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Tumor pH-functionalized and charge-tunable nanoparticles for the nucleus/cytoplasm-directed delivery of oxaliplatin and miRNA in the treatment of head and neck cancer

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ABSTRACT

Prospective tumor pH-responsive and charge-convertible nanoparticles have been utilized to reduce side effects and improve the active tumor-targeting ability and nuclear/cytoplasmic localization of chemo- and gene therapeutics for the treatment of head and neck cancer (HNC). Oxaliplatin (Oxa) is a third-generation platinum compound that prevents DNA replication. miR-320 may regulate cancer cell apoptosis, resistance, and progression. Innovative nanoparticles incorporating miR-320 and Oxa were modified with a ligand, cell-penetrating peptide, and nucleus-targeted peptide. The nanoparticles were coated with a charge/size-tunable shield to prevent peptide degradation and decoated at acidic tumor sites to expose peptides for active targeting. Results indicated that the designed nanoparticles exhibited a uniform size and satisfactory drug encapsulation efficiency. The nanoparticles displayed the pH-responsive release and uptake of Oxa and miR-320 into human tongue squamous carcinoma SAS cells. The nanoparticles successfully delivered Oxa and miR-320 to the nucleus and cytoplasm, respectively. This work is the first to demonstrate the concurrent intracellular modulation of the NRP1/Rac1, PI3K/Akt/mTOR, GSK-3β/FOXM1/β-catenin, P-gp/MRPs, KRAS/Erk/Oct4/Yap1, and N-cadherin/Vimentin/Slug pathways to inhibit the growth, progression, and multidrug resistance of cancer cells. In SAS-bearing mice, co-treatment with Oxa- and miR-320-loaded nanoparticles exhibited superior antitumor efficacy and remarkably decreased Oxa-associated toxicities. The nucleus/cytoplasm-localized nanoparticles with a tumor pH-sensitive and size/charge-adjustable coating may be a useful combinatorial spatiotemporal nanoplatform for nucleic acids and chemotherapeutics to achieve maximum therapeutic safety and efficacy against HNC.

Statement of significance

Innovative nanoparticles incorporating miR-320 and oxaliplatin were modified with a ligand, cell-penetrating peptide, and nucleus-targeted peptide. The tumor pH-sensitive and charge/size-adjustable shield of polyglutamic acid–PEG protected against peptide degradation during systemic circulation. This work represents the first example of the concurrent intracellular modulation of the NRP1/Rac1, PI3K/Akt/mTOR, GSK-3β/FOXM1/β-catenin, P-gp/MRPs, KRAS/Erk/Oct4/Yap1, and N-cadherin/Vimentin/Slug pathways to inhibit cancer cell growth, cancer cell progression, and multidrug resistance simultaneously. The versatile nanoparticles with a tumor pH-functionalized coating could deliver chemotherapeutics and miRNA to the nucleus/cytoplasm. The nanoparticles successfully reduced chemotherapy-associated toxicities and maximized the antitumor efficacy of combinatorial therapy against head and neck cancer.

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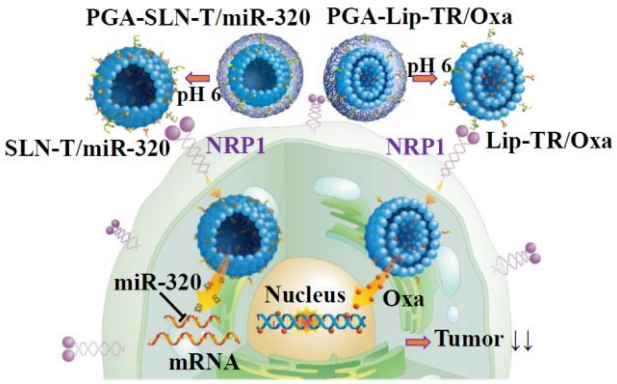

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