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Review

Future of nanotherapeutics: Targeting the cellular sub-organelles

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ABSTRACT

Many diseases originate from alterations at nanoscale levels. Precise drug delivery should be achieved not only at cell level, but also at organelle level to achieve maximum therapeutic responses as well as avoiding possible toxic side effects of the drugs. However, organelles and subcellular structures are natural barriers that hampering many therapeutics from taking effects. Nanodelivery vehicle is a favorable platform to navigate across physiological barriers and to achieve selective delivery of therapeutic and diagnostic agents to intracellular targets. In this review, we have highlighted recent innovations in organelle-targeted nanomaterials designed to treat a variety of currently challenging diseases. Targeting strategies of four main kinds of organelles: mitochondria, nucleus, lysosomes and endoplasmic reticulum are discussed in detail. This review will help to clarify the intracellular nanomaterial-organelle interactions, and understand the fundamentals of organelle-targeted drug delivery strategies, which is of vital importance for the design and successful biomedical applications of nanomaterials in therapeutic treatments. At the end of this review, challenge and perspectives of organelle-targeted nanotherapy are discussed.

1. Introduction

In traditional medicine, it has been hypothesized more than a century ago that the selective and targeted delivery of drugs will potentially overcome many problems caused by random drug distribution, such as reducing toxicity as well as lowering the dosage requirement for efficacy. Lacking of target-specificity is the real bottleneck associated with systemic drug administration [1,2]. Scientists have taken great efforts on searching strategies for targeting specific tissues and cells. Especially, in the tumor targeting field, tumor vasculature markers, targeting integrins, tumor penetrating peptides and some other molecules have been widely used [3]. After entering specific cells, many drugs act on molecular targets associated with certain organelles, therefore, intracellular transport of different active molecules is also an important aspect in drug delivery. Traditionally, most of the drugs reach its targets by simple diffusion and interact randomly with organelles in the cell [4]. To solve this problem, besides targeting specific tissues and cells, scientists have taken one step further by targeting specific sites inside the targeted cells, and the concept of organelle and subcellular drug targeting has gained increasingly acceptance in recent years. It is an attractive strategy to increase drug therapeutic index by applying sub-cellular targeting, since therapeutics are directly delivered to its intracellular therapeutic active site. Chemical conjugation of targeting ligands to drug molecules is a commonly used approach to achieve subcellular targeting. However, such scenario brings problems such as losing drug activities and changing the toxic profiles of the drug. Also only a small proportion of molecules can be modified. Nanomaterials afford a particularly unique set of physiological properties which can be leveraged in applications ranging from *in vitro*/*vivo* therapeutics and drug delivery to imaging and diagnostics, surgical guidance, and treatment monitoring [5]. Although both drugs and nanoparticles can be engineered to target tumor, nanoparticles can be engineered to perform more complex and cooperative targeting functions. Multifunctional nano-delivery systems, such as liposomes, micelles, grapheneoxide, gold nanoparticles and inorganic mesoporous nanoparticles have been described previously for co-delivering of therapeutic agent with distinct organelle targeting effects [6–8]. Nano-formulations are considered to be the most appropriate dosage forms to carry anticancer drugs as they can incorporate unique functions that cannot be engineered into simple drugs such as helping the endosome/lysosome escape of therapeutic molecules [9,10]. Since therapeutics are “carried” by the organelle-targeted nanoplatforms, chemical conjugation of

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organelle-targeting ligands to the drug molecules is not required, which will significantly increase the therapeutic index of a greater variety of drug molecules. In this review, we highlighted the use of organelle-targeted nanopreparations for therapeutic treatments. We have summarized current strategies for engineering targeting nanoplatforms to specific cellular organelles and conclude with future directions for nanoparticle-based organelle-targeting treatments.

2. Fundamentals of organelle targeting by nanopreparations

Traditional cytosolic internalization of drugs might be sufficient for molecules with high intracellular stability. However, not all biologically active molecules fit this method, such as peptide drug conjugates and therapeutic oligonucleotides. In the cytoplasm, therapeutic molecules face many challenges including acidic and enzymatic degradation. After being safely delivered into the cytoplasm, therapeutic molecules still have to find their way to specific organelles and subcellular structures. Besides protecting the therapeutic compounds from degradation, subcellular targeting is one of the biggest promises nanotechnology offers to achieve therapeutic dosing [11]. Nanomaterial platforms capable of organelle targeting have been referred to as the third generation of nanomedicines. The chemical properties, size, and shape of nanomaterials can be applied to dictate the transport of therapeutic molecules to specific organelles or biologic compartments [12].

