

Nutlin-3 loaded nanocarriers: preparation, characterization and in vitro antineoplastic effect against Primary Effusion Lymphoma

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Purpose

Nutlin-3 (Nut3) is a novel anticancer small-drug antagonist of MDM2, a tumor over expressed protein able to induce p53 degradation. Since MDM2 is expressed only in malignant cells, the specific inhibition of MDM2-p53 interaction represents a possible strategic target for therapeutic development against cancer. Unfortunately, Nut3 is sparingly soluble in aqueous buffer causing difficulty during administration (frequently per os) and poor bioavailability. In this investigation, Nut3 was loaded into liposomes (Lipo-Nut3), polymeric nanoparticles (NPs-Nut3) and nanoparticles engineered with an antibody direct against Syndecan-1/CD 138 (Syn-NPs-Nut3) to ameliorate drug administration, promoting a selective targeting to PEL (Primary Effusion Lymphoma).

Methods

Lipo-Nut3 were formulated by a thin layer evaporation method followed by extrusion using neutral and non-toxic lipids (DOPC/Chol 9:1 molar ratio).

NPs-Nut3 were formed according to nanoprecipitation method using biocompatibility and biodegradable PLGA. Moreover, an antibody selective for PEL cell line was conjugated to the surface of NPs by NHS-EDC method obtaining **Syn-NPs-Nut3**.

All systems were characterized using PCS, AFM and ESCA analyses. By performing cytofluorimetric analyses and bromodeoxyuridine (BrdU) assay, the efficacy of nanocarriers to deliver Nut3 into a PEL cell line namely BCBL-1 (immortalized body cavity B-cell lymphoma) was investigated.

Results

AFM showed that all the particles were spherical in shape. The presence of the antibody on surface (AFM and ESCA analyses), led to a significant increase of mean diameter (280 ± 63 nm), PDI (0.3) and the shift of zeta potential towards neutrality (-1 mV). The entrapment efficiency of Lipo-Nut3, NPs-Nut3 and Syn-NPs-Nut3 was 30, 52 and 29%, and drug loading was 1.4, 4.5 and 2.6%, respectively.

Two days after the treatment with 20 μ M of Syn-NPs-Nut3, the cell density decreased at about 60% while the cell viability decreased at 56% only 5 days after transfection, when compared with untreated cells. A cell cycle arrest was observed with a significant decrease of cells in S-phase and increasing of apoptotic cell, if compared with untreated control.

Conclusion

The results strongly suggest that Syn-NPs-Nut3 can be a valuable drug carrier system for the treatment of PEL lymphoma.