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EDITORIAL

Submicron-sized superantigen biomimetic liposomes: enhanced lung accumulation and synergistic chemoimmunotherapy

KEY WORDS

Chemoimmunotherapy;
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Metastatic lung cancer remains a formidable adversary in oncology, accounting for a staggering global mortality burden due to its high malignancy and poor prognosis[1]. In recent years, the integration of chemotherapy and immunotherapy has emerged as a promising strategy for synergize killing of tumor cell[2]. However, the strategy often faces challenges due to poor pulmonary accumulation and targeting therapeutics, leading to suboptimal efficacy and systemic toxicity. Conventional drug carriers often exhibit inadequate retention in the lungs, with small particles (<500 nm) tend to accumulate in the reticuloendothelial system such as the liver, spleen, and lung[3,4], and larger particles posing risks of causing pulmonary embolism[5]. Moreover, the systemic release of immunomodulators like bacterial superantigens can induce cytokine storms, limiting their clinical utility. Against this backdrop, developing a novel delivery vehicle that achieves both lung-targeted delivery and co-delivery of therapeutic agents has become critically important.

Recently, in *Acta Pharmaceutica Sinica B*, Yuan et al.[6] explored a submicron-sized biomimetic liposome for lung-targeted co-delivery of the bacterial superantigen recombinant staphylococcal enterotoxin C2 (rSEC2) and paclitaxel, which was denoted as TSPLs. The authors discussed the utilization of biomembrane materials and size control to improve the lung targeting of SEC2 and paclitaxel for the chemoimmunotherapy of metastatic lung cancer. The findings indicated that the submicron-sized (∼800 nm) biomimetic liposomes exhibited high lung-accumulation efficacy. Due to the diameter of pulmonary capillaries, the submicron-sized liposomes can be effectively entrapped in the lungs, leading to lung targeting. Moreover, the hybridization of biomembrane exhibits high affinity for homologous tumor cell membranes, thereby enhancing lung retention efficacy. The proposed TSPLs exhibit desired antimetastatic effects both *in vivo* and *in vitro* (see Fig. 1).

Firstly, the authors successfully obtained high purity rSEC2 with high immunostimulatory activity through recombinant expression. Then, they use biomimetic liposome hybridized with homologous 4T1 tumor cell membranes as a vehicle to improve the distribution of rSEC2 at the tumor site. To optimize the preparation methods of TSPLs, the reverse-phase evaporation (RSLs) and freeze-drying (FSLs) methods were conducted and compared by the analysis of CD spectrum to evaluate the maintenance of rSEC2 structure. The results showed that FSLs maintained the CD spectrum of active SEC2, while RSLs lost their original CD spectral characteristics. These findings highlight the superiority of the freeze-drying methods in preserving the structural integrity and biological activity of protein-based therapeutics like SEC2, while minimizing exposure to organic solvents that compromise functionality.

TSPLs were intravenously administered to model mice to evaluate *in vivo* lung targeting. Unexpectedly, the liposomes exhibited preferential accumulation in the liver and kidneys over the lungs. Subsequently, given the abundance of capillaries in the lungs, the authors investigated the critical role of particle size in lung accumulation. Based on the *In vivo* Imaging System imaging of main organs and semi-quantitative analysis, smaller liposomes (∼200 nm) exhibited poor lung targeting and accumulated primarily in the liver and kidneys. In contrast, the submicron-sized TSPLs (∼800 nm) were proven to be the expected lung targeting, which was a satisfactory biodistribution. This size-dependent

