Enhancing Hepatocellular Carcinoma Therapy with DOX-Loaded SiO_2 Nanoparticles via mTOR-TFEB Pathway Autophagic Flux Inhibition

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Chemotherapeutic drugs often fail to provide long-term efficacy due to their lack of specificity and high toxicity. To enhance the biosafety and reduce the side effects of these drugs, various nanocarrier delivery systems have been developed. In this study, we loaded the anticancer drug doxorubicin (DOX) and an MRI contrast agent into silica nanoparticles, coating them with pH-responsive and tumor cell-targeting polymers. These polymers enable the carrier to achieve targeted delivery and controlled drug release in acidic environments. This integrated diagnostic and therapeutic strategy successfully achieved both the diagnosis and treatment of liver cancer. Additionally, we demonstrated that the nanocarrier inhibits autophagic flux in liver cancer cells by targeting the autophagy-lysosome pathway and regulating the nuclear translocation of TFEB, thereby promoting tumor cell death. This novel diagnostic-integrated nanocarrier is expected to be a promising tool for targeted liver cancer treatment.

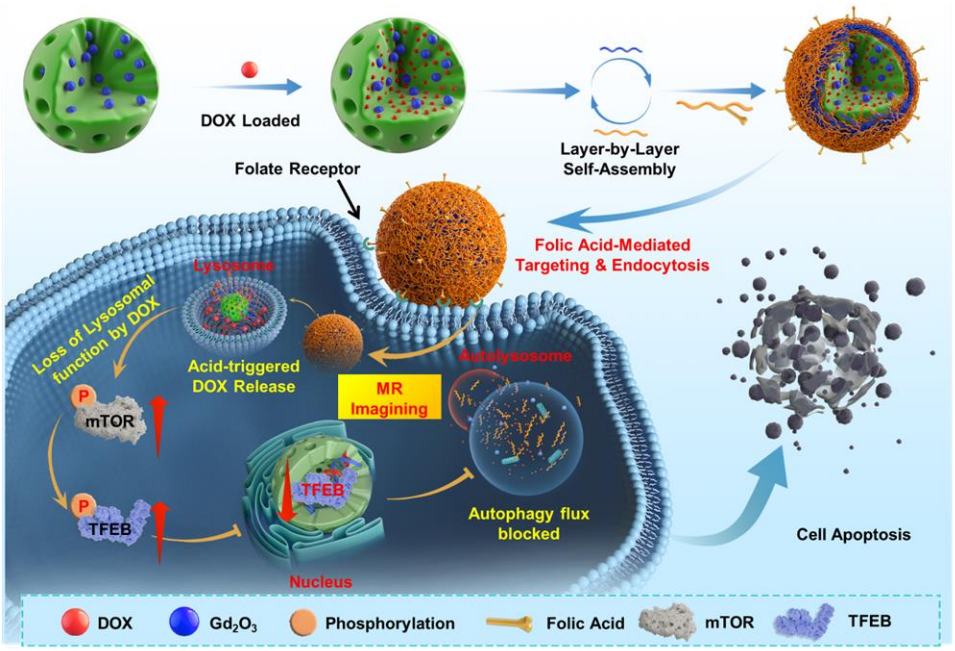

Figure 1: Schematic illustration for the preparation and inhibiting tumor progression through mTOR-TFEB signaling pathway of FA-Gd_2O_3@MSN-DOX. FA-Gd_2O_3@MSN-DOX can be internalized by cancer cells via FA receptor-mediated endocytosis. Within acidic organelles, the pH-responsive polyelectrolytes undergo charge reversal, leading to the release of DOX. Subsequently, FA-Gd_2O_3@MSN-DOX inhibits TFEB nuclear translocation by activating mTOR activity, thereby reducing the expression of autophagy-lysosomal-related genes and blocking the autophagic flux in cancer cells. Additionally, this pH-responsive theranostic nanocarrier can serve as a new MRI contrast agent, leveraging the paramagnetic properties of Gd_2O_3 nanoparticles.