Title: Combined administration by nanomedicine: an effective treatment against insufficient chemotherapy-promoted tumor metastasis

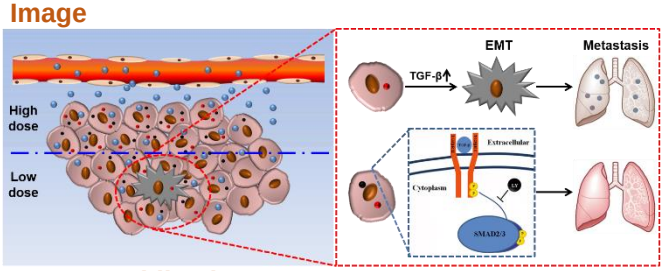
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Abstract

Statement of the Problem: Although nanoparticles could enhance the delivery efficiency of chemotherapeutics, the percentages accumulating at tumor site is still low, with a median of 0.7% for the last decade. Tumor tissue with insufficient chemotherapy might be the crime culprit of tumor metastasis. In this research, we adopted a combined-administration strategy by nanoparticle to prevent the insufficient chemotherapy-promoted tumor metastasis. DOX and TGF-β receptor inhibitor, LY2157299, were co-delivered by HES-PLA nanoparticle. With suppression of EMT process by blocking the TGF-β path, the distant metastasis were dramatically inhibited. Meanwhile, DOX exhibited better anti-tumor efficacy on the primary tumor. **Methodology & Theoretical Orientation**: HES-PLA nanoparticles was obtained by a three-step preparation procedure and characterized by TEM, AFM and DLS. Anti-tumor efficacy *in vitro* was evaluated with 4T1 cell by MTT assay. Western blot was applied to evaluate the expression of EMT-related proteins. ELISA was used to quantify TGF-β. The metastatic capabilities of cell treated with different administrations were evaluated by transwell assay (*in vitro*) and zebrafish model (*in vivo*). Mice bearing subcutaneous 4T1 tumor were ultimately used to examine its efficacy of anti-primary tumor and anti-distant metastasis. **Findings**: The transwell assay and zebrafish model reveal that low dose of DOX could enhance the metastasis ability of 4T1 cell. Importantly, the *in vivo* study demonstrate that co-deliver of DOX and LY2157299 by nanoparticle could simultaneously suppress the primary tumor (TIR, 80.7%) and distant metastasis (no nodule on the lung). **Conclusion & Significance**: *In vivo* biological barriers always deteriorate the delivery efficacy of DOX, causing insufficient chemotherapy and therefore promoting metastasis. Combined administration of DOX and LY2157299 could significantly suppress the insufficient-chemotherapy-enhanced EMT process by blocking the TGF-β path, decreasing the distant metastasis and intensifying the anti-tumor efficacy of DOX.

Image



Recent Publications

- Hu, H.; Li, Y.; Zhou, Q.; Ao, Y.; Yu, C.; Wan, Y.; Xu, H.; **Li, Z.***; Yang, X., Redox-Sensitive Hydroxyethyl Starch–Doxorubicin Conjugate for Tumor Targeted Drug Delivery. *ACS Applied Materials & Interfaces* **2016**, *8* (45), 30833-30844.
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- **Li, Z.**; Ngai, T., Microgel particles at the fluid-fluid interfaces. *Nanoscale* **2013**, *5* (4), 1399-1410.
- **Li, Z.**; Geisel, K.; Richtering, W.; Ngai, T., Poly(N-isopropylacrylamide) microgels at the oil-water interface: adsorption kinetics. *Soft Matter* **2013**, *9* (41), 9939-9946.
- **Li, Z.**; Kwok, M. H.; Ngai, T., Preparation of Responsive Micrometer-Sized Microgel Particles with a Highly Functionalized Shell. Macromol Rapid Comm 2012, 33 (5), 419-425.
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- **Li, Z.**; Ming, T.; Wang, J. F.; Ngai, T., High Internal Phase Emulsions Stabilized Solely by Microgel Particles. Angew Chem Int Edit 2009, 48 (45), 8490-8493.



Biography

Dr. Zifu Li is currently a Professor in College of Life Science and Technology at Huazhong University of Science and Technology. Dr. Li obtained his PhD, majored in polymer physics, in 2012 from the Chinese University of Hong Kong. Afterwards, he worked in University of Alberta as a postdoc. During March 2015 and January 2016, Dr. Li worked as a research scientist in Georgia Tech. Now, Dr. Li is focusing on hydroxyethyl starch (HES) based smart nanomedicine, for cancer immunotherapy applications.

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