Marine bioactive products as anti-cancer agents: Effects of sea anemone venom on breast and lung cancer cells

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Introduction

Marine organisms abound that have a rich heritage as therapeutics resources that have been exploited for effective and beneficial use against many human cancers. Many of these natural compounds in are venom used to acquire prey and as chemical defence against predators in nature [1]. Numerous toxic peptides are found within these venoms, and some of them have been used to investigate biomedical problems including designing novel drugs [2]. Sea anemones are one of the most ancient predatory animals and various in vitro and in vivo studies have demonstrated that more than 32 species of sea anemones studied produce lethal cytolytic peptides and proteins [3]. Many biological assays have been carried out to evaluate toxicity of the venoms. Studies of hemolytic activities [4, 5] immunomodulating activities [6, 7], neurotoxic [8], cardiotoxic [9] and cytolytic tests [10, 11] have all produced interesting outcomes. Some recent observations of the venom from the sea anemone Heteractis magnifica, have shown that it can induce apoptosis in human breast and lung cancer cell lines [12, 13]. Cell cycle deregulation is an important feature of many cancers and therefore control of cell cycle progression is suggested to be an effective strategy to inhibit cancer growth [14]. Clear evidence of cell cycle arrest and apoptosis was observed in our previous study.

A549 cancer cells treated with of H. magnifica venom showed delayed progression through the cell cycle and a marked reduction in the number of cells in S phase with an associated accumulation of cells in G0/G1 phase [13]. In contrast, H. magnifica venom applied to human breast cancer T47D and MCF7 cells was found to induce cell cycle arrest in sub G1 phase with a concomitant decrease in the G1 phase, indicating induction of apoptosis [13]. This discrepancy might be due to the difference in cell type analysed. Apoptosis is an important defence against cancer [15]. However, the resistance of human cancer to apoptosis may be due to inactivation of proapoptotic effectors (e.g., loss of the p53 pathway) or overexpression of Bcl-2 family, which can block apoptosis [16, 17]. Therefore, apoptotic pathways are emerging as promising targets for cancer therapy. We used flow cytometry assay for apoptosis, and the experimental data confirmed that venom from H. magnifica could induce apoptosis (Figure 1). However, far fewer papers are published each year on apoptosis in lung cells than in the other major organs. H. magnifica venom is a candidate to induce apoptosis in non-small-cell lung cancer A549 cells [13].

Apoptosis occurs via two principal pathways, the death receptor pathway (extrinsic) and the mitochondrial pathway
The extrinsic pathway is triggered by the binding of death inducing ligands to cell surface receptors, which results in the activation of caspase 8. The intrinsic pathway, in contrast, is triggered by cytotoxic stress, which converges at the mitochondria, leading to the release of cytochrome c from mitochondria. In the cytosol, cytochrome c binds Apaf to form an active complex called the apoptosome. Activation of caspase 3/7 (effector caspases) is involved in both pathways, while caspase 8 and 9 (initiator caspases) are involved in extrinsic and intrinsic pathway, respectively [15, 18, 19]. Effector caspases, including caspase 3/7, activate DNase resulting in fragmentation of DNA in response to various apoptotic stimuli [20-24]. Recently, we reported that venom from *H. magnifica* was able to induce cell death by activation of the caspase pathway. *H. magnifica* venom significantly increased the levels of caspase 3/7, enzyme activity in A549, T47D and MCF7 cell lines (Figure 2) [12, 13]. It has been reported that MCF7 cells do not show an increase in the sub-G1 in response to anti-cancer drug treatment [23] and also did not express detectable level of caspase 3 [26]. *H. magnifica* venom however, could interfere with the cell cycle at the sub G1 phase, induce apoptosis and increase the activation of caspase 3/7 [12].

An increase of mitochondrial membrane permeability is one of the key events in apoptotic pathway by releasing apoptogenic proteins into the cytosol [27-29]. Our previous work demonstrated that *H. Magnifica* venom induced apoptosis by loss of mitochondrial membrane potential in human non-small cell lung cancer A549 cells [13]. These findings are consistent with our previous study on T47D and MCF7 cell lines that the venom significantly increased the percentage of cells positive for JC-1 monomers [12].

Many previous reports have shown that sea anemone venoms exert cytotoxic effects on different cancer cell lines. We have developed the mechanisms action of the *H. magnifica* venom. *H. Magnifica* venom has great potential to induce significant apoptosis and cell cycle arrest in lung and breast cancer cell lines. Further study could be carried out using more cancer cell line with different background to design of combination treatment using the *H. magnifica* venom with other therapies, based on molecular targets.

**Conflicting interests**

The authors have declared that no competing interests exist.

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**References**
