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Cytosolar protein delivery for therapeutic purpose

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Proteins are an integral part of every organism [1]. It plays a crucial role in performing essential functions in growth, development and metabolic regulation [2]. Many diseases arise due to any abnormality in the functioning of proteins. Therefore, protein therapeutics has a tremendous opportunity in alleviating diseases. Thus, far, protein therapeutics has increased in number and their frequency of use since insulin being used as a therapeutic. Currently, more than 100 proteins or peptides have been approved as drug by FDA. However, protein therapeutics is still in infancy.

The key aspect of using protein for therapy is to deliver proteins into cells [3]. However, there are two major challenges for intracellular protein delivery: 1. Delivering unmodified functional protein into cells; 2. Rapid cytosolic release of the protein after delivery. Mechanical delivery methods such as electroporation or microinjection have been widely used to deliver protein into cells [3]. However, these methods require specialized equipment and are disruptive in nature, limiting their use in vivo. Another popular approach is covalent modification of proteins using cell penetrating peptides (CPP) [4]. Here, CPP linked proteins are uptaken by cells via endocytic mechanism, resulting in slow or no release of proteins in cytosol.

Supramolecular carriers-based delivery methods, on the other hand, operate via non-covalent association with proteins. This allows transport of unmodified proteins into cells, retaining its structure and function. To date, various supramolecular carriers such as polymers, liposomes, nanoparticles stabilized nanocapsules (NPSCs) have been developed to facilitate protein delivery into cells. Among these, NPSCs are significant. In the recent studies, NPSCs have been shown to deliver GFP directly and rapidly into the cytosol [5]. The delivered protein was distributed throughout the cell uniformly. No sign of endosomal entrapment was observed. Further, NPSCs were used to achieve intracellular targeting to peroxisomes and nucleus [6]. Additionally, therapeutic protein caspase-3 (CASP3) was efficiently delivered into cells using NPSCs, resulting in induction of apoptosis. Therefore, NPSCs proved to be effective vehicle for intracellular delivery and hence for protein therapy.

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