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SGLT2 inhibitors loaded magnetic nanoparticles combined with radiotherapy for the treatment of hypoxic tumors

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Hypoxia in solid tumors leads to the development of resistance of tumor cells to chemotherapy and radiotherapy and is a negative prognostic factor linked to invasiveness, metastasis, and increased mortality of the patients. Hypoxic cells are particularly susceptible to inhibition of glycolysis. We have developed hybrid organic-inorganic, magnetic nanocarriers for the selective delivery of sodium-glucose transport protein inhibitors (SGLT2 inhibitors) to tumors. Dynamic light scattering measurements showed that the average hydrodynamic diameter of the nanocarriers was around 68 nm and the zeta potential around -18 mV. The nanocarriers exhibited excellent stability in aqueous and biological media. Drug (SGLT2 inhibitors) release was accelerated at acidic pH approximating tumor pH conditions. Furthermore, triggered drug release was observed under the influence of an alternating magnetic field. The drug-loaded nanocarriers exhibited *in vitro* anticancer activity under aerobic and hypoxic conditions against cancer cell lines, which was higher than that of free drug at the drug levels studied. The *in vitro* anticancer activity increased in the presence of an external magnetic field, which is probably related to the higher cell uptake of the nanocarriers under the influence of the magnetic field. The combination of selective SGLT2 inhibitors delivery combined with radiotherapy was proven to be a highly efficient therapy in delaying tumor growth in an animal model of cancer.

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