Moreover, nanoprepartions overcome many problems caused by simple cytosolic internalization of drugs. Firstly, randomly internalization of drugs might cause toxicity to some organelles and subcellular structures, it is therefore important to address the subcellular fate of molecules in any strategy designed to potentiate the therapeutic effects. Secondly, by specific organelle targeting, even a small amount of drug might take great efficacy, which is beneficial for some precious pharmaceuticals. Being able to target not only cells (diseased/normal), but also the subcellular site of action, specific targeting moieties of the particle surface, change of nanoparticle size to match the biological properties of organelles, appropriate charge and biocompatibility are important aspects to consider [13]. Targeting the organelles that are in charge of cellular energy level, digestion, replication and protein synthesis are the most important 4 aspects in organelle based therapeutic strategies. Mitochondria, nucleus, lysosomes and endoplasmic reticulum, are therefore the primary targets for various therapies because their functions are intimately linked to cell growth, proliferation, differentiation and death. A general picture describing the delivery strategies to different organelles is shown in Fig. 1. Targeting specific organelle is beneficial for cellular metabolic disorder and human disease treatment since many diseases are associated with impaired organelles and subcellular structures. For example, Mitochondria diseases are associated with unbalanced energy production of the cell: various types of mitochondrial dysfunctions have been implicated in a variety of human disorders, ranging from neurodegenerative and neuromuscular diseases, obesity, diabetes, ischemia-reperfusion injury, and cancer. Therefore, targeting mitochondria is a prime way to regulate numerous fundamental metabolic pathways [14]. Targeting the nuclear is a direct way to interfer DNA transcription and genetic programming, thus regulating cellular signaling events and determining cell fate. By monitoring the nuclear transport using nanoformulations, it is possible to treat a variety of diseases such as cancer, leukemia, infection, degenerative diseases and inflammatory conditions [15].

3. Mitochondria targeting nanotherapy

Mitochondria are the energy factories of the cell, which play a crucial role in the normal functioning of the cell and body. Mitochondria are in charge of many particular important functions such as electron transport, ATP synthesis, ROS generation, calcium metabolism and initiation of apoptotic pathways [16]. It is also involved in many metabolic pathways, such as fatty acids oxidation, citrate cycle, and synthesis of gluconeogenesis and steroid hormones. Therefore, mitochondria contribute immensely in cellular mortality management. Mitochondrial diseases commonly involve tissues that have high energy requirements, such as muscle, endocrine systems, retina and the brain. Many clinically approved drugs directly act on mitochondria by triggering apoptosis [17]. This suggests that mitochondria would be a privileged pharmacological target, and the concept of targeting mitochondria has emerged as an attractive strategy to regulate cellular metabolism and control mitochondrial dysfunction-related diseases.

3.1. Delivery of therapeutics to mitochondria by nanomaterials

Despite the desire to direct therapeutics to the mitochondria, the actual task is more complicated due to the highly complex nature of the mitochondria. A typical mitochondrion is composed of four parts: the outer mitochondrial membrane, the inner mitochondrial membrane, the inner membrane space, and the matrix. Specific delivery of drugs to the mitochondria depends not only on intracellular trafficking routes, but also on monitoring of mitochondrial entry. Both of the outer and the inner mitochondrial membranes present barriers to nanoplatforms that are destined for the mitochondrial matrix. It has been reported by Salnikov et al. that 3 nm gold nanoparticles could translocate across the outer mitochondrial membrane, but not 6 nm gold nanoparticles [18]. Since the major role of mitochondria is ATP synthesis by oxidative phosphorylation via the respiratory chain, this process creates a trans-membrane electrochemical gradient, which leads to a membrane potential (negative inside) and a pH difference (acid outside). The strong negative membrane potential (−160 mv to −180 mv) presents a main hurdle for many therapeutics since these molecules lack the structural components required to cross the complex mitochondrial membrane network to reach into the mitochondrial matrix.

Currently, the transport of bioactive molecules into mitochondria is based on two mitochondrial features: the mitochondrial membrane potential and the organelle's protein import machinery. The most widely used approach that have been tried by scientists is the use of mitochondriotropics. Mitochondriotropics presents molecules that target mitochondria and harness the mitochondrial membrane potential to enter the organelle. Mitochondriotropic molecules are amphiphilic in common, which is crucial for their accumulation inside the matrix of mitochondria. Till now, there has already been hundreds of mitochondriotropics reported, such as hydrophilic permanent cations, lipophilic weak acids, lipophilic cations of partially ionized bases, and hydrophilic cations of partially ionized bases, etc. The high net positive charge from lipophilic cationic molecules has the potential to promote endosomal escape and participate in delivering drugs to the mitochondria. For example, Yoong et al. loaded platinum prodrugs inside multi-walled carbon nanotubes (MWCNTs) and functionalized MWCNTs with Rhodamine-110 as mitochondria-targeting group to direct MWCNTs to mitochondria for anticancer treatment. The results indicate that using Rho-family of lipophilic cation is preferential for mitochondrial accumulation of MWCNTs [19]. Among the mitochondriotropics, triphenylphosphonium(TPP) cation is the most widely used one, which has previously been conjugated to various biologically active molecules to facilitate the selective accumulation of these molecules in mitochondria [20]. Micelles and liposomes-based nanocarriers are commonly used since they