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Inhibition of Tumor-Promoting Stroma to Enforce Subsequently Targeting AT_1R on Tumor Cells by Pathological Inspired Micelles

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ABSTRACT

Cancer associated fibroblasts (CAFs) are the most abundant, genetically stable stroma cells and localize near blood vessels within "finger-like" collagen-rich stroma, which lead to restrained drug transport in dense stroma instead of tumor cells inside tumor mass, especially for targeting micelles. Meanwhile, the bioactive cytokines secreted by stroma cells result in microenvironment mediated drug resistance (TMDR). Hence, a biologically inspired Telmisartan (Tel) grafting glycolipid micelles (Tel-CSOSA) are constructed, which can sequentially target angiotensin II type I receptor (AT_1R) overexpressed on both CAFs and tumor cells. More Tel-CSOSA are demonstrated to specifically accumulate in tumor site compared to CSOSA. In addition, the retention of Tel-CSOSA is primarily prolonged around tumor vessel in virtue of CAFs targeting and the stroma barrier. In contrast, the elimination of "finger-like" ECM resulting from CAFs apoptosis by Tel-CSOSA/DOX contributes to a more uniform and deeper penetration post-administration, which can enforce subsequently tumor cells targeting. Meanwhile, cytokines are decreased along with CAFs apoptosis so that tumor cells are more vulnerable to chemotherapeutics.