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Recombinant human serum albumin: molecular mechanisms, production technologies, and application prospects

Chaojian Han

School of Life Sciences, Shandong University, Qingdao, China

DQHCJ@qq.com

Abstract. Human Serum Albumin (HSA) is the most abundant protein in human plasma and plays essential physiological roles, including the maintenance of colloid osmotic pressure and the transport of a wide range of endogenous and exogenous substances. Recombinant Human Serum Albumin (rHSA), produced through genetic engineering technologies, effectively overcomes the inherent limitations of plasma-derived Human Serum Albumin (pHSA) in terms of raw material availability and biosafety. Consequently, it has attracted sustained attention in the biopharmaceutical field. This review systematically summarizes the molecular basis, production strategies, and current applications of rHSA, with particular emphasis on comparing the technical characteristics and applicability of different expression systems. In addition, future directions for process innovation and industrial translation are discussed, with the aim of providing references for further research and development in this area.

Keywords: recombinant human serum albumin, molecular mechanisms, production technology, clinical application, industrial prospects

1. Introduction

Human Serum Albumin (HSA) is a single-chain, non-glycosylated protein synthesized by hepatocytes. It is present in human plasma at a concentration of approximately 35–50 g/L and accounts for 55%–60% of total plasma protein. HSA has attracted considerable attention in both clinical medicine and biopharmaceutical research because of its multiple physiological functions, including the transport of diverse substances, buffering of blood pH, and maintenance of nutritional homeostasis. In addition, it serves as an important pharmaceutical excipient and cell culture supplement, further enhancing its practical value in biomedical applications [1].

Traditionally, clinical HSA has been obtained almost exclusively through fractionation of donated human plasma. However, this approach faces several major challenges, including a limited supply of raw materials and a continually widening gap between supply and demand. Moreover, the risk of contamination by blood-borne pathogens, such as hepatitis viruses and Human Immunodeficiency Virus (HIV), cannot be completely eliminated. Variability in the quality of plasma collected from different donors also makes it difficult to ensure

consistent product quality across manufacturing batches [2]. Against this backdrop, advances in genetic engineering have opened a new avenue for HSA production. Since the first successful expression of recombinant Human Serum Albumin (rHSA) in *Escherichia coli* in 1982 [3], the field has undergone decades of continuous development. Multiple expression platforms have since been established, and several rHSA products have already received regulatory approval outside China [4]. This review summarizes current research on rHSA from four perspectives: its structural basis, production technologies, applications, and future development trends.

2. Literature review

Research on rHSA spans more than four decades. From the initial attempts at heterologous gene expression to the establishment of relatively mature industrial manufacturing processes, the field has undergone several important stages of technological advancement. A systematic review of the literature helps clarify the trajectory of these developments and provides an integrated understanding of the key challenges that remain.

2.1. Overview of research progress at home and abroad

In 1982, the HSA coding gene was successfully isolated and cloned, and recombinant HSA was expressed in *Escherichia coli* for the first time in the same year [3]. However, because prokaryotic expression systems are incapable of performing the post-translational folding required for eukaryotic proteins, the recombinant product was largely produced as inactive inclusion bodies. Consequently, labor-intensive denaturation and refolding procedures were required to restore its native conformation, resulting in low overall yields [2, 5]. The introduction of the *Pichia pastoris* expression system in the 1990s marked a significant technological breakthrough [6]. This system combines the rapid growth characteristics of microorganisms with the ability to perform certain eukaryotic post-translational modifications, enabling gram-scale production of the target protein through high-cell-density fermentation [7-9]. During the same period, the *Hansenula polymorpha* expression system was also successfully developed for rHSA production [10]. In 2009, Chinese researchers established a plant-based expression platform using rice endosperm cells as bioreactors, achieving efficient accumulation of rHSA at levels exceeding 10% of the total seed protein [11]. The corresponding product was subsequently approved to enter clinical trials in 2017 [12, 13]. Although mammalian cell expression systems, such as Chinese Hamster Ovary (CHO) cells, remain considerably more expensive, recent advances in process optimization have improved their feasibility for applications requiring exceptionally high product quality [14]. Purification technologies have likewise undergone substantial evolution. Early methods based on salt precipitation and cold ethanol fractionation have gradually been replaced by integrated multi-step purification strategies centered on ion-exchange chromatography, hydrophobic interaction chromatography, and gel filtration chromatography. These modern processes consistently achieve product purities exceeding 99.5% [15, 16]. In parallel, quality control methodologies have advanced from conventional analytical techniques to high-resolution mass spectrometry, providing more comprehensive characterization of recombinant products [17].

