Nanovehicles for Intracellular Protein Delivery

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Protein therapeutics holds significant promise for improving human health [1,2]. Our organism contains thousands of proteins, which perform essential functions in growth, development and metabolism regulation. Many diseases arise from the alterations in the functions of intracellular proteins [1]. Therefore, the administration of therapeutic proteins has shown great potential in the treatment of many diseases, including cancer and diabetes. Protein therapeutics has emerged since the 1980s and represents currently a significant part of biopharmaceuticals [2]. For example, Lantus®, an engineered protein (insulin) was one of the top ten selling biopharmaceuticals in 2009 [1]. Moreover, protein drugs with much better therapeutic performance are developed every year. The pharmaceutical research and manufacturers of America (PfRMA) listed 78 therapeutic proteins in 813 new biotechnology medicines related to more than 100 diseases in 2011, including virus infectious, cancer and autoimmune diseases [3]. The high intracellular activity and specificity of proteins compared to more conventional, low molecular weight drugs often allows for a better treatment of diseases. Moreover, protein drugs may be safer than gene therapy because no random or permanent genetic changes are involved [4]. Despite their potential medical applications, effective delivery of the proteins to a target site remains a challenge due to rapid clearance from the body. To achieve effective intracellular protein release, delivery platforms that overcome various biological barriers - from the system level, to the organ level, to the cellular level – are needed [4,5]. For example, the protein delivery carrier in the bloodstream needs to avoid kidney filtration, uptake by phagocytes, aggregation with serum proteins, and degradation by endogenous nucleases. Also, the delivery vehicle needs to transport the protein from the bloodstream through the vascular endothelial barriers. Moreover, once the carrier has been uptaken by the targeted cell, it must escape during early stages of the endolysosomal pathway, to avoid degradation by low pH and various hydrolytic enzymes in the lysosomes. Therefore, the clinical success of many therapeutic proteins is intimately dependent on the development of safe and efficient targeted protein delivery technologies.

The application of nanotechnology in the field of drug delivery systems has attracted much attention in the latest decades [6,7]. Recent breakthroughs have demonstrated that nanoparticle-based drug delivery platforms are an excellent alternative for the efficient delivery of, not only low molecular weight therapeutic agents, but for the release of genes and proteins as well [4,5,8,9]. In the case of intracellular protein delivery, these nanovehicles can accomplish critical functions to achieve the optimal therapeutic effect of protein drugs. For example, one of the roles of nanoparticles is to protect proteins from premature degradation within the biological environment. In principle, these nanocarriers can also avoid the uptake by the macrophagocytic system (MPS) by attenuating the receptor-mediated pathway. Moreover, the high surface to volume ratio of nanoparticles also leads to improved pharmacokinetics and biodistribution of the therapeutic proteins. A crucial feature of this delivery approach is the flexibility of tailoring the chemical and physical properties of the nanovehicle through controlled synthesis, assembly and chemical modifications. In summary, nanocarriers show several advantages for the effective and safe intracellular delivery of therapeutic proteins [4,5,9].

To date, various nanovehicles have been explored to facilitate intracellular delivery of proteins, such as liposomes, polymers, gold nanoparticles, mesoporous silica nanoparticles, quantum dots and carbon nanotubes [4,5,9,10]. Different approaches have been reported on the delivery of protein drugs using polymeric and liposomal carriers [11,12]. Unfortunately, no single formulation has been considered ideal for all types of protein drugs and approaches. Some of the main issues associated with these strategies are protein denaturation and deactivation due to the use of organic solvents to prepare some of the polymeric formulations. Moreover, liposomes usually display low protein loading, have inadequate stability, and exhibit sluggish protein release inside the cells. On the contrary, inorganic nanomaterials offer particular advantages for protein delivery. For example, quantum dots based protein delivery carriers can serve as both delivery and imaging agents. Gold nanoparticles can exhibit hyperthermia properties. However, these inorganic nanomaterials cannot be degraded by intrinsic mechanism in human body, bringing up huge safety concerns for the clinical application [4]. Mesoporous silica nanoparticles have attracted a great deal of attention in last few decades for their application as delivery systems [10,13]. Mesoporous silica materials can be used as efficient multifunctional nanocarrier for drug delivery, imaging agents, and stimuli-responsive platforms. Nevertheless, the pore size can be a limitation for loading proteins into the preformed mesoporous silica scaffolds [10,14]. New strategies are being explored to expand the scope of mesostructured materials toward protein delivery [15]. Recent breakthroughs in the synthesis of core-shell nanostructured materials have shown their potential application as carriers for imaging agents.
[16]. We are currently exploring the development of a "ship-in-a-bottle" approach using core-shell nanostructured particles for the intracellular delivery of therapeutic proteins (research in progress). We are expecting to synthesize core-shell nanostructures, with tunable size, pore size and surface chemistry, able to carry and deliver protein drugs in a stimuli-responsive and spatio-temporal fashion. We envision that this strategy will move forward the application of protein therapeutics to clinical settings (Figure 1).

References


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