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The reduction of tumor interstitial fluid pressure by liposomal imatinib and its effect on combination therapy with liposomal doxorubicin

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ABSTRACT

Interstitial fluid pressure (IFP) in tumor is much higher than that in normal tissue and it constitutes a great obstacle for the delivery of chemodrugs, which makes it a potential target for cancer therapy. In this study, imatinib, a molecular targeting drug, was loaded in sterically stabilized liposomes (SSL-IMA) to reduce the tumor IFP, in an attempt to deliver more liposomal doxorubicin (SSL-DOX) into tumor tissue. In a mouse B16 melanoma model, intravenous injection of 20 mg/kg SSL-IMA achieved the most reduction of tumor IFP and the effect lasted for at least 50 h with the least hematotoxicity. However, intragastric administration of 100 mg/kg free IMA did not decrease the tumor IFP significantly. Mechanisms of the reduction of tumor IFP by SSL-IMA were proved to be the inhibition of PDGF receptor beta, the inhibition of tumor fibroblasts as well as the anti-angiogenesis effect of SSL-IMA. Then it was demonstrated by *in vivo* imaging that the decrease of tumor IFP by SSL-IMA led to a more and longer intratumoral distribution of the lipid vehicles. The improved delivery was proved again in the anti-tumor study. The combination of SSL-IMA and SSL-DOX inhibited tumor growth and induced apoptosis of tumor cells the most, at a low dose in which neither SSL-DOX nor SSL-IMA showed obvious anti-tumor efficacy. Since no synergy against B16 cells was found between SSL-IMA and SSL-DOX, it was clear that the improved combinational therapy was basically due to the decrease of tumor IFP by SSL-IMA. In conclusion, reducing tumor IFP by SSL-IMA seems to be a promising strategy to potentiate chemotherapies.

1. Introduction

Successful drug delivery to tumor stroma is the premise of efficacious cancer therapy. Transcapillary drug delivery is hindered by the combined effect of microvascular pressure, colloid osmotic pressure inside and outside the vessel, and the interstitial fluid pressure (IFP) [1,2]. In normal tissue, the net outward transport is realized by an IFP value of −1 to −3 mmHg, whereas this pressure will be significantly elevated to about 10–20 mmHg in tumor tissue [1]. Therefore, the tumor IFP becomes a major obstacle for the tumoral penetration and distribution of therapeutic particles. Several key features of solid tumors are responsible for the high tumor IFP, including defected lymphatics, hyperpermeable vessels and the stromal burden imposed by over-proliferated tumor cells, increased contractility of fibroblasts and dense matrix collagen and elastin [1,3].

Tumor IFP is found to be elevated in various solid tumors, including colon adenocacinoma, glioma, mammary tumor, melanoma, etc [4]. Among them, melanoma is associated with high mortality, progressive potential and lack of effective therapeutics. PEGylated liposomes, also known as sterically stabilized liposomes (SSL) are promising drug delivery systems because of their less arrestment by the reticuloendothelial system (RES) [5] and more tumoral accumulation by the enhanced permeability and retention (EPR) effect [6]. However, the doxorubicin (DOX) loaded SSL (SSL-DOX) achieve limited therapeutic efficacy against melanomas in several pre-clinical studies [7,8]. Therefore, better therapies, which can increase the efficacy of drug-loading SSL against melanomas, are still in great need.

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Table 1
Characteristics of SSL-IMA and SSL-DOX (mean ± SD, $n = 3$).

Formulations	Size (nm)	PDI	Zeta potential (mV)	Encapsulation efficiency (%)
SSL-IMA	106.7 ± 2.3	0.1827 ± 0.011	−1.244 ± 0.39	83.53 ± 1.9
SSL-DOX	92.68 ± 1.9	0.1687 ± 0.013	−0.3587 ± 0.29	95.18 ± 2.3

Several agents have been used to reduce the tumor IFP, such as collagenase [9] and the antagonists of VEGF receptor [10,11] or PDGF receptor [12,13]. Imatinib (IMA) is a potent inhibitor of Bcr-Abl gene, tyrosine-protein kinase Kit (c-Kit) and PDGF receptors (PDGFR) [14] and it has been approved to treat chronic myeloid leukemia and gastrointestinal stromal tumor, which are related with the mutations of Bcr-Abl and c-Kit, respectively. It is reported that IMA can reduce the tumor IFP by inhibiting PDGFR-beta [12,13] and therefore improve the delivery and efficacy of chemotherapeutic drugs [15,16]. However, a high dose of IMA (50 mg/kg or 100 mg/kg) has to be intragastrically administrated successively for several days in those studies. Besides, the specific mechanism of the reduction of tumor IFP by SSL-IMA is worthy of careful investigations, since there lacks a relationship between the inhibition of PDGFR-beta at the molecular level and the reduction of tumor IFP at the tissue level.

