2-Methoxy-1,4-naphthoquinone (MNQ) induces apoptosis of A549 lung adenocarcinoma cells via oxidation-triggered JNK and p38 MAPK signaling pathways

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Aim: The compound 2-methoxy-1,4-naphthoquinone (MNQ) was previously shown to be cytotoxic against several cancer cell lines, but its mode of action is poorly understood. In this study, we aimed to explore the molecular mechanism of MNQ-induced cytotoxicity of A549 lung adenocarcinoma cells.

Main methods: The growth inhibition potential of MNQ was analyzed using sulforhodamine B assay, flow cytometry cell cycle analysis and Annexin V apoptosis assay. Oxidative stress was determined using 2′,7′-dichlorofluorescein diacetate to measure intracellular reactive oxygen species level and comet assay to measure DNA damage. Western blotting was performed to study the activation of mitogen-activated protein kinase signaling pathways.

Key findings: MNQ induced apoptosis of A549 cells independent of cell cycle arrest, and is mediated by the JNK and p38 MAPK signaling pathways. Further analysis demonstrated that these signaling pathways were stimulated by oxidative DNA damage caused by increased ROS generation in MNQ-treated A549 cells.

Significance: This study is the first to provide an insight into the molecular mechanism of MNQ-induced cytotoxicity of a lung cancer cell, which demonstrates the potential of MNQ as a potential chemotherapeutic drug for lung cancer treatment.

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1. Introduction

Lung cancer causes the highest cancer-related mortality globally [1], with an estimate of 1.59 million deaths reported in the year 2012 [2]. This disease can be generally categorized as either non-small cell lung carcinoma (NSCLC), which comprises 85% of the total lung cancer cases reported, or small cell lung carcinoma (SCLC) which accounts for the remaining 15% [3]. Despite the various treatments available for lung cancer management, the survival rates reported are usually low [4,5,6]. In addition, the current chemotherapeutic regimens are compromised with detrimental side effects [7]. Therefore, this warrants the need for more efficient therapeutic approaches.

Quinones are a class of organic compounds in which many of its members were observed to possess anticancer properties by modulating intracellular processes to trigger the cell death mechanisms. These processes include the MAPK signaling pathways, which are deregulated in different types of cancers to promote cell survival and proliferation while evading growth suppression and cell death [8,9,10,11,12]. However, certain anticancer quinones have been observed to overcome this aberration by stimulating the MAPKs to activate the apoptotic pathways [13,14,15,16].

In addition, several quinones were also observed to promote cancer cell death in a reactive oxygen species (ROS)-dependent mechanism [17,18,19,20]. The redox systems in most cancer cells were observed to be aberrant, with higher levels of ROS higher compared to normal cells [21]. This higher but non-lethal level of ROS is believed to play an important role in carcinogenesis as they serve as second messengers to alter the signaling pathways, thus promoting proliferation and survival of cancer cells [22,23]. Nevertheless, it is also known that high concentrations of ROS will completely overwhelm the antioxidant defense mechanism, causing extreme oxidative damage to cellular components and results in cell death [24,25]. In fact, several chemotherapeutic drugs function by inducing ROS generation in cancer cells in order to eliminate them [26,27].

The compound 2-methoxy-1,4-naphthoquinone (MNQ) (Fig. 1) is a quinone extracted from garden balsam (Impatiens balsamina). This compound has been observed to exert an anticancer effect against several cancer cell lines, including HepG2 hepatocarcinoma cells, MDA-MB-231 breast cancer cells, and MKN45 gastric adenocarcinoma cells [28,29,30]. Nevertheless, its mechanism of action is not fully understood. In this study, we investigated the growth inhibitory potential of MNQ on A549