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Smart R848-Loaded Nanoparticles Based on Copper Chelate Copolymer for Combining Anti-Angiogenesis and Immunotherapy to Inhibit Breast Cancer Growth and Metastasis

Ping Zhou1, Jiaqi Qin[2], Ning Zhang[1]✉, Yinsong Wang[2]✉

[1]Tianjin Medical University Cancer Institute and Hospital, Tianjin 300060, China.
[2]School of Pharmacy, Tianjin Medical University, Tianjin 300070, China.

✉ Corresponding authors. E-mail: zhangning@bjmu.edu.cn; wangyinsong@tmu.edu.cn

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Abstract

Copper plays an important role in tumor angiogenesis. Copper chelation has been confirmed as an effective strategy to inhibit tumor growth and metastasis via the suppression of tumor angiogenesis. Though small molecule copper chelator, TM, has been tested in clinical trials of breast cancer, some unavoidable side effects limit its potency, probably resulting from TM nonselectively eliminating copper from the whole body. In this work, a copper chelating coil-comb block copolymer RGD-PEG-b-P(GA-g-(TETA-DTC-PHis))n (RPTDH) possessing tumor-targeting capability and pH-sensitivity was synthesized and used to prepare nanoparticles for loading and controlled release of the immunoregulator R848. The linear segment of the copolymer consisted of hydrophilic PEG chain with RGD end group, which aims to target tumor microenvironment. The backbone of the comb segment was composed of biodegradable poly-γ-glutamic acid, and the side chain of the comb segment contained triethylenetetramine-bis(dithiocarbamate) midblock and poly-L-histidine block. The comb segments of triethylenetetramine-bis(dithiocarbamate) were used to chelate copper, while poly-L-histidine was introduced to form hydrophobic core at weak alkali conditions to load R848, a TLR7/8 agonist, thus combining antiangiogenesis and immunotherapy to treat breast cancer. RPTDH/R848 nanoparticles significantly inhibited the mobility, invasion and vascular tube formation of HUVEC cells via copper chelation. In weakly acid media simulating tumor microenvironment, R848 was efficiently released from RPTDH/R848 nanoparticles and exhibited strong efficacy in the activation of human pDC-like CAL-1 cells. In breast tumor-bearing mice, RPTDH/R848 nanoparticles displayed excellent targeting ability for both tumor in situ and lung metastases, and furthermore dramatically inhibited tumor growth and metastasis through angiogenesis suppression and $CD8^+$ T cells accumulation in tumor microenvironment. In conclusion, RPTDH/R848 nanoparticles significantly suppress breast cancer growth and metastasis by combining antiangiogenesis with immunotherapy.

Keywords: Copper chelator; Antiangiogenesis; Immunotherapy; Tumor microenvironment