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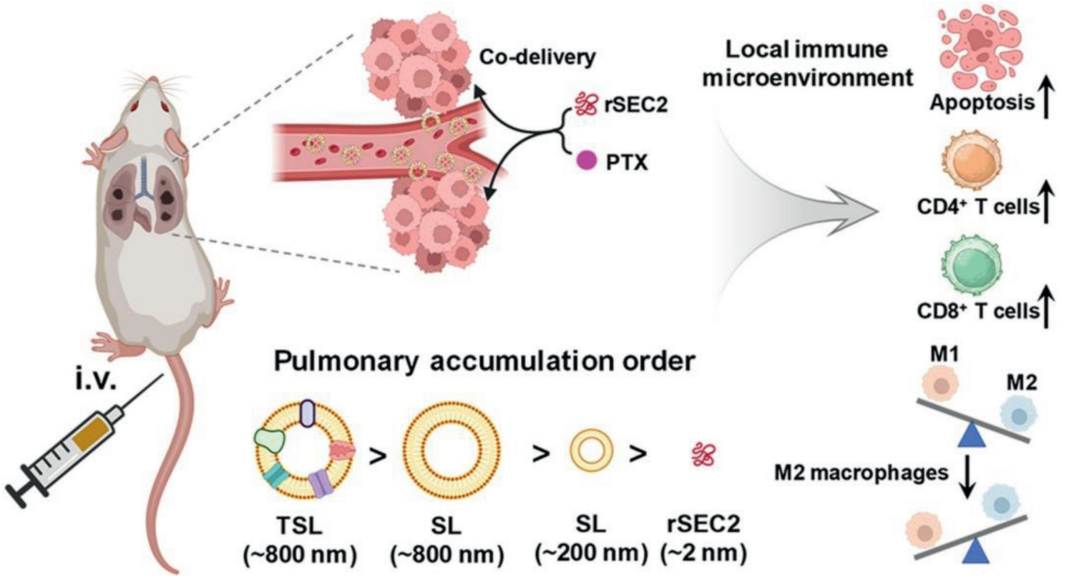

Figure 1 A submicron-sized biomimetic liposome loaded with bacterial superantigen and paclitaxel efficiently accumulates in the lungs for cancer chemoimmunotherapy, reducing the systemic side effect of the superantigen and remodeling the local immune microenvironment.

effect is attributed to the trapping of larger particles in pulmonary capillaries, combined with membrane hybridization that further improves retention through tumor cell adhesion.

Having discussed the association of size effects with lung accumulation, the authors further explored the pharmacodynamics of the liposomes. In the metastatic lung cancer model, TSPLs significantly inhibited tumor growth. The combination of rSEC2-mediated immune activation and paclitaxel-induced apoptosis synergistically remodeled the tumor microenvironment, as evidenced by increased IFN-γ, IL-2, and IL-10 levels in lung tissue and reduced systemic cytokine release. Additionally, the liposomes reversed the polarization of macrophages from the immunosuppressive M2 to the immunostimulatory M1 state. In summary, the submicron SEC2-paclitaxel liposomes hybridized with tumor cell membranes effectively reduced lung tumor burden without causing excessive systemic immune responses.

In addition, based on the current encouraging outcome, more efforts should be put into the study to promote clinical translation. Herein, we would like to provoke some discussion. (I) The authors claimed that the TSLPs might release the cargoes in the intercellular spaces. However, the direct experimental data demonstrating that remains absent. Additional *in vitro* and *in vivo* imaging investigations could be evaluated to characterize the complex TSLPs-tumor cell interactions. (II) Long-term safety experiment could be conducted, as bacterial superantigens are prone to induce systemic cytokine storms leading to a toxic shock syndrome. Chronic toxicity studies in preclinical models, including histopathological analysis and organ function monitoring, could be critical to validate translational potential. (III) The production of TSLPs with accurate size (like 800 nm) could be optimized for industrial scalability. Current methods using Sephadex column separation for size selection are complicated and materials-waste. Developing environmentally friendly and scalable techniques to achieve precise size control would enhance clinical viability. Overall, the strategy of integrating size-based targeting with biomembrane hybridization offers a versatile platform for delivering protein-based immunomodulators and chemotherapeutics, with broader implications for treating metastatic cancers.

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