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Recent advances in mechanism-based chemotherapy drug-siRNA pairs in co-delivery systems for cancer: A review

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ABSTRACT

Co-delivery of chemotherapy drugs and siRNA for cancer therapy has achieved remarkable results according to synergistic/combined antitumor effects, and is recognized as a promising therapeutic modality. However, little attention has been paid to the extremely complex mechanisms of chemotherapy drug-siRNA pairs during co-delivery process. Proper selection of chemotherapy drug-siRNA pairs is beneficial for achieving desirable cancer therapeutic effects. Exploring the inherent principles during chemotherapy drug-siRNA pair selection for co-delivery would greatly enhanced therapeutic efficiency. To achieve ideal results, this article will systematically review current different mechanism-based chemotherapy drug-siRNA pairs for co-delivery in cancer treatment. Large-scale library screening of recent different chemotherapy drug-siRNA pairs for co-delivery would help to establish the chemotherapy drug-siRNA pair selection principle, which could pave the way for co-delivery of chemotherapy drugs and siRNA for cancer treatment in clinic. Following the inherent principle of chemotherapy drug-siRNA pair, more effective co-delivery vectors can be designed in the future.

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1. Introduction

The co-delivery of chemotherapy drugs and siRNA for combination cancer therapy has been recognized as a promising therapeutic modality and has drawn attention worldwide. Also, the great progress in nanotechnology has provided cancer therapy novel approaches [1,2]. Many studies have demonstrated that co-delivery of chemotherapy drugs and siRNA could not only achieve a synergistic/combined antitumor effect, through siRNA-related oncogene interference [3] and chemotherapy drug-mediated tumor cells killing, but also reduce side effects of chemotherapy drug [4].

Chemotherapy, as one of the most efficient methods for cancer treatment, has a high cure rate against many cancers. However, various problems caused by chemotherapy drugs, such as undesirable damage to normal cells and multidrug resistance (MDR) [5,6], still exist and negatively affect therapeutic results. These drawbacks limit the use of chemotherapy drugs in successful treatment of cancers. Hence, seeking a novel direction in cancer therapy is important. RNA interference (RNAi)-based cancer therapy is emerging as a potential tool in cancer treatment, with many related studies confirming its relevance. [7–10] However, many challenges have also persisted, and only a very limited repertoire of siRNA drugs has been marketed [11,12]. Avoiding the existing defects of siRNA is of vital importance.

In recent years, the combination use of chemotherapy drugs and siRNAs has provided new approach for cancer treatment and has generated widespread attention. The two-dimensional mechanisms of chemotherapy drug and siRNA not only are able to reverse chemotherapy drug resistance and reduce undesirable damage to normal cells, but can also achieve synergistic/combined antitumor effects. Regarding the synchronized pharmacokinetic characteristics, co-delivery of chemotherapy drugs and siRNA in same platform reduces the cargo dosage while maintaining equal therapeutic efficacy, as shown in Fig. 1. Proper choice of chemotherapy drug-siRNA pair is one of the key steps in developing effective combination cancer therapy. Little attention has been focused to explore inherent principles of chemotherapy drug-siRNA pair selection during cancer therapy. This article reviewed the recent large-scale library screening of different chemotherapy drug-siRNA pairs for co-delivery. We would expect that this work could provide suggestions for proper selection of chemotherapy drug-siRNA pairs during co-delivery in cancer therapy, possibly paving the way for co-delivery of chemotherapy drug-siRNA pairs for cancer treatments in the clinic.

2. Strategies of selecting chemotherapy drug-siRNA pairs for co-delivery in combination cancer therapy

Regarding highly heterogeneous and extremely complex mechanisms of cancer, proper selection of chemotherapy drug-siRNA pairs is very beneficial for achieving desirable cancer therapeutic effects. Selection of correct chemotherapy drug-siRNA pair is based on thoroughly understanding of siRNA-related antitumor mechanisms and chemotherapy drug properties. The following sections systematically review current mechanism-based chemotherapy drug-siRNA pairs for co-delivery in cancer treatment. Large-scale library screening of different chemotherapy drug-siRNA pairs for co-delivery would help to explore effective cancer therapy strategies.

2.1. Different mechanism-based siRNAs in co-delivery systems for cancer therapy

Regarding the diversity of siRNAs that used in co-delivery systems for combination cancer therapy, selecting suitable siRNAs is vital to exert desired anti-tumor effects. The different mechanism-based siRNAs used in co-delivery systems for cancer therapy have been summarized below.

2.1.1. Co-delivery of chemotherapy drug and drug efflux pump-related gene silencing siRNA to overcome multidrug resistance (MDR) in cancer therapy

MDR is a major cause of treatment failure and relapse or recurrence of cancer, thus overcoming MDR in cancer treatment is vital to acquire ideal therapeutic effects. The co-delivery of chemotherapy drug and drug efflux pump-related gene silencing siRNA to overcome MDR provides a novel cancer treatment method. Fig. 2 shows chemotherapy drug-based tumor cell killing combined with siRNA-related effects of silencing efflux pumps in cancer therapy. Efflux pump related cell resistance is widely known as a self-defense mechanism of cells [13] that is closely related to MDR. P-glycoprotein (P-gp) is a primary drug efflux pump, which is also known as multidrug resistance protein 1 (MDR1). In healthy cells, P-gp is not only involved in efflux of undesirable molecules but also involved in transporting beneficial molecules and nutrients across cellular and intracellular membranes into the cell [14]. P-gp has been found to be over expressed in malignant tumor tissues, and is responsible for pumping chemotherapy drugs out of cells. Silencing of P-gp expression in tumor tissues is important for enhancing efficiency of chemotherapy. Delivery of drug efflux pump-related gene silencing siRNA would help to overcome undesirable effects brought by chemotherapy drugs. Studies have suggested that co-delivery of chemotherapy drugs and P-gp siRNA could achieve excellent therapeutic efficiency [15,16]. For example, delivery of P-gp siRNA and doxorubicin (DOX) by PLGA nanobubbles could enhance cellular uptake and nuclear accumulation of DOX in MCF-7/ADR cells compared with free DOX, and the IC50 of P-gp and DOX co-loaded PLGA nanobubbles against MCF-7/ADR cells was 2-fold lower than that of free DOX [17].

Other important efflux pump-related proteins, including multidrug resistant protein 1 (MRP1), 2 (MRP2), 3 (MRP3), 4 (MRP4), 5 (MRP5) and breast cancer resistance protein (BCRP, encoded by ABCG2 gene) [13,18], have been found to be over expressed in many tumors, and are able to bind to negatively charged molecules. Among them, MRP1 and BCRP are most frequently used in chemotherapy drug and siRNA co-delivery courses to reverse multidrug resistance. *In vivo* and *in vitro* results confirmed that co-delivery of chemotherapy drugs and MRP1 siRNA (BCRP siRNA) significantly enhanced antitumor effects [19]. Previously reported instances of co-delivery of chemotherapy drug and drug efflux pump-related gene silencing siRNA to overcome MDR in cancer therapy are summarized in Table 1.

2.1.2. Co-delivery of chemotherapy drug and anti-apoptosis-related gene silencing siRNA for enhancing efficiency of cancer therapy

Apoptosis is a natural programmed cell death process and a necessary part of cell cycle. The anti-apoptotic mechanism prevents tumor cells from undergoing apoptosis, which often fails to halt the