Breaking Through Barriers:

Next-Generation Drug Delivery Systems for Cancer Therapy

Yunching Chen

Institute of Biomedical Engineering, National Tsing Hua University, Hsinchu 30013, Taiwan

E-mail: yunching@mx.nthu.edu.tw

Tumor microenvironment has a significant impact on tumor progression and response to therapy. Nitric oxide (NO) regulates angiogenesis and fibrosis, suggesting that it may serve as a candidate anti-cancer agent via modulation of tumor microenvironment. However, the lack of a tumor-targeting NO delivery system, with a prolonged half-life and sustained NO release mechanism, has hindered the application of this approach to cancer treatment. We engineer several nanoscale NO carriers with a sustained release profile that efficiently delivers NO into hepatocellular carcinoma (HCC) and pancreatic ductal adenocarcinoma (PDAC). We demonstrate that targeting the tumor microenvironment with nanoscale NO results in tumor vessel normalization and desmoplasia alleviation, leading to the enhanced delivery and effectiveness of chemotherapeutic and macromolecular tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-based biological therapies. Furthermore, nanoscale NO polarizes tumor-associated macrophages towards an immune stimulatory phenotype and increases T cell tumor infiltration, thereby improving the efficacy of cancer vaccine immunotherapy. Our findings demonstrate the delivery of NO by the tumor-targeted nanocarriers to efficiently remodel tumor vasculature and immune/fibrotic microenvironments and overcome resistance to cancer therapy, resulting in a therapeutic benefit for cancer.

References

1. H-C Huang, Y-C Sung, C-P Li, D Wan, P-H Chao, B-W Liao, H-T Cheng, F-F Hsu, C-C Huang, Y-H Liao, H-T Hsieh, Y-C Shih, I-J Liu, H-C Wu, T-T Lu*, J Wang*, Y Chen*. *Gut 2022 Sep; 71:1843-1855.*
2. Y-C Sung, P-R Jin, L-A Chu, F-F Hsu, M-R Wang, C-C Chang, S-J Chiou, J T Qiu, D-Y Gao, C-C Lin, Y-S Chen, Y-C Hsu, J Wang, F-N Wang, P-L Yu, A-S Chiang, Y-T Wu, J-S Ko, Charles P-K Lai,

T-T Lu*, Y Chen***,** *Nature Nanotechnology,* 14, 1160–1169.