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Targeted nano-based proteostasis-inhibition for controlling lung cancer pathogenesis & progression

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We recently identified valosin-containing protein (VCP)/p97-retrograde translocation as a novel proteostasis mechanism involved in non-small cell lung cancer (NSCLC) pathogenesis and progression. Since VCP is involved in homeostatic processes (proteostasis), we developed a nano-based targeted proteostasis-inhibitor delivery system for targeting lung tumors as a novel selective proteostasis-inhibition strategy to control NSCLC progression and metastasis. We identified that the PLGA-PEG based bio-degradable nanoparticles (NPs) are safer for selective molecular targeting of proteostasis-inhibitor over polymeric chitosan-dextran sulphate (CS-DS; $p<0.02$; 24hrs) NPs as they did not inhibit non-tumor lung epithelial (Beas2b) cell proliferation. We encapsulated potent VCP-proteostasis-inhibitor (N^2, N^4-dibenzylquinazoline-2, 4-diamine; DBeQ) in PLGA-PEG (PLGA-PEG^{DBeQ}) NPs for targeted release of the drug without affecting the non-tumor cells. Next, we standardized the efficacy of PLGA-PEG^{DBeQ} NPs (~15μM) to control NSCLC growth and progression. We found that PLGA-PEG^{DBeQ} NPs significantly inhibit NSCLC migration (n=6, $p<0.001$; 24hrs) and proliferation (n=6, $p<0.03$; 24hrs & $p<0.002$; 48hrs) while inducing apoptosis (n=5, $p<0.01$; 48hrs). Moreover, we evaluated the anti-proliferative, apoptotic and tumor inhibitory efficacy of PLGA-PEG^{DBeQ} NPs in athymic-nude mice (n=6; xenograft-model) injected with GeltrexTM-H1299 ($4x10^6$; day-0) tumors. We observed that PLGA-PEG^{DBeQ} NPs (~15μM; day-10) induce anti-tumor activity within 48hrs, as seen by significant ($p<0.005$; day-12) reduction in tumor sizes (~1.44-fold), without any significant body weight loss. The data demonstrates the safety and efficacy of novel PLGA-PEG based selective proteostasis-inhibition strategy (PLGA-PEG^{DBeQ}) for lung cancer therapy.

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