2.2. Major research directions and recent advances

A review of the existing literature indicates that research on rHSA has primarily followed three major directions. The first focuses on the engineering optimization of expression systems. In the *Pichia pastoris* platform, in addition to optimizing conventional fermentation parameters such as temperature, pH, and carbon-to-nitrogen ratio [18, 19], targeted disruption of protease-encoding genes has proven effective in reducing product degradation and improving recombinant protein yield [20]. In plant-based expression

systems, molecular engineering of promoters and signal peptides has continuously enhanced expression efficiency [21]. The second direction concerns advances in purification and quality control technologies. Comparative studies of the adsorption performance of different chromatographic media [15], the development of purification protocols tailored to specific expression platforms [16, 22], and the application of high-resolution mass spectrometry for batch-to-batch consistency assessment [16] have collectively established a robust technical foundation for ensuring product quality. The third research direction involves functional modification and the exploration of novel applications. Fusion protein engineering has been employed to prolong the plasma half-life of therapeutic agents [23, 24], while albumin-based targeted drug delivery systems have opened new avenues for expanding the biomedical applications of rHSA [25].

2.3. Current research hotspots and controversial issues

Although the technological roadmap for rHSA production has become increasingly well established, several important issues remain under debate. One continuing controversy concerns the relative merits of different expression systems. Microbial fermentation is operationally straightforward and cost-effective, but it generally requires more demanding downstream purification. Plant-based production offers substantial advantages in terms of raw material costs, yet its scalability is constrained by the seasonal and geographical limitations inherent to agricultural cultivation. Mammalian cell expression systems provide the highest product quality; however, their widespread adoption is hindered by limited production capacity and high manufacturing costs [5, 26]. In addition, the clinical adoption of rHSA continues to face challenges related to acceptance by the medical community [4, 27]. Differences among national pharmacopoeias in quality control requirements further complicate international regulatory approval and product registration [17].

2.4. Current limitations and objectives of this review

Overall, previous studies have generated substantial knowledge regarding the optimization of rHSA production processes and the evaluation of its therapeutic applications. Nevertheless, two important gaps remain. First, systematic comparisons of the overall costs associated with different large-scale production strategies are still lacking. Second, although novel albumin-based drug delivery systems have shown promising results in preclinical animal studies, evidence supporting their clinical translation remains limited. Building upon the existing literature, this review comprehensively examines the structural basis, manufacturing technologies, and application potential of rHSA. Particular emphasis is placed on comparing the advantages, limitations, and appropriate applications of the major production platforms, with the aim of providing a clear analytical framework to guide future research and industrial development.

3. Molecular structure and physiological mechanisms of recombinant human serum albumin

3.1. Molecular structural characteristics

The HSA gene is located on the long arm of human chromosome 4 (4q13.3). It spans approximately 16 kb and consists of 15 exons and 14 introns. Its translation product is a precursor protein comprising 585 amino acid residues, which is processed by signal peptide cleavage to generate the mature protein with a molecular weight of approximately 66.5 kDa [21]. When the HSA coding sequence is introduced into heterologous host cells using recombinant DNA technology, the expressed protein possesses an amino acid sequence identical to that of native HSA, thereby fully preserving its biological functions [28].

The three-dimensional structure of HSA resembles a heart-shaped molecule composed of three homologous domains (DI, DII, and DIII), each of which is further divided into subdomains A and B [21]. This highly organized topology forms a central hydrophobic cavity lined predominantly with hydrophobic amino acid residues, enabling the protein to accommodate and bind a broad spectrum of ligands, including long-chain fatty acids, bilirubin, steroid hormones, and numerous therapeutic drugs. Ligand binding is mediated through a combination of hydrophobic interactions, hydrogen bonding, and electrostatic forces, providing the molecular basis for HSA's function as a versatile transport protein. In addition, the abundance of charged amino acid side chains distributed across the molecular surface ensures the protein's excellent solubility in plasma and its strong colloid osmotic activity [28].

