Simultaneous Delivery of Drugs and Genes by Multi-block Polymeric Nanomicelles for Synergistic Cancer Therapy

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Abstract

Presently cancer remains one of the most predominant incurable diseases and it is estimated that its worldwide incidence will continue to increase in the future [1]. From a clinical perspective chemotherapy is one of the best established methodologies for cancer treatment, being generally applied either as first line therapy for early stage disease, or palliative care in later phases. However, the administration of anti-tumoral drugs generally induces systemic cytotoxicity due to their poor selectivity to target cancer cells and tissue partition. Moreover, cancer drug resistance following a multi-stage treatment regime is common and this phenomenon further contributes to the ineffectiveness of chemotherapy. In this context the simultaneous delivery of different anti-tumoral drugs or drug-nucleic acid combinations arises as an exceptionally promising strategy for improving treatment efficacy and overcome cancer drug resistance [2]. Nonetheless, combinatorial therapy is remarkably challenging since nucleic acids are readily degraded in circulation and the simultaneous administration of multiple drugs provokes intolerable cytotoxicity.

The use of polymeric micelles is a valuable option to overcome such problems since these nanosized carriers can increase the bioavailability of bioactive molecules, i.e., drugs and genes, in the tumor site by the enhanced permeability and retention (EPR) effect. This characteristic contributes for reducing systemic cytotoxicity and improves treatment efficacy. Also, due to micelles unique hydrophobic-hydrophilic character which self-assembles into a core-shell structure, they can be used as a reservoir for encapsulating hydrophobic anti-tumoral drugs. In turn, this encapsulation promotes a sustained release during an extended time frame and increases intracellular drug concentration. These two parameters contribute for an enhanced therapeutic effect in comparison to standard chemotherapy. Including drug gene combinations is significantly more challenging as the physicochemical nature of these distinct bioactive molecules demands a multi-block co-polymer with both hydrophobic and cationic properties so as to encapsulate drugs and complex DNA at the same time [2]. Thus for co-delivering drugs and nucleic acids the micelles must be self-assembled from polymeric nanomaterials in which the building blocks ought to be specifically tailored to have these properties.

Herein we provide, a brief focus on the different biocompatible and biodegradable polymers for micelles self-assembly will be provided. The use of biocompatible micelles for co-delivery of anti-tumoral compounds for cancer therapy will presented. Also, a particular emphasis will be given in the synthesis of innovative tri-block copolymers for gene-drug co-delivery (Figure 1) [3]. The application of this system for the delivery of Doxorubicin and Minicircular DNA (mcDNA) will be presented and the evaluation of its biological performance *in vitro* and *in vivo* will be provided.

References

[1] Rebecca Siegel, Jiemin Ma, Zhaohui Zou and Ahmedin Jemal, CA: A Cancer Journal for Clinitians, 64(**1)**, (2014), 9-29.

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Figures

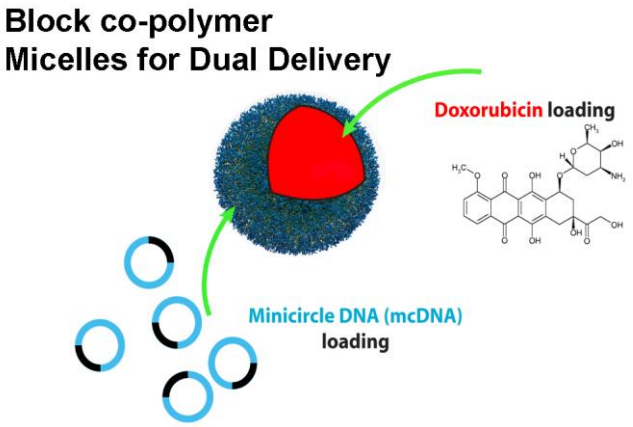

Figure 1. Schematics of gene-drug (minicircle DNA-Doxorubicin) co-delivery concept using multi-block co-polymer micellar carriers.