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Co-delivery of drugs and plasmid DNA for cancer therapy☆

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ABSTRACT

Cancer is an extremely complex disease involving multiple signaling pathways that enable tumor cells to evade programmed cell death, thus making cancer treatment extremely challenging. The use of combination therapy involving both gene therapy and chemotherapy has resulted in enhanced anti-cancer effects and has become an increasingly important strategy in medicine. This review will cover important design parameters that are incorporated into delivery systems for the co-administration of drug and plasmid-based nucleic acids (pDNA and shRNA), with particular emphasis on polymers as delivery materials. The unique challenges faced by co-delivery systems and the strategies to overcome such barriers will be discussed. In addition, the advantages and disadvantages of combination therapy using separate carrier systems versus the use of a single carrier will be evaluated. Finally, future perspectives in the design of novel platforms for the combined delivery of drugs and genes will be presented.

Contents

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1. Introduction

The first medical description of cancer was found in an ancient Egyptian text written in 2500 BC which described it as "a bulging tumor in the breast like touching a ball of wrappings", for the case of breast cancer. Regarding treatment, the ancient script noted that "There is none" [1].

Since then, the knowledge of cancer biology has grown tremendously and it is now widely understood to originate from genetic instability as well as microenvironment factors [2]. Cancer cells contain oncogenic and tumor suppressor mutations, which enable them to sustain proliferative signaling, evade growth suppressors, resist cell death, induce angiogenesis, enable replicative immortality and activate invasion and metastasis [2,3]. The complex signaling pathways involved combined with the multiple mechanisms that enable tumor cells to evade programmed cell death make cancer treatment extremely challenging. Debulking surgery and chemotherapy remain the mainstream treatments of various cancers. However, for many patients, the incomplete removal of tumors as well as problems of chemo-resistance demonstrates the need for continual development of efficacious and safe treatments.

Since as early as 1975, there has been strong evidence that combination chemotherapies can exert synergistic effects and bring about more efficacious therapies than single treatments [4]. Examples of combination chemotherapies commonly used in clinic include carboplatin and paclitaxel (PTX) for treatment of ovarian cancer [5] and a cocktail of drugs 5-Fluorouracil (5-FU), leucovorin, irinotecan (Camptosar), and oxaliplatin (Eloxatin) for the treatment of pancreatic cancer [6]. However, as most chemotherapeutic drugs are cytotoxic small hydrophobic molecules, problems of systemic toxicity and insolubility of drugs are common place. To overcome solubility problems, drugs such as PTX need to be administered by a co-solvent named Cremophor EL, which is a mixture of polyoxyethylated castor oil in 49.7% dehydrated alcohol [7]. Unfortunately, Cremophor EL is also cytotoxic and has limited use in clinical applications [8]. In addition, the lack of cellular specificity and the development of multidrug resistance increase the challenges of effective chemotherapy. To circumvent these problems, researchers have proposed using drug delivery carriers for the transport of anti-cancer drug to cancer cells. These delivery systems may comprise of liposomes [9,10], polymers [11,12], inorganic materials [13,14] as well as peptides [15,16]. The focus of this review will be on polymeric delivery systems and readers are referred to other recent reviews on alternative carrier systems [17–19].