3.2. Mechanisms underlying the core physiological functions

HSA contributes approximately 80% of the total plasma colloid osmotic pressure, a property that results from its high plasma concentration and relatively large molecular size. By regulating the movement of water across the vascular endothelium, HSA maintains circulating blood volume and tissue perfusion. This mechanism provides the physiological basis for the clinical use of rHSA in the treatment of hypovolemic shock and edema [1, 29]. With respect to molecular transport, the hydrophobic cavity of HSA functions as a multifunctional "molecular cargo compartment", carrying lipophilic compounds from their sites of synthesis to metabolic organs or target tissues. For example, HSA mediates the transport of fatty acids from adipose tissue to the liver and facilitates the movement of bilirubin through the circulation for subsequent metabolism and excretion. Many therapeutic agents also form reversible complexes with HSA after entering the bloodstream. Such interactions substantially influence the apparent volume of distribution, clearance rate, and ultimately the therapeutic efficacy of these drugs [28]. Furthermore, the Cys34 residue, which constitutes the most abundant free thiol group in human plasma, endows HSA with potent free radical-scavenging activity. Its ability to bind metal ions such as Cu^{2+} and Fe^{3+} further limits metal ion-catalyzed oxidative reactions, thereby protecting vascular endothelial cells and hepatic tissues against oxidative damage [29]. Finally, the numerous amino and carboxyl side chains distributed throughout the HSA molecule enable it to donate or accept protons in response to fluctuations in blood pH, allowing it to function as an important component of the plasma buffering system [1].

4. Production technologies for recombinant human serum albumin

The production of recombinant Human Serum Albumin (rHSA) depends on the establishment of an expression platform that combines high production efficiency with accurate protein folding, together with an effective downstream purification strategy. To date, reported expression systems can be broadly classified into three categories: microbial, plant-based, and mammalian cell expression systems. Each platform offers distinct advantages and limitations with respect to productivity, manufacturing cost, and product quality [26].

4.1. Microbial expression systems

Microbial expression systems currently dominate industrial rHSA production. Their widespread adoption is attributable to several advantages, including rapid cell growth, inexpensive culture media, and well-established large-scale fermentation technologies. Among these systems, *Escherichia coli* and *Pichia pastoris* are the two most extensively employed hosts [5].

Escherichia coli offers the advantages of simple genetic manipulation and a comprehensive set of molecular biology tools. By placing the HSA expression cassette under the control of a strong promoter and

transforming it into an appropriate bacterial strain, large quantities of recombinant protein can be produced [2, 3]. However, because *Escherichia coli* lacks the intracellular organelles required for the proper folding and post-translational processing of eukaryotic proteins, overexpressed HSA is frequently accumulated as inactive inclusion bodies. Conversion of these aggregates into biologically active protein with its native conformation requires multiple downstream steps, including solubilization, dilution refolding, or on-column refolding. These procedures are labor-intensive and often result in variable product recovery [5].

Pichia pastoris provides an attractive alternative. Possessing both the endoplasmic reticulum and Golgi apparatus, this yeast is capable of correct disulfide bond formation and can secrete properly folded recombinant proteins into the culture medium. Systematic optimization of the culture conditions for the GS115/HSA strain has been reported to yield approximately 150 mg/L of rHSA in shake-flask cultures [7]. Following scale-up to high-cell-density fermentation, protein production can be further increased to several grams per liter [8, 9]. Nevertheless, this system is not without limitations. During the later stages of fermentation, host-derived proteases accumulate in the culture broth and may degrade the target protein. Subsequent studies have demonstrated that optimizing fermentation temperature, controlling pH, and selecting appropriate nitrogen sources can effectively suppress protease activity and thereby reduce product degradation [18, 19]. In addition, *Hansenula polymorpha* has also been investigated as an alternative expression host. After codon optimization, engineered strains have achieved efficient secretion of recombinant HSA [10].

