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Recently Reported Dual-Drug Co-Delivery of Liposomal-Based Chemotherapeutics to Treat Breast Cancer

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ABSTRACT

The use of nanocarriers such as liposomes to co-encapsulate more than one anticancer drug has been shown to be a promising strategy in cancer treatment with respect to overcoming multidrug resistance (MDR). This is in part not only due to the many advantages associated with the use of liposomes, but also the effectiveness of using this dual-drug strategy to overcome potential drug resistance when compared to a single chemotherapeutic. In this review, we report promising recently reported dual-drug co-delivery of liposomal-based chemotherapeutics in order to treat breast cancer and provide some perspectives on possible future constructs.

Keywords: Breast Cancer; Nanocarriers; Liposomes; Dual-Drug; Co-Delivery; Chemotherapeutics

Abbreviations: MDR: Multidrug Resistance; EPR: Enhanced Permeability and Retention Effect; Pgp: P- Glycoprotein; TNBC: Triple Negative Breast Cancer; Res: Resveratrol; PTX: Paclitaxel; DT: Docetaxel; TQ: Thymoquinone

Introduction

Globally, breast cancer is the leading cause of cancer death amongst women [1], and the administration of currently available chemotherapeutics can not only have negative side-effects associated with their use, but also can have limited overall drug efficacy. The use of nanocarriers can serve to alleviate potential deleterious side-effects of cytotoxic agents, and there are many different types of nanocarriers available for such delivery. Liposomes, however are currently of great interest with respect to the development of improved chemotherapeutics largely due to their clinical success. For example, Doxil is a clinically approved drug currently used to treat metastatic breast cancer [2-4], and there are various other liposomal-based chemotherapeutics in either preclinical stages or various phases of clinical trials [5-7]. The clinical success of liposomal-based drugs can be explained for many reasons. For example, their phospholipid bilayer not only makes them biocompatible, but also serves to shield the encapsulated drug from coming into contact with healthy tissue while in circulation. Furthermore, their size can be fine-tuned to the desired size (usually 100 nm in diameter or less) to take advantage of the enhanced permeability and retention (EPR) effect known to occur *in-vivo* [8-10]. The EPR effect arises from deregulated angiogenesis that occurs in and around solid tumors, as well as the poor lymphatic drainage associated with tumor sites. However, while these nanocarriers can effectively deliver cytotoxic agents to solid tumors such as breast cancer while minimizing negative unwanted side effects, there are still many challenges associated with the overall effectiveness of the drug.

In fact, one of the arguably biggest obstacles to overcome with respect to drug efficacy is multidrug resistance (MDR), which is the primary means by which cancer cells develop resistance to various

chemotherapeutic agents [11,12]. For example, this is the case with doxorubicin, which is the encapsulated cytotoxic agent within the clinically approved drug Doxil, and the most widely- used drug to treat breast cancer [13,14], as well as many other commonly used chemotherapeutics [15]. Therefore, several research groups are working on the co-encapsulation of dual drugs in a single nanocarrier such as a liposome in order to improve overall drug efficacy. The strategy here being the use of two drugs, in some cases one is a chemosensitizer and the other a cytotoxic agent, or in other cases two cytotoxic agents with completely different mechanisms of action. For example, Rolle et al. have recently reported a dual-drug liposomal formulation involving the chemosensitizer drug disulfiram and the cytotoxic agent doxorubicin [14]. In this study, this formulation effectively reversed doxorubicin resistance in P-glycoprotein (Pgp)-expressing breast cancer cells. The authors also point out the benefits of using liposomes to both improve the solubility and enhance the stability of the disulfiram. In another recently reported study, Ghosh et al. co-loaded liposomes with two cytotoxic agents, vincristine and doxorubicin, and have determined that the synergistic effect of this combination significantly improved the therapeutic efficacy when tested on triple negative breast cancer (TNBC) cells [16].

Meng et al. have also reported promising *in vitro* and *in vivo* results using resveratrol (Res) and paclitaxel (PTX) co-encapsulated into a liposomal formulation [17]. In fact, PTX has also been successfully used in combination with rapamycin in both *in vitro* and *in vivo* experiments when co-loaded into liposomes [18]. Another commonly used taxane drug in the treatment of breast cancer is docetaxel (DT), which has also been co-encapsulated into liposomes along with thymoquinone (TQ) [19]. This dual-drug liposomal formulation demonstrated enhanced synergistic activity against breast cancer cells. In yet another interesting study, Jose et al. reports a liposomal formulation involving the co-delivery of tamoxifen and imatinib [20]. The combination of these two drugs demonstrated synergistic growth inhibition in various breast cancer cell lines. An interesting aspect of this study is the use of temperature-sensitive liposomes, which are designed to release encapsulated drugs at the tumor-site following application of external hyperthermia.

Conclusion and Discussion

The use of dual-drug liposomal-based systems to treat breast cancer in order to overcome multidrug resistance is a promising area of study, and several encouraging formulations have been reported here. In fact, in the last study mentioned, Jose et al. uses temperature-sensitive liposomes in order to better facilitate the release of encapsulated drugs so that they can then be internalized into cancer cells. The transfer of encapsulated materials within liposomes to cancer cells can be challenging, and therefore many research groups are currently working on targeted drug delivery [5,21]. Generally, this type of delivery involves liposomal surface modification to include the addition of a targeting ligand that is specific to a known overexpressed breast cancer cell surface receptor. In fact, an interesting future construct may involve dual-drug targeted liposomal formulations, either a chemosensitizer and cytotoxic agent or two cytotoxic agents with completely different mechanisms of action as reported here, for improved delivery of co-encapsulated drugs to breast cancer cells.

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