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Synergistic anti-cancer effect of stable nitric oxide releasing nanoparticles, SMA-tDodSNO and Doxorubicin

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Obstacles such as non-specific distribution and inadequate accumulation of therapeutic in hypoxic regions of tumor, low cell membrane penetration and low lysosomal escape remain formidable challenge to the enhanced permeability and retention (EPR) effect based therapeutic systems. To overcome this limitation, we have developed a stable nitric oxide (NO) releasing nanoparticles (NPs) named as SAM-tDodSNO and used it in combination with Doxorubicin (Dox) loaded NPs (SMA-Dox) and their effects on cell proliferation, induction of apoptosis, the changes of lysosomal membrane permeabilization and mitochondrial membrane potential and tumor growth were studied. Combination of SMA-tDodSNO to Dox showed a synergistic anti-proliferative effect in $4T_1$ breast cancer cells and when used in xenografted mice it resulted more than 5.5 folds reduction in tumor size compared with Dox alone. We also found, the SMA-tDodSNO could enhance the endocytosis of SMA-Dox and inhibit Dox efflux from the cells resulting higher concentration of Dox in the cells. Local administration of SMA-tDodSNO in tumor area increased the concentration of Dox in tumor when combined with free Dox or SMA-Dox. SMA-tDodSNO promoted the lysosomal membrane permeabilization and the reduction of mitochondrial membrane potential induced by doxorubicin and resulted enhanced intracellular calcium concentration. In conclusion, the SMA-tDodSNO as novel NO releasing NPs showed significant cytotoxicity in breast cancer cells and was able to decrease the tumor growth and potentiated the anticancer potency of Dox both *in vitro* and *in vivo* models. Due to NO release it enhanced the endocytosis of a Dox loaded NPs and increased permeability of endosomal membrane hence facilitate the escape of the NPs and inhibited Dox efflux from the cells.

Biography

Houman Alimoradi is a PhD candidate at the Department of Pharmacology and Toxicology, University of Otago. He has obtained his MSc in Medical Toxicology and a Bachelor's degree in Chemistry and his research interest focuses on two major categories: Synthesis of stable and stimuli-responsive nitric oxide donors for intelligent therapy of disease such as cancer; challenging problems in the delivery of therapeutic agents notably in cancer by regulation of hypoxia and redox balance of cells and synthesis of redox and hypoxia responsive nanocarriers.

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