4.2. Plant-based expression systems

Plant-based expression systems employ transgenic crops, such as rice, maize, and tobacco, as bioreactors for recombinant protein production. Target genes are integrated into the plant genome through Agrobacterium-mediated transformation or particle bombardment, allowing rHSA to accumulate in seeds or leaves. The principal advantages of this approach include its low cultivation cost, elimination of the need for large-scale fermentation facilities, and the presence of a complete eukaryotic protein-processing machinery within plant cells [21].

Among these platforms, the rice endosperm expression system has attracted particular attention. Through the rational design of promoters and signal peptides, rHSA accumulation in rice seeds has been increased to more than 10% of the total seed protein, and the recombinant protein can be recovered using conventional milling and extraction procedures [11]. Based on this platform, a research team at Wuhan University established a plant-derived rHSA production process, and the corresponding injectable formulation entered clinical trials in 2017 [12, 13]. Despite these advantages, plant-based expression systems also present notable challenges. Their relatively long cultivation cycles and susceptibility to climatic and soil conditions can lead to fluctuations in production yield. Furthermore, meeting large-scale commercial demand would require substantial agricultural land resources. Consequently, this technology has not yet achieved widespread commercial-scale production [26].

4.3. Mammalian cell expression systems

Mammalian cell expression systems, including Chinese Hamster Ovary (CHO) cells and Human Embryonic Kidney (HEK293) cells, most closely resemble human cells in their protein processing machinery. Consequently, the rHSA produced by these systems exhibits structural conformation, charge variant profiles, and post-translational modification patterns that closely approximate those of native human serum albumin, thereby ensuring excellent biological activity and safety. A study published in 2023 reported that process optimization had enabled highly efficient production of HSA in CHO cells [14]. These expression platforms are particularly well suited for manufacturing high-value specialty products that require exceptionally stringent

quality standards. However, their application to routine pharmaceutical production remains limited because of the substantially higher costs associated with culture media and production facilities, as well as their relatively low production yields, which generally remain at the milligram scale [5].

4.4. Purification processes and quality control

The downstream purification of rHSA must satisfy exceptionally stringent impurity specifications. Current manufacturing processes generally employ integrated multi-step chromatographic purification strategies. Typically, ion-exchange chromatography, hydrophobic interaction chromatography, and size-exclusion (gel filtration) chromatography are performed sequentially to remove host cell proteins, nucleic acids, endotoxins, and other process-related impurities, consistently yielding products with purities exceeding 99.5%. Because different anion-exchange chromatography media exhibit distinct adsorption capacities and elution characteristics for rHSA, their selection must balance dynamic binding capacity with separation efficiency [14]. For recombinant proteins produced from transgenic animal-derived materials, purification strategies that combine cold ethanol fractionation with chromatographic purification have also demonstrated satisfactory performance [16, 22].

Quality evaluation encompasses both physicochemical characterization and biological activity assessment. Routine analytical testing includes determination of protein purity by SDS-PAGE, molecular weight verification, peptide mapping coverage, and quantification of residual host cell proteins, endotoxins, and nucleic acid contaminants. In addition, biological activity is evaluated by measuring the product's colloid osmotic properties and its capacity to bind characteristic physiological ligands. In industrial practice, multiple analytical techniques—including High-performance Liquid Chromatography (HPLC), Liquid Chromatography–Mass Spectrometry (LC–MS), and Enzyme-Linked Immunosorbent assay (ELISA)—are typically used in combination to establish a comprehensive, multidimensional quality control system [30]. In recent years, advanced high-resolution analytical platforms such as Ultra-performance Liquid Chromatography–Traveling Wave Ion Mobility Quadrupole Time-of-Flight Mass Spectrometry (UPLC-TWIM-QTOF MS) have been increasingly incorporated into batch release testing and comparability studies of rHSA products. Their superior structural characterization capabilities enable the detection of subtle molecular differences among products generated by different expression systems, thereby providing powerful analytical tools for establishing more rigorous quality standards [17].

