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Enhanced Functional Production of a Crucial Biomolecule Human Serum Albumin in Escherichia coli

Authors : Ashima Sharma

Abstract : Human Serum Albumin (HSA)- one of the most demanded therapeutic proteins with immense biotechnological applications- is a large multidomain protein containing 17 disulfide bonds. The current source of HSA is human blood plasma which is a limited and unsafe source. Thus, there exists an indispensable need to promote non-animal derived recombinant HSA (rHSA) production. Escherichia coli is one of the most convenient hosts which had contributed to the production of more than 30% of the FDA approved recombinant pharmaceuticals. It grows rapidly and reaches high cell density using inexpensive and simple substrates. E. coli derived recombinant products have more economic potential as fermentation processes are cheaper compared to the other expression hosts. The major bottleneck in exploiting E. coli as a host for a disulfide-rich multidomain protein is the formation of aggregates of overexpressed protein. The majority of the expressed HSA forms inclusion bodies (more than 90% of the total expressed rHSA) in the E. coli cytosol. Recovery of functional rHSA from inclusion bodies is not preferred because it is difficult to obtain a large multidomain disulfide bond rich protein like rHSA in its functional native form. Purification is tedious, time-consuming, laborious and expensive. Because of such limitations, the E. coli host system was neglected for rHSA production for the past few decades despite its numerous advantages. In the present work, we have exploited the capabilities of E. coli as a host for the enhanced functional production of rHSA (~60% of the total expressed rHSA in the soluble fraction). Parameters like intracellular environment, temperature, induction type, duration of induction, cell lysis conditions etc. which play an important role in enhancing the level of production of the desired protein in its native form in vivo have been optimized. We have studied the effect of assistance of different types of exogenously employed chaperone systems on the functional expression of rHSA in the E. coli host system. Different aspects of cell growth parameters during the production of rHSA in presence and absence of molecular chaperones in E. coli have also been studied. Upon overcoming the difficulties to produce functional rHSA in E. coli, it has been possible to produce significant levels of functional protein through engineering the biological system of protein folding in the cell, the E. coli-derived rHSA has been purified to homogeneity. Its detailed physicochemical characterization has been performed by monitoring its conformational properties, secondary and tertiary structure elements, surface properties, ligand binding properties, stability issues etc. These parameters of the recombinant protein have been compared with the naturally occurring protein from the human source. The outcome of the comparison reveals that the recombinant protein resembles exactly the same as the natural one. Hence, we propose that the E. coli-derived rHSA is an ideal biosimilar for human blood plasma-derived serum albumin. Therefore, in the present study, we have introduced and promoted the E. coli- derived rHSA as an alternative to the preparation from a human source, pHSA.

Keywords : recombinant human serum albumin, Escherichia coli, biosimilar, chaperone assisted protein folding
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