

COMMENTARY

Drugs from Marine Sources: Modulation of TRAIL Induced Apoptosis in Cancer Cells

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Abstract

There have been overwhelming advances in molecular oncology and data obtained through high-throughput technologies have started to shed light on wide ranging molecular mechanisms that underpin cancer progression. Increasingly it is being realized that marine micro-organisms and the biodiversity of plankton are rich sources of various anticancer compounds. Marine derived compounds play major roles in inducing apoptosis in cancer cells. More importantly, various agents have been noted to enhance TRAIL induced apoptosis in cancer cells by functionalizing intrinsic and extrinsic pathways. In this commentary, a list of marine derived compounds reported to induce apoptosis is discussed.

Keywords: TRAIL - cancer - apoptosis - influence of marine drugs

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Introduction

Cancer is a multifaceted and genomically complex disease. Research over decades has shown involvement of different biological mechanisms including suppression of tumor suppressor genes, overexpression of oncogenes, genetic/epigenetic mutations, intra-tumor heterogeneity, genomic instability and loss of apoptotic signaling network that signals through membrane death receptor-mediated intracellular cascade. Accumulating experimentally verified evidence is providing in-depth analysis of molecular mechanisms of common signaling nodes, pathway crosstalk and the role of multi-functional proteins in regulation of cell death.

Biochemical and structural biological studies have shown that tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) signals through death receptors which possess a cytoplasmic death domain (DD) and belong to tumor necrosis factor receptor superfamily. TRAIL discovery revolutionized the field of molecular oncology and attracted researchers world-wide to unravel the signal transduction machinery triggered by this ligand. Adaptor protein Fas-associated death domain (FADD) is positioned at Death Receptor and forms a signalosome termed as death-inducing signaling complex (DISC). DISC consisting of FADD and Pro-caspase-8 is formed at the death receptor and is negatively regulated by its key inhibitor c-FLIP, has been extensively investigated. Downstream from DISC, the apoptotic signals are transduced through two deeply studied pathways including extrinsic and intrinsic pathway. Caspase-8 activates its

downstream effector caspase-3 thus functionalizing extrinsic pathway. Intrinsic pathway is activated via Caspase-8 mediated processing of Bid into truncated Bid. tBid moves into mitochondrion to promote release of cytochrome c, SMAC/DIABLO, Omi/Htra. Decrease in cytosolic levels of Smac/Diablo released from the mitochondria and considerably higher expression of inhibitor of apoptosis (IAP) proteins are some of the mechanisms which induce TRAIL resistant phenotype. Cytochrome c, co-operates with Apaf-1 to form apoptosome, which results in activation of caspase-9. There is a list of newly emerging scientific evidence highlighting molecular mechanisms to enhance or restore TRAIL induce apoptosis in cancer cells (Huang et al, 2012; Jiang et al, 2013; Silva et al, 2014). Natural agents have gained tremendous appreciation as evidenced by encouraging results obtained from cell culture studies and xenografted mice (Sehitoglu et al, 2014; Aras et al, 2014).

Wealth of information indicated that different marine compounds had been tested for wide ranging biological activities. These marine compounds have also displayed potential application as novel anticancer agents. In this commentary we have attempted to summarize and discuss compounds reported to be involved in restoration of TRAIL induced apoptosis in cancer cells.

Marine Compounds have Notable Apoptosis-inducing Activity

Pseudoboydins isolated from marine fungus, *Pseudallescheria boydii* are isobenzofuranone derivatives.

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Moderate cytotoxic activity was noted upon treating nasopharyngeal carcinoma cell lines with Pseudoboydin A (Lan et al., 2014). Stelletin B, isolated from Marine Sponge *Jaspis stellifera* is a triterpene. In-vitro assays revealed Stelletin B induced ROS generation in glioblastoma cancer SF295 cells. Phosphorylated Akt levels were also remarkably reduced in Stelletin B treated SF295 cells (Tang et al., 2014). JG6, is a marine-derived oligosaccharide. Results revealed that JG6 occupied actin-binding sites of cofilin thus inhibiting cofilin mediated disassembly actin filaments. JG6 also considerably inhibited cancer metastasis in xenografted mice (Huang et al., 2014). Lamellarin O isolated from marine sponge, *Lanthella* sp is a pyrrole alkaloid. Lamellarin has been shown to exert its biological effects by inhibiting ATP binding cassette (ABC) transporters, BCRP in drug resistant cancer cell lines (Huang et al., 2014).

Marine Sponges

Manzamine A

Marine sponges are rich sources of alkaloids. Manzamine A is extracted from Marine sponges and has shown considerable efficacy and restored TRAIL induced apoptosis in AsPC-1 pancreatic cancer cells. Moreover, it was also noted that Manzamine A did not exert its biological effects via suppressing pErk levels in treated AsPC-1 cells. It was also indicated that pGSK3 β levels were considerably enhanced in Manzamine A treated AsPC-1 cells. It was concluded that Manzamine A may exert its anticancer effects by increasing pGSK3 β levels (inactive form) in AsPC-1 cells (Guzman et al., 2011).

Ilimaquinone

Ilimaquinone, is a marine sponge metabolite (Lu et al., 2007). It has recently been convincingly revealed that Ilimaquinone treated colon cancer cells had considerably enhanced expression of DR4 and DR5. Mechanistically it was shown that Ilimaquinone exerted its stimulatory effects on DR4 and DR5 by increasing ROS generation in cells. It is now well known that CCAAT/enhancer-binding protein homologous protein (CHOP) is involved in regulation of DR4 and DR5 expression. In-vitro analysis also indicated that ERK and p38 MAPK signaling pathways were activated in Ilimaquinone treated colon cancer cells (Do et al., 2014).

Marine actinomycetes

Chromomycins, isolated from marine actinomycetes have also been shown to significantly inhibit TCF/ β -catenin transcription in gastric adenocarcinoma (AGS) cell line. It was also noted that cell viability of cancer cells treated with Chromomycins and TRAIL was 52% lower (Toume et al., 2014).

Ecteinascidia turbinata

Trabectedin, an alkaloid extracted from *Ecteinascidia turbinata* has been reported to effectively enhance expression of DR4, DR5 and FADD in trabectedin treated MCF-7 breast cancer cells. However, trabectedin induced expression of pro-apoptotic genes including Bad, Bax,

Smac/DIABLO and Cytochrome c in MDA-MB-453 cells (Atmaca et al., 2013).

Sphingoid bases from sea cucumber

Interestingly, Sphingoid bases from sea cucumber remarkably enhanced expression levels of DR5, GADD45 and Bax in hepatoma HepG2 cells. Moreover, pAkt levels were markedly reduced in treated cancer cells (Hossain et al., 2013).

Siphonaxanthin from green algae

Similar effects have been noted to be exerted by Siphonaxanthin, a carotenoid isolated from green algae on human leukemia (HL-60) cells. GADD45 and DR5 expression levels were notably increased in Siphonaxanthin treated HL-60 cells (Ganesan et al., 2011).

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