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Review

Apoptosis inducing lead compounds isolated from marine organisms of potential relevance in cancer treatment

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ABSTRACT

Apoptosis is a critical defense mechanism against the formation and progression of cancer and exhibits distinct morphological and biochemical traits. Targeting apoptotic pathways becomes an intriguing strategy for the development of chemotherapeutic agents particularly if the process is selective to cancer cells. Marine natural products have become important sources in the discovery of antitumour drugs, especially when recent technological and methodological advances have increased the scope of investigations of marine organisms. A high number of individual compounds from diverse organisms have induced apoptosis in several tumour cell lines *via* a number of mechanisms. Here, we review the effects of selected marine natural products and their synthetic derivatives on apoptosis signalling pathways in association with their pharmacological properties. Providing an outlook into the future, we also examine the factors that contribute to new discoveries and the difficulties associated with translating marine-derived compounds into clinical trials.

Contents

Abbreviations: MNPs, marine natural product; FDA, Food And Drug Administration; TNFR, tumour necrosis factor receptor; TRAIL, TNF-related apoptosis inducing ligand; FasL, Fas ligand; FADD, Fas-associated protein with death domain; RIP1, receptor-interacting protein 1; ROS, reactive oxygen species; Apaf-1, apoptotic protease activating factor 1; Bid, BH3 interacting-domain; Bak, BCL2 antagonist/killer; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; Bcl-XL, B-cell lymphoma-extra large; Mcl-1, myeloid cell leukaemia sequence 1; Bim, B-cell lymphoma 2 interacting mediator; Puma, p53 upregulated modulator of apoptosis; PI3K, phosphatidylinositol 3 kinase; AKT, serine/threonine-specific protein kinase; ET-743, Ecteinascidin-743; STS, soft tissue sarcoma; NER, nucleotide excision repair; Smac, second mitochondria-derived activator of caspases; DIABLO, IAP binding protein with low pI; PARP, poly ADP ribose polymerase; GTP, guanosine-5′-triphosphate; NCI, National Cancer Institute; MAPKs, mitogen-activated protein kinases; JNK, Jun N-terminal kinases; VEGF, vascular endothelial growth factor; KF, Kahalalide F; Her2/neu, human epidermal growth factor receptor 2; NSCLC, non-small-cell lung carcinoma; PC-3, prostate cancer-3 cell line; SKBR3, breast cancer cell line; ERBB3, receptor tyrosine-protein kinase erbB-3 enzyme; COX-2, cyclooxygenase-2; c-Myc, c-myelocytomatosis; cflip, FADD-like IL-1β-converting enzyme-inhibitory protein; TRAF1, TNF receptor-associated factor 1; IAP, inhibitors of apoptosis; Endo G, endonuclease G; HtrA2/Omi, mitochondrial serine protease; XIAP, X-linked inhibitor of apoptosis protein; MMP-9, matrix metallopeptidase 9; ICAM-1, intercellular adhesion molecule 1; MCF-7, breast cancer cell line; AIF, apoptosis inducing factor; NMR, nuclear magnetic resonance.

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1. Introduction

Cancer is a disease of worldwide importance. Its incidence in the developed countries is rising and its mortality occupies second rank in the order of cause for death. About 12.7 million cancer cases and 7.6 million cancer deaths are estimated to have occurred in 2008 worldwide [1]. According to Dr. Lee Jong-Wook, former Director General of the WHO, "*by the year 2020, cancer could kill more than 10.3 million people per year unless action is taken in both the field of prevention and treatment*." Cancer results from a multi-stage and multi-mechanism process consisting of initiation, promotion, and progression phases. Epigenetic changes and in particular aberrant promoter hypermethylation associated with inappropriate gene silencing contribute significantly to the initiation and progression of human cancer [2]. Currently available anticancer treatments such as ionising radiation, hyperthermia, alkylating agents, DNA topoisomerase inhibitors and platinum compounds induce DNA damage indiscriminately killing both normal and rapidly proliferating cancer cell. Since these drugs are not specifically selective, cancer patients suffer from adverse side effects including nausea, anaemia, fatigue, hair loss and infections [3].

