Targeted Drug Delivery for Drug Resistant Cancer

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Cancer stem cells are a subset of cells that are able to survive chemo, differentiate, and repopulate the tumor, leading to increased survival and disease progression. P53 suppression is linked to increased resistance and survival in cancer stem cells as DNA damage and mutations proliferate without regulation. Many small molecules target p53 suppression, specifically related to the negative feedback loop with MDM2, and rehabilitate p53. However, both typical chemotherapy drugs and small molecules exhibit toxicity and side effects. Liposomes are non-toxic, biocompatible nanoparticles composed of a lipid bilayer. Liposomes can encapsulate both hydrophilic and hydrophobic drugs and be conjugated with targeting ligands. It was hypothesized that the combination of a p53 stabilizing agent and Doxorubicin, a chemotherapeutic agent, in a liposomal nanoparticle conjugated with the targeting ligand iRGD would increase drug sensitivity and promote cancer stem cell (CSC) death. The liposome was formulated and tested in breast cancer stem cell lines. Liposomes were approximately 100 nm in size and formed uniformly. iRGD increased cellular uptake in vitro. In ANV5 cell lines (p53 wild type) the combination therapy was eight times as effective as a single drug and in MDA-MB-231 cell lines (mutant p53) the combination therapy was 4 times as effective (p value < 0.001). The combination therapy decreased stemness, shown by decreased wound healing and proliferative abilities. Additionally, the combination therapy increased p53 protein expression and decreased MDM2 expression, indicating a synergistic mechanism. This combination therapy formulation significantly improved therapeutic response which suggests promising clinical application.

Awards Won:

Third Award of $1,000

Drug, Chemical &amp

Associated Technologies Association (DCAT): Award of $3,000.