Polymers are a popular class of materials for constructing therapeutic delivery carriers due to the relative ease of tailoring their chemical and physical properties to meet specific needs in different situations [20,21]. Drugs with low aqueous solubility may be encapsulated by amphiphilic polymers to form micelle structures where, drugs reside within the hydrophobic core and hydrophilic chains form the shell of the micelle. One example is the use of block co-polymers comprising of hydrophilic polyethylene glycol (PEG) chain and hydrophobic cholesterol-functionalized polycarbonate for the delivery of PTX [22]. To increase the drug loading capacity and stability of polymeric carriers, functional groups such as urea, acid stereoisomers may also be incorporated into the hydrophobic polycarbonate block to form non-covalent interactions like hydrogen bonding and/or ionic interactions with the anti-cancer drugs such as doxorubicin (DOX) [12], phenformin [23], thioridazine [24] and PTX [25]. Moreover, the inclusion of PEG chain not only helps to improve drug solubility but also forms a steric barrier between the particle and plasma proteins reducing the formation of a protein corona and opsonisation [26]. As a consequence, PEG-shielded nanoparticles have been shown to avoid recognition by the reticuloendothelial system (RES) and have longer systemic circulation times [27]. Therefore, the encapsulation of hydrophobic drugs by polymeric nanoparticles has been widely utilized to improve the solubility, stability and systemic circulation time of anti-cancer drugs. In addition, drug delivery systems have also been demonstrated to overcome multidrug resistance (MDR) of cancer cells. MDR occurs due to the presence of membranous ATP-dependent drug efflux pumps, which actively pump hydrophobic drugs such as mitotic inhibitors (e.g., PTX and docetaxel) and the anthracyclines (e.g., DOX and daunorubicin) out, resulting in lower intracellular drug concentrations [28]. Drug-loaded nanoparticles avoid the drug efflux pumps of MDR by entering the cell via endocytotic pathways, which sequester the drugs in acidic intracellular compartments that traffic them away from the drug efflux mechanisms located on the cell membranes. Furthermore, the conjugation of drug delivery carriers to targeting ligands such as folic acid (FA) [29–31], transferrin [32], galactose [33] and cell penetrating peptides [34] increases the cellular uptake of nanoparticles into target cells, via receptor mediated endocytosis, and helps to overcome MDR further. Indeed, folate decorated micelles loaded with DOX [35] as well as transferrin-conjugated PTX-loaded nanoparticles [36] have been shown to have greater cytotoxicity against drug-resistant MCF-7 breast cancer cells compared to their non-targeted free drug counterparts.

However, due to the complexity of cancer as a disease, it has become increasingly clear that drugs targeted to specific molecular pathways have limitations [2]. A deeper understanding that cancers arise from various genetic disorders involved in cancer cell signaling, prompted the use of combination therapy involving both gene therapy and chemotherapy. Gene therapy involves the delivery of genes in the form of plasmid DNA (pDNA) to supplement down-regulated or replace mutated genes and/or in the form of small interfering RNA (siRNA), short hairpin RNA (shRNA) or micro RNA (miRNA) to reduce the expression of proteins by RNA interference [37]. Gene therapy thus has the potential to alter the expression of any gene of interest. Cancer gene therapy usually encompasses the downregulation of proteins involved in multidrug resistance (e.g., P-glycoprotein (P-gp), multidrug resistance protein 1, 2 (MDR1 and MDR2) and breast cancer resistance protein (BCRP)), the upregulation of proteins which promote apoptosis (e.g., TNF-related apoptosis-inducing ligand (TRAIL), p53 and tumor necrosis factor alpha (TNF-α)) as well as the upregulation of cytotoxic immune cytokines (e.g., interleukin-12). Importantly, the co-administration of chemotherapy and gene therapy has resulted in enhanced anti-cancer effects and has become an increasingly important strategy in medicine [38–41]. The majority of research in this area has been focused on the co-delivery of drug and gene using separate carriers to the same target tissue. However, this method fails to normalize their pharmacokinetic and pharmacodynamics properties and hardly allows the therapeutic agents to reach the same target for combinatory effects. On the other hand, the co-delivery of drug and gene using a single carrier with rationally designed doses and release profiles provides significant and unique advantages. The development of delivery systems that load both drug and gene in a single carrier is however a challenging task due to the stark differences in the physicochemical properties, such as hydrophobicity, molecular weight and metabolic stability, of drug and genes. As a consequence, this may result in sub-optimal gene transfection efficiencies and drug release in target cells. Recent advances in the development of co-delivery carriers for loading both drug and