67% helical structures next to 33% of turn and extended chain configurations without any β-sheets [9] (**Figure 1**). The three-dimensional structure of HSA was resolved rather late, only in the 1990s [10]. A similar structure of BSA was obtained in 2012 [11], but the three-dimensional structure of albumin of rats, the principal animals used in pharmacological and toxicological experiments, has not been obtained yet. Three homologous domains (I, II, III), consisting of two subdomains (A, B) form a three-dimensional structure of the protein, which is rather labile (**Figure 1**).

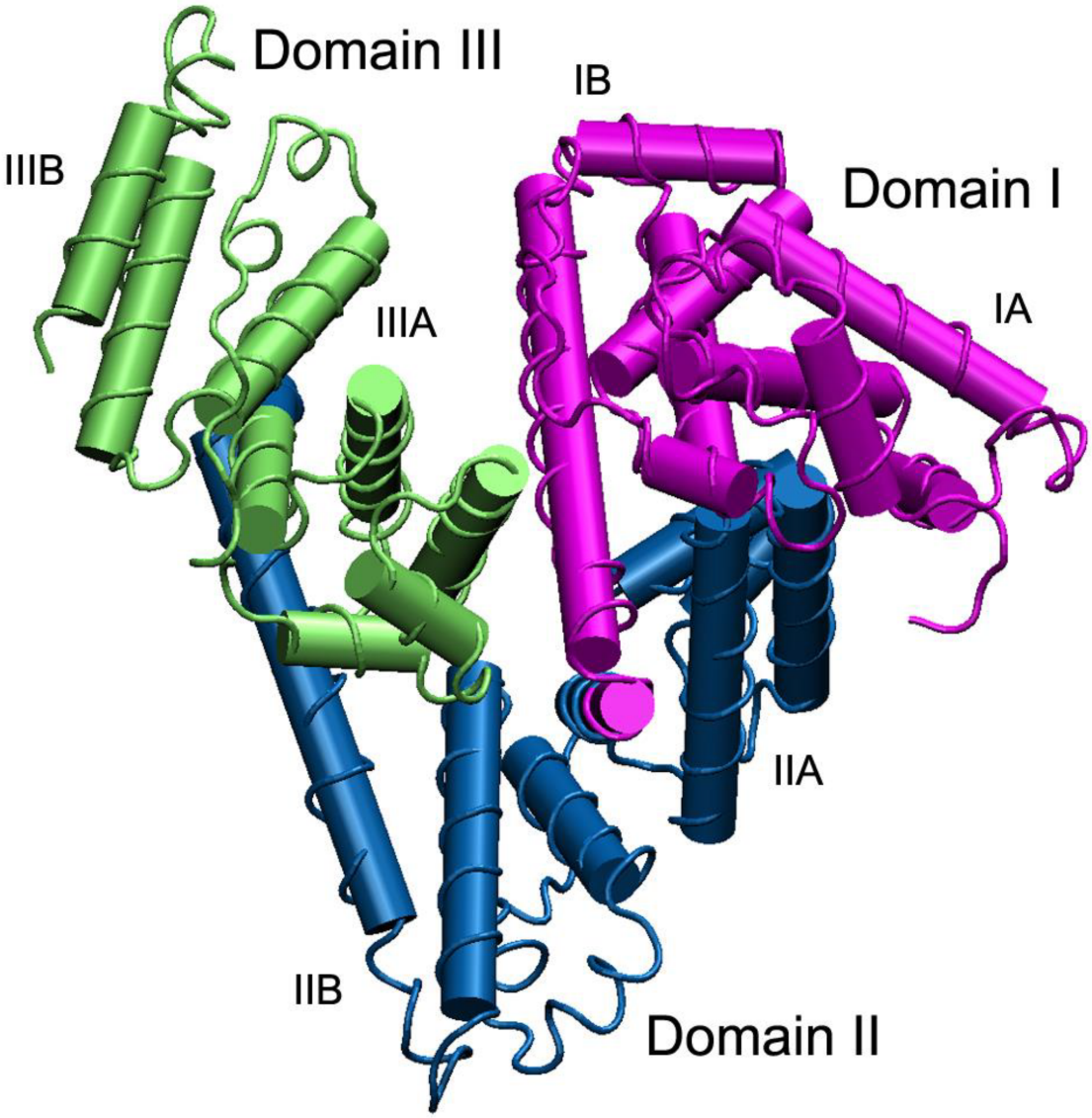

Figure 1. The structure of serum albumin. Domains I, II and III are shown in purple, blue and green, respectively; each domain consists of two subdomains A and B. The albumin molecule does not contain β-sheets, α-helices are presented as cylinders. To create the figure, a three-dimensional structure of human serum albumin from the PDB database, code 3JQZ [12], was used.

There are dozens of genetic variants of HSA (for exhaustive list see [6]). Possible effects of some single point mutations on the ligand-binding capabilities of HSA were investigated by studying the interactions between the strongly bound drugs warfarin, salicylate and diazepam, and five structurally characterised genetic variants of the protein [13]. Equilibrium dialysis data revealed pronounced reductions in high affinity binding of all three ligands to HSA Canterbury (313 Lys→Asn) and to HSA Parklands (365 Asp→His). By contrast, unchanged binding of the drugs was found in the case of HSA Verona (570 Glu→Lys). Salicylate was the only drug bound with a lower affinity to HSA Niigata (269 Asp→Gly), whereas binding of both salicylate and diazepam to HSA Roma (321 Glu→Lys) were moderately reduced. In about half of the cases of diminished binding, the primary association constant was reduced by 1 order of magnitude, giving rise to an increase in the unbound fraction of the drugs of 500% or more at therapeutically relevant molar ratios of drug and protein. Changes in protein charge play minor importance for reduced binding, though conformational changes in the 313–365 region of the proteins seem to be the main cause for diminished binding of these ligands [13].

Albumin normally is not covered with hydrocarbons and can bind different endogenous and exogenous ligands: water and metal cations, fatty acids, hormones, bilirubin, transferrin, nitric oxide, aspirin, warfarin, ibuprofen, phenylbutazone, etc. [14]. Ligand binding occurs at two primary sites (Sudlow site I in subdomain IIA and Sudlow site II in subdomain IIIA) and several secondary ones. When albumin interacts with different substances, the effects of cooperativity and allosteric modulation occurs, which is usually inherent to multimeric macromolecules [15][16]. The albumin molecule contains 17 disulfide bonds and one free thiol group in Cys34, which determines the participation of albumin in redox reactions.

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