5. Applications of recombinant human serum albumin

5.1. Clinical applications

The clinical indications for recombinant Human Serum Albumin (rHSA) largely parallel those of plasma-derived Human Serum Albumin (pHSA). However, because rHSA completely eliminates the risk of transmission of blood-borne pathogens, it offers a superior safety profile [1, 4]. Its clinical value is particularly evident in several major therapeutic settings.

For patients with hypoalbuminemia caused by liver cirrhosis or nephrotic syndrome, administration of rHSA rapidly restores plasma colloid osmotic pressure, thereby alleviating ascites and peripheral edema [31]. Animal studies have likewise demonstrated that rHSA significantly reduces ascites formation in mice with puromycin aminonucleoside-induced nephropathy [32]. In cases of acute hemorrhage, severe burns, or major surgery, rHSA serves as an effective colloidal plasma volume expander, facilitating rapid restoration of circulating blood volume and stabilization of hemodynamic parameters [4, 33]. In critically ill patients with conditions such as sepsis, rHSA supplementation not only corrects hypoalbuminemia but may also improve

nutritional status and modulate inflammatory responses [33]. Neonatal hyperbilirubinemia represents another important clinical indication. By binding free bilirubin with high affinity, albumin promotes its transport and subsequent elimination, thereby reducing the risk of bilirubin-induced neurological damage (kernicterus). Furthermore, complexation with rHSA can substantially improve the aqueous solubility of certain poorly soluble antineoplastic agents, facilitating pharmaceutical formulation and clinical administration [1, 29].

5.2. Applications as a pharmaceutical excipient

In the biopharmaceutical industry, rHSA is widely used as an excipient in the formulation of therapeutic products. It stabilizes protein-based pharmaceuticals—including monoclonal antibodies, insulin, and interferons—by preventing denaturation and aggregation in liquid formulations, thereby extending product shelf life and maintaining therapeutic efficacy [34]. Some vaccine formulations also incorporate rHSA to enhance antigen stability, improve immunogenicity, or reduce local adverse reactions following vaccination [27]. Another rapidly expanding area of research involves the development of rHSA-based drug delivery systems [35]. Through chemical conjugation or genetic fusion strategies, small-molecule chemotherapeutic agents, therapeutic peptides, and even nucleic acid drugs can be linked to albumin molecules. These delivery platforms exploit albumin's prolonged circulation time and the Enhanced Permeability and Retention (EPR) effect of tumor tissues to achieve passive targeted drug delivery [36]. A number of rHSA-based drug delivery systems have already entered preclinical evaluation and have demonstrated promising therapeutic potential in both oncology and antiviral therapy [25, 37].

5.3. Applications in cell culture

Cell culture represents another important application of rHSA. In serum-free or low-serum culture media, supplementation with rHSA provides essential nutritional support while helping to maintain appropriate osmotic pressure and pH stability within the culture environment. More importantly, rHSA effectively reduces shear stress caused by mechanical agitation and aeration, while also mitigating oxidative stress associated with the accumulation of metabolic by-products. These protective effects contribute to improved cell viability and enhanced recombinant protein production. Compared with Fetal Bovine Serum (FBS), the use of rHSA as a culture medium supplement eliminates batch-to-batch variability and minimizes the risk of contamination by adventitious animal-derived pathogens. Consequently, its application significantly improves manufacturing consistency and regulatory compliance in biopharmaceutical production [34].

6. Future perspectives and challenges of recombinant human serum albumin

6.1. Technological development trends

Looking ahead, technological advances in the rHSA field are likely to concentrate on several key areas. With respect to expression system engineering, genome-editing technologies such as CRISPR-Cas9 have already been applied to genetically modify *Pichia pastoris* and rice expression hosts. Common strategies include deleting nonessential metabolic genes, increasing the copy number of the target gene, and suppressing host protease expression. For example, deletion of the YPS1 gene has been shown to significantly reduce rHSA degradation during *Pichia pastoris* fermentation [20]. In addition, nonconventional expression platforms, including insect cells and microalgae, are currently under preliminary investigation, although their feasibility as alternative production systems remains to be fully established [5, 21]. At the process engineering level, integration of continuous perfusion culture with online chromatographic purification is expected to shorten

batch turnaround times while reducing manual intervention. Furthermore, the incorporation of membrane separation technologies and affinity purification strategies may simplify downstream processing and improve overall product recovery [22]. At the molecular level, site-directed mutagenesis and chemical modification are increasingly being employed to endow rHSA with novel functional properties, such as enhanced affinity for specific target molecules or prolonged in vivo residence time. For instance, HSA–interferon fusion proteins have demonstrated more favorable pharmacokinetic profiles than the corresponding free drugs in animal studies. These advances suggest that rHSA may evolve from serving merely as a replacement therapy to functioning as an active therapeutic platform [6, 35, 37].

