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Review

Albumin based versatile multifunctional nanocarriers for cancer therapy: Fabrication, surface modification, multimodal therapeutics and imaging approaches

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ABSTRACT

Albumin is a versatile protein used as a carrier system for cancer therapeutics. As a carrier it can provide tumor specificity, reduce drug related toxicity, maintain therapeutic concentration of the active moiety like drug, gene, peptide, protein etc. for long period of time and also reduce drug related toxicities. Apart from cancer therapy, it is also utilized in the imaging and multimodal therapy of cancer. This review highlights the important properties, structure and types of albumin based nanocarriers with regards to their use for cancer targeting. It also provides brief discussion on methods of preparation of these nanocarriers and their surface modification. Applications of albumin nanocarriers for cancer therapy, gene delivery, imaging, phototherapy and multimodal therapy have also been discussed. This review also provides brief discussion about albumin based marketed nano formulations and those under clinical trials.

1. Introduction

Cancer is a deadly and life threatening disease with high mortality rate worldwide. According to GLOBOCAN, it caused 8.2 million deaths in 2012 [1]. The most common cancer deaths were due to lung cancer (1.6 million deaths), liver cancer (745,000 deaths), and stomach cancer (723,000 deaths) [2]. This high mortality rate may be due to several reasons like late diagnosis and detection of cancer, inability of therapeutic moiety to reach the tumor site, adverse and toxic effects towards the normal cells etc. [3]. The current strategy for the treatment of cancer lies in chemotherapy, radiotherapy, hormonal therapy and surgery. The existing conventional chemotherapy has several draw backs like less concentration of therapeutic moiety to the tumor site, less target specificity, toxicity towards normal cells and tissues, inability to cross different biological barriers like blood brain barrier, and drug and dosage form related factors which includes less solubility, less permeability, poor dissolution, less stability (photo, thermal and pH stability), degradation of drug, variable drug release from dosage form, multi drug resistance etc. [4,5].

So there is a need to develop novel delivery system which has ability to overcome all these drawbacks of conventional chemotherapy. In past several decades, nanoparticles have gained lots of attention for treatment of cancer. Nanoparticles have potential to overcome the drawbacks of conventional cancer chemotherapy because of unique properties like small size, surface charge, variable shape, several binding sites for the attachment of target specific ligands, antibodies, peptides etc. They can also enhance the tumor targeting by both passive and active targeting mechanism. Passive targeting is possible due to enhanced permeability and retention (EPR) effect [6,7]. Nanoparticles based delivery systems are also approved by the FDA for clinical use (Abraxane, Doxil, Genexol-PM, DepoCyt, Myocet etc.) and many more are in the clinical trials (NK105, CYt-6091, Genexol-PM, Rexin-G etc.) [6,8]. As compared to conventional chemotherapy, nanoparticles based delivery systems have several advantages and features, including: 1) improved delivery of poorly water soluble drugs, peptides, and genes; 2) better protection of drugs, peptides or genes from harsh environments (e.g., enzymatic degradation and the highly acidic environment in the lysosomes or stomach); 3) enhanced treatment efficiency and reduced systemic side effects by cell or tissue specific targeted delivery of drugs, peptides or genes; 4) overcome multidrug resistance by co delivery of drugs, peptides, genes and/or diagnostic agents; 5) stimuli-responsive systems (pH sensitive, temperature sensitive, redox sensitive) can control release of drugs, peptides or genes over a manageable period of time at precise doses [6,9].

Nanoparticles used as a carrier for cancer therapeutics may be of several types viz. protein based nanoparticles (albumin nanoparticles, gelatin nanoparticles etc.) [10,11], polymer based nanoparticles (poly lactide co glycolide nanoparticles, polycaprolactone nanoparticles,

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polylactide nanoparticles, chitosan nanoparticles etc.) [12–15], lipid based nanoparticles (solid lipid nanoparticles, nanostructured lipid carriers, liposomes etc.) [16–18], lipid polymer hybrid nanoparticles [19], metal nanoparticles [20–22], polymeric micelles (cationic micelles, unimolecular micelles, dual responsive and triple responsive micelles etc.) [23–31], dendrimers [32] etc. Among all these nanoparticles, protein based nanoparticles have gained much more attention in cancer therapy due to unique properties viz. relatively safe and easy to prepare, capability to deliver proteins, peptides, genes, nucleic acid, and hydrophilic as well as hydrophobic anticancer molecules, site specific targeting by surface modification, greater stability profile during storage, etc. [33]. In this review, albumin based nanocarriers and their role in cancer therapy have been discussed in detail.

2. Albumin

Albumin is a protein based macromolecule and the most abundant plasma protein (35–50 g/L human serum) of human blood which is synthesized in the liver at the rate of approximately 0.7 mg/h for every gram of liver (10–15 g daily) [34,35]. It is nontoxic, biodegradable, biocompatible, highly water soluble, non-immunogenic, easy to purify and stable plasma protein [36].

2.1. Types of albumin

Albumins are of various type viz. Ovalbumin (OVA), bovine serum albumin (BSA), human serum albumin (HSA), rat albumin etc. Commercially, albumins are obtained from egg white, bovine serum and human serum. Apart from these, it can also obtained from soybeans, milk and grains [36].

