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RESEARCH ARTICLE

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Evaluation of curcumin nanoparticles of various sizes for targeting multidrug-resistant lung cancer cells via inhalation

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ABSTRACT

Introduction: Inhalation drug delivery can deliver high doses of chemotherapeutic drugs to the lung tumor. This study evaluates the efficacy and the mechanistic pathways of nebulized Cur NPs at various sizes to treat multidrug resistant lung cancer.

Methods and results: Cur-NPs (30 nm and 200 nm) were nebulized separately onto the multidrug-resistant lung cancer cells (H69AR). Smaller NPs induced significantly higher cell death owing to a higher rate of particle internalization via dynamin-dependent clathrin-mediated endocytosis. Owing to the higher lysosome trafficking of Cur-NP30 nm compared to Cur-$NP_{200\ nm}$, oxidation of lysosome was higher (0.47 ± 0.08 vs 0.38 ± 0.08), contributing to significantly higher mitochondrial membrane potential loss (1.57 ± 0.17 vs 1.30 ± 0.11). MRP1 level in H69AR cells was reduced from 352 ± 12.3 ng/µg of protein (untreated cells) to 287 ± 12 ng/µg of protein (Cur-$NP_{30\ nm}$) and 303 ± 13.4 ng/µg of protein (Cur-$NP_{200\ nm}$). NF-κB, and various cytokine expressions were reduced after treatment with nebulized Cur-NPs.

Conclusions: Nebulized Cur-NPs formulations could be internalized into the H69AR cells. The Cur-NPs toxicity toward the H69AR was size and time-dependent. Cur-NP30 nm was more effective than Cur-NP200 nm to retain within the cells to exert higher oxidative stresss-induced cell death.

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Curcumin nanoparticles; drug-resistant; endocytosis; H69AR; inhalation; lysosome

1. Introduction

Lung cancer is classified as one of the deadliest cancer-related diseases. In 2020, more than 2 million new lung cancer cases and 1.8 million lung cancer-related deaths were estimated, which were responsible for 11.4% and 18% of the total cancer cases and total cancer deaths, respectively [1]. These data are expected to increase due to various factors such as i) environmental-related factors—occupation and pollution; and ii) socioeconomic factors—unhealthy lifestyle including smoking, unbalanced diets, and lack of physical activities, and iii) genetic factors (for example, mutation of tumor suppressor protein and abnormality in chromosome) [2]. The National Cancer Institute has established a standard treatment protocol for lung cancer based on the tumor stage at the time of diagnosis [3]. Although treatment methods are tailored to the patient's health conditions and susceptibility, the size and origin of the tumor, along with traditional modalities, such as surgery, stereotactic radiosurgery, radiation, and chemotherapy, remain the "gold standard" for lung cancer [3]. Besides chemotherapy, targeted therapy and immunotherapy are more patient-friendly, with fewer side effects, and are integral to lung cancer treatment protocols. However, lung tumors often manage to survive these treatments, progressing into aggressive, multidrug-resistant cells that can metastasize to other organs [4].

Data from phytochemical research have highlighted the potential of polyphenol compounds such as curcumin (Cur), resveratrol, and capsaicin to target both the metastatic and drug-resistant tumors via inhibition of respective proteins such as matrix metalloproteinase, metastasis-associated protein 1, p-glycoprotein (p-gp), and multidrug resistance protein (MDR). Cur is well known for its ability to downregulate important molecular targets instrumental in cancer progression such as epidermal growth factor receptor (EGFR) kinase, mitogen-activated protein kinase (MAPK), and nuclear factor kappa beta (NF-κB) [5]. Both *in vitro* (immortalized cell line and patient tissue) and *in vivo* (xenograft mice) data have confirmed that Cur could effectively improve the therapeutic index of non-small cell lung cancer and small cell lung cancer by inhibiting cell migration, invasion, angiogenesis, and cell cycle arrest [5]. The induction of apoptosis by Cur is believed to occur via the inhibition of Akt dephosphorylation, DNA damage, NF-κB activation as well as caspase expression thus leading to the activation of intrinsic (mitochondrial) and extrinsic apoptotic pathways. Nagahama et al. [6] reported that protonation of Cur at acidic pH in the endosome caused an influx of calcium ion as well as water molecules into the organelle. The increased osmotic pressure disrupted membrane stability and thus promoted the escape of Cur into the

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