2-Methoxy-1,4-Naphthoquinone (MNQ) suppresses the invasion and migration of a human metastatic breast cancer cell line (MDA-MB-231)

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Abstract

Metastasis contributes to the escalating mortality rate among cancer patients worldwide. The search for novel and more effective anti-metastatic agent is crucial owing to the lack of anticancer drugs that can successfully combat metastasis. Hence, this study aims to examine the effects of 2-Methoxy-1,4-Naphthoquinone (MNQ) towards the metastasis of MDA-MB-231 cells. In invasion assays, the number of cells permeating across a Matrigel barrier was found to be decreased in a dose-dependent manner upon treatment with MNQ (0–7.5 μM). In wound-healing migration assays, MNQ exhibited dose-dependent inhibition of cell migration in which significant reduction in the zone of closure was observed as compared to untreated controls. Furthermore, the proteolytic activity of a pivotal metastatic mediator, matrix metalloproteinase-9 (MMP-9) was also downregulated by MNQ as determined by gelatin zymography. This study reports for the first time, the ability of MNQ to inhibit the invasion and migration characteristics of a highly metastatic MDA-MB-231 cancer cell line.

1. Introduction

2-Methoxy-1,4-Naphthoquinone (MNQ) (Fig. 1) isolated from a local Malaysian medicinal plant, Impatiens Balsamina Linn., was previously shown to be cytotoxic against a panel of human cancer cell lines (Teng, 2010). A subsequent proteomic study by Tan (2011) revealed that MNQ induced differential expressions of proteins that are implicated in the antioxidative, stress response and detoxification pathways; thereby triggering apoptosis and cell cycle arrest in a human leukemic cell line, K562. The observed cytotoxicity of MNQ is in agreement with other works that report the cell-killing effect of MNQ on human liver and gastric cancer cell lines (Ding et al., 2008; Wang and Lin, 2012). Mori et al. (2011) further demonstrated that MNQ inhibited the Wnt signaling pathway which is crucial for cancer progression. Despite the growing number of reports on its anticancer effects, the anti-metastatic potential of MNQ has not been documented.

Globally, metastasis accounts for more than 90% of cancer-related death (Sethi and Kang, 2011). Metastatic processes in general, involve the invasion and degradation of the basement membrane barrier by cancer cells via secretion of proteolytic enzymes such as the matrix metalloproteinases (MMPs). MMP-2 and -9 in particular, play critical roles in remodeling the extracellular matrix (ECM) by digesting various types of ECM proteins in the basement membrane (Lynch and Matrisian, 2002). Both MMPs differ in terms of their transcriptional regulations. Unlike MMP-2 which is usually constitutively expressed, the expression of MMP-9 is highly inducible by various growth factors, cytokines and other stimulatory signals. This difference can be explained by the presence of inducible promoter elements such as the activator protein-1 (AP-1) binding site which is seen in MMP-9 but not in MMP-2 (Yan and Boyd, 2007). For this reason, it has been suggested that the regulation of MMP-9 expression is a feasible approach for the development of anti-metastatic drugs (Zhang et al., 2006; Ling et al., 2011).

As a result of the proteolytic action of MMPs and other proteases, the remodeled ECMs assist the passage and the migration of the cancer cells. This in turn, facilitates their dissemination to the secondary target organs via the blood and lymph circulatory systems. The cancer cells will then further proliferate, differentiate and survive after successfully colonizing their new-found environment (Nabeshima et al., 2002; Geiger and Peeper, 2009). Hence, interference of these processes represents promising intervention strategies in anti-metastatic therapy (Valastyan and Weinberg, 2011).