In this study, IMA was loaded in SSL (SSL-IMA) for the first time in order to decrease tumor IFP more efficiently, reduce the times of

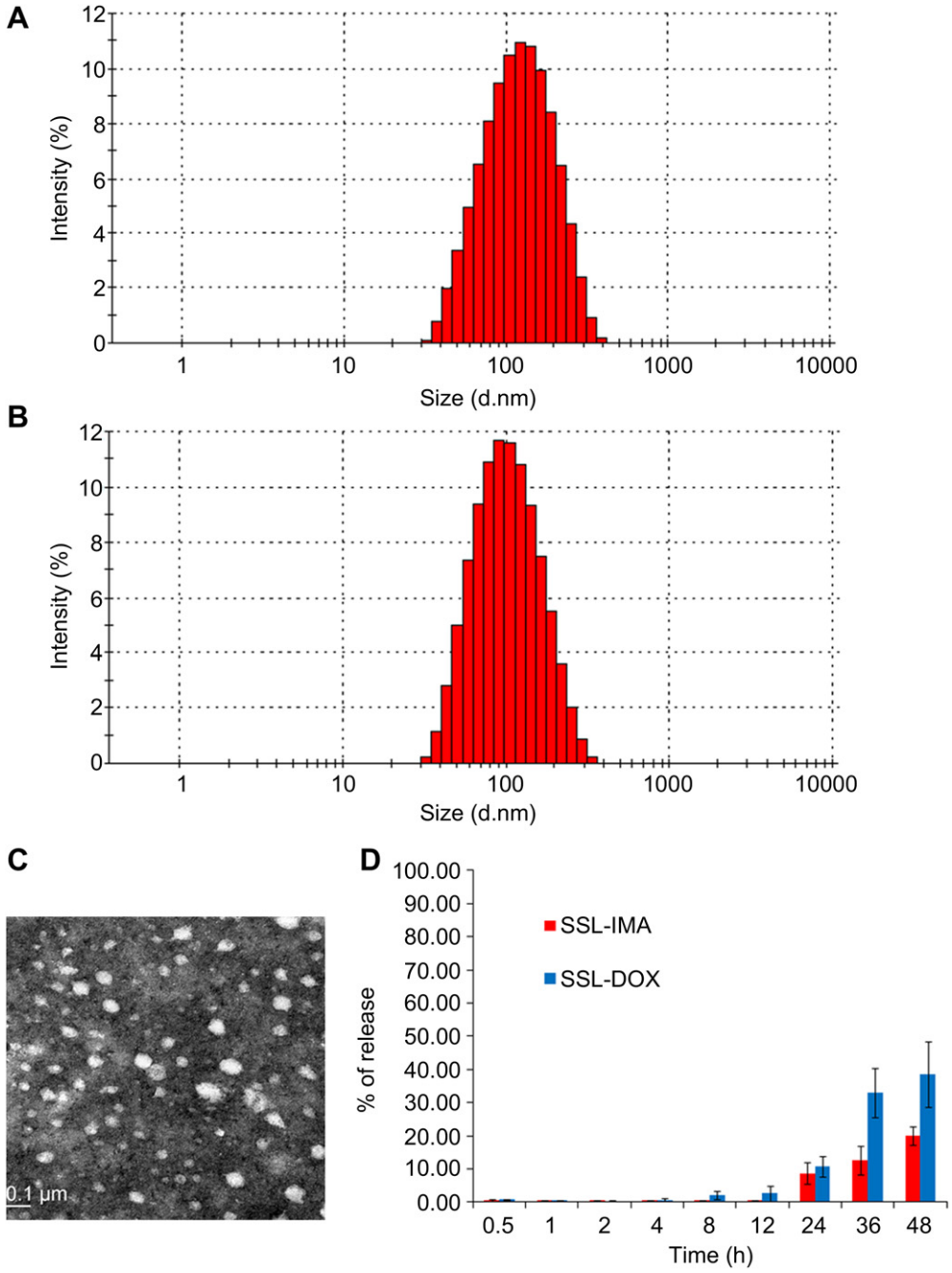

Fig. 1. Characteristics of IMA and DOX liposomes: Size distributions of SSL-IMA (A) and SSL-DOX (B) by intensity. (C) Morphology of SSL-IMA identified by TEM. (D) *In vitro* release rate of SSL-IMA and SSL-DOX at 37 °C, 100 rpm ($n = 3$).