Ovalbumin (OVA) is monomeric phosphoglycoprotein obtained from egg white and is utilized in designing food matrix as it is a food protein. It has molecular weight of 4.7 kDa, isoelectric point (pI) of 4.8 and consists of 385 amino acid residues, with each molecule having one internal disulfide bond and four free sulphydryl groups and has 3D structure with helical reactive loop arrangement. It is used as a drug delivery carrier due to its properties like low cost, easy availability, emulsion and foam stabilization ability, pH and temperature sensitive properties [36,37].

Bovine serum albumin (BSA) is obtained from bovine serum and has a molecular weight of 6.93 kDa with pI of 4.7 in water at 25 °C. It is a water soluble monomeric protein that consists of 583 amino acid residues and contains 17 disulfide bonds resulting in nine loops formed by the bridges, one cysteine and 8 pairs of disulfide bonds. It also contains high content of aspartate (Asp), glutamic acid (Glu), alanine (Ala), luciene (Luc) and lysine (Lys). It is also used as a drug carrier because of its low cost, ease of purification, unusual ligand binding properties, biocompatibility, biodegradability, non-toxicity, lesser immunogenicity (as compared to OVA and rat albumin) and wide acceptance in pharmaceutical industry [36,38].

Human serum albumin (HSA) is heart shaped monomeric globular protein obtained from human serum. It consists of 585 amino acid residues and contains 17 disulfide bridges and 1 sulfhydryl group which is formed by cysteinyl (Cys35) residues. It contains single tryptophan residue (Trp 214) and one free cysteine (Cys34) and high amount of glutamic acid, arginine, and lysine. HSA contains negative charge due to presence of more acidic amino residue as compared to basic amino acid. Disulfide bridges provide stability and longer biological half life (~19 days). It has similar properties as BSA and is also used as a versatile carrier for drugs, genes, hormones, peptides and several other molecules [36,39].

HSA and BSA are homologous proteins and share 76% sequential identity. The major difference between the two is with respect to the number and positioning of tryptophan residues in them. HSA has only one tryptophan, located at position 214 which is equivalent to Trp-212 for BSA present buried in a hydrophobic pocket at sub domain IIA. BSA has one more additional tryptophan Trp-134, which is more exposed to solvent and found at sub domain IB. As compared to other albumins, HSA is more non immunogenic plasma protein due to which it is widely used as a safe and effective carrier protein in different delivery systems [40,41].

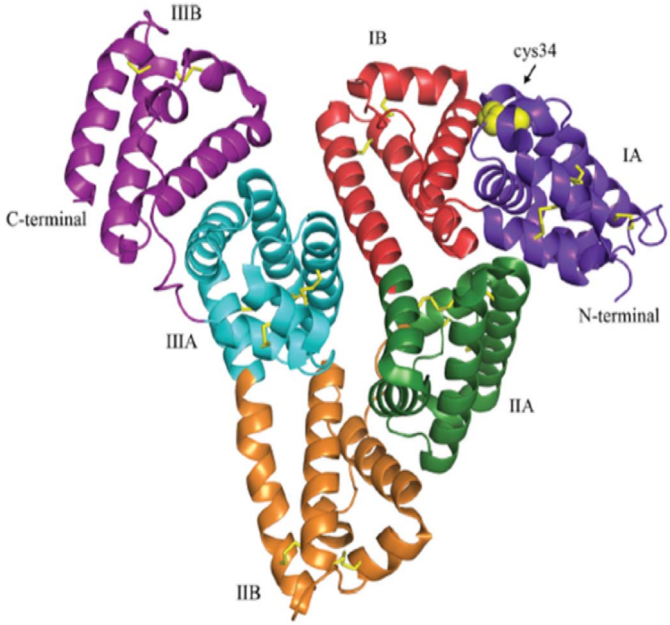

Fig. 1. Structure of human serum albumin.

2.2. Structure of albumin

The three dimensional (3D) structure of HSA (Fig.1), shown by X-ray crystallography, proposed that HSA molecule is formed from three homologous domains I, II and III which themselves contain two separate helical sub-domains A (4 α-helices) and B (6 α-helices) [35]. A heart shaped albumin with 67% α-helix and no β sheet is very stable to changes in pH, denaturating solvents and exposure to heat because it contains 17 disulfide bonds and one free thiol from an unpaired cysteine (Cyc34) in domain I [42].

2.3. Binding sites in albumin

HSA has two main binding sites namely, Sudlow site I (present in sub-domain IIA) and Sudlow site II (present in sub-domain IIIA). Bulky heterocyclic anions such as anticoagulant drug warfarin bind to site I and aromatic carboxylates such as diazepam bind to site II. Apart from these two binding sites, albumin also contains other binding sites like Cys34 (binding site for Au(I), Hg(II) and complexed Pt(II) in the form of cisplatin, nitric oxide) and fatty acid binding sites. Cys34 site is also used to conjugate small molecules as well as protein and peptide based drugs [42]. Different ligand binding sites are summarized in Table 1.

3. Albumin based nanocarriers

Albumin is a versatile protein used as a carrier system for cancer therapeutics. As a carrier it can provide tumor specificity, reduce drug related toxicity, maintain therapeutic concentration of therapeutic moiety like drug, gene, peptide, protein etc. for long period of time and also reduce drug related toxicities. It also has the potential in the half life extension of drug. As albumin has various binding sites, ligand functionalized delivery of therapeutic moiety is also possible which can provide site specific delivery of the therapeutic moiety [11]. Two basic approaches are utilized in the development of albumin based cancer