6.2. Emerging applications

The application scope of rHSA is also expected to expand considerably. If the safety and efficacy of rHSA-based targeted drug delivery systems can be confirmed in clinical trials, these platforms may fundamentally improve therapeutic strategies for certain refractory malignancies and chronic inflammatory diseases [37]. Promising exploratory studies have also been conducted in tissue engineering, where rHSA has been incorporated into collagen- or alginate-based scaffolds to exploit its antioxidant properties and nutritional support functions for promoting wound healing and tissue regeneration. In the field of diagnostics, analytical methods employing rHSA either as a matrix component or as a biomarker have been investigated for early cancer detection and therapeutic monitoring, with encouraging preliminary results [30].

6.3. Challenges ahead

Despite these promising developments, several significant challenges remain. Although rHSA has demonstrated a superior safety profile compared with plasma-derived HSA, some clinicians continue to express reservations regarding its structural equivalence to the native protein and its long-term clinical safety. Addressing these concerns will require robust long-term follow-up studies together with well-designed cost-effectiveness analyses to provide stronger clinical evidence [4, 27]. Economic considerations also remain important. Although technological advances have substantially reduced manufacturing costs over the past several decades, the market price of rHSA in certain regions remains higher than that of conventional plasma-derived products. Further improvements in fermentation productivity and downstream purification efficiency therefore remain key priorities for industrial manufacturers [5, 26]. Regulatory harmonization presents an additional challenge. Major regulatory authorities continue to differ in their requirements for impurity control and reference standard characterization of rHSA products. Consequently, manufacturers pursuing global product registration are often required to perform redundant validation studies to satisfy region-specific regulatory requirements, increasing both development time and compliance costs. Promoting international harmonization and mutual recognition of quality standards will therefore be essential for facilitating the global commercialization and distribution of rHSA products [17].

7. Conclusion

The foregoing discussion leads to the conclusion that recombinant Human Serum Albumin (rHSA) is highly comparable to plasma-derived Human Serum Albumin (pHSA) at the molecular level, while offering decisive advantages in terms of raw material availability and the elimination of risks associated with blood-borne pathogens. Following several decades of technological development, rHSA production has progressed from laboratory-scale experimentation to a manufacturing platform with a considerable degree of industrial

maturity. Today, rHSA has been successfully applied in a wide range of fields, including clinical infusion therapy, pharmaceutical formulations, and cell culture [26, 33].

In China, significant progress has also been achieved. A pharmaceutical excipient-grade recombinant human serum albumin production line has been established by North China Pharmaceutical Group, and a plant-derived rHSA injectable formulation has advanced into clinical trials [12, 13, 38]. As technologies such as genome editing, automated fermentation, and continuous chromatography continue to mature, the unit production cost of rHSA is expected to decline further. At the same time, its role in emerging fields—including targeted therapeutics and regenerative medicine—is likely to evolve from that of a passive replacement protein to an active therapeutic agent capable of mediating targeted biological interventions [25, 39]. Nevertheless, several practical challenges must still be addressed before rHSA can fully replace plasma-derived HSA. These include updating established clinical practice patterns, further optimizing production economics, and achieving greater international harmonization of regulatory standards. From the demand perspective, the clinical need for safe and reliable albumin products is expected to remain strong. From the supply perspective, advances in genetic engineering and biomanufacturing technologies continue to accelerate. Taken together, these factors strongly suggest that rHSA will continue to expand its market share and is well positioned to become one of the fundamental biomaterials underpinning the modern biopharmaceutical industry [4, 27].

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