These cytotoxic anticancer treatments are currently being supplemented by targeted therapies to improve treatment efficacy and reduce side effects. Targeted therapies include apoptosis-inducers, angiogenesis inhibitors, signal-transduction inhibitors, monoclonal antibodies and gene therapy [4]. Apoptosis-inducers, in particular chemopreventive agents can be used to induce cell death *via* genes and proteins that control apoptosis, since tumour-specific alterations in apoptotic programmes provide opportunities to target cell death in a selective manner [5]. Chemoprevention as first defined by Sporn in 1976, entails the use of specific natural products or synthetic chemical agents to reverse, suppress, or prevent premalignancy before the development of invasive cancer [6]. This approach is particularly of interest since it is based on the concepts of multifocal field carcinogenesis and multistep carcinogenesis [7]. Several epidemiological and experimental studies have reported the apoptotic effect of natural products including sulphoraphane [8,9], resveratrol [10,11], genistein [12,13], cucurmin [14,15], and caffeic acid phenyl ester [16,17] in the containment of carcinogenesis. Hence, since natural products can modulate apoptosis pathways in human cancers, these compounds may provide novel opportunities for cancer drug development.

Over the last two decades, thousands of bioactive natural products have been isolated from nature for biomedical research. Most of these natural compounds, especially those from edible and natural sources such as fruits, vegetables and plants, have long been an attractive source of drug molecules [18] mainly because of their easy availability and also folk traditions have described beneficial effects from their uses [19]. Even today natural compounds remain a high-output source of promising chemotherapeutic or chemopreventive agents with substantial numbers of anticancer agents used in the clinic being either natural or derived from natural products from various sources such as plants, animals and microorganisms. Indeed, almost 60% of drugs approved for cancer therapy are of natural origin: vincristine (VCR), irinotecan etoposide, taxanes and campthotecins are all examples of plant derived anticancer agents while actinomycin D, mitomycin C, bleomycin, doxorubicin and L-asparaginase are drugs isolated from microbial sources [20]. However, in contrast to the above described terrestrial sources of anticancer agents, a still almost completely unexplored potential source of bioactive natural agents is represented by the sea [19]. Although oceans have attracted the attention of researchers since the 1950s with the discovery of the *Cryptotheca crypta* sponge-derived nucleosides spongothymidine and spongouridine, the technical difficulties of collecting marine organisms together with the poor knowledge of their habitat have posed relevant obstacles. Nevertheless, the implementation of scuba diving tools and the development of instruments for the isolation of natural products from marine organisms have rejuvenated research in the area of marine natural product [21–23].

1.1. Marine natural product

The world's ocean, covering 70% of the earth's surface and 95% of its tropical biosphere represents an extraordinarily rich source of chemical and biological diversity, surpassing that of the terrestrial diversity [24,25]. It is home to nearly one million multicellular (plants and animals) and one billion unicellular organisms [26]. Particularly, the marine reef is a highly crowded ecosystem where more than 1000 species are sheltered per m^2 and live side by side in fierce competition for the limited space and nutrients [25]. Living in such a highly competitive environment, marine organisms have evolved biochemical and physiological mechanisms that include the production of secondary metabolites that are involved in ecological processes such as reproduction, communication and protection against predation, infection and competition. Light, water current, and temperature represent additional growth limiting components, further fueling competition [27]. Sessile and soft bodied marine invertebrates like sponges, bryozoans, tunicates, mostly lacking morphological defense structures usually depend heavily on secondary metabolites that are toxic or objectionable to their competitors for survival [24]. These chemical adaptations generally take the form of so called "marine natural product" (MNPs) that involve such well known chemical classes as terpenoids, alkaloids, polypeptides, peptides, shikimic acid derivatives, sugars, steroids, and a multitude of mixed biogenesis metabolites [28]. In addition, and unique to the marine environment, these metabolites possess structural features which are distinct from their terrestrial counterparts due to their frequent incorporation of halogen atoms from the surrounding sea water [29]. Therefore, it is clear that the marine environment represents an important source of unknown natural compounds whose medicinal potential must be evaluated.