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Short Communication

Holothurian Triterpene Glycosides as Modulators of Cellular Functions

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Sea cucumbers (or holothurians) belonging to the class Holothuroidea (Echinodermata) are marine invertebrate habitually found in the benthic areas and deep seas across the world. This class of animals has about 1100 described species. Some of them are edible, are considered a delicacy and healthy in many Far Eastern countries such as Japan, China, Singapore, Malaysia, Korea and Indonesia, and have high commercial value [1]. Many holothurians are known to be toxic. It is well known that the indigenous people of Guam, the Marshall Islands and other regions of the tropical Pacific and Indian oceans used some sea cucumbers, which were cut into pieces and thrown into the water to "lull", immobilize and catch fish in the small sea lagoons formed during low tide [2]. These animals produce special low-molecular metabolites, triterpene glycosides. The content of triterpene glycosides in the tissues of holothurians can reach a significant amount of up to 1 g/kg, and especially many of these compounds are localized in the Cuvierian tubules - special organ presents in a number of tropical holothurians. Triterpene glycosides of holothurians are quite toxic, they exhibit ichthyotoxic, hemolytic, cytotoxic and neurotoxic activity. These compounds are the main poison substances of the sea cucumbers and play a role in the chemical defense of holothuroids against predators [3].

The triterpene glycosides are composed of a carbohydrate chain and triterpene aglycone and are widely distributed in sea cucumbers. Most aglycones have 18(20)-lactones and belong to the holostane type. Carbohydrate chains of sea cucumber glycosides have from two to six monosaccharide residues including xylose, quinovose, glucose and 3-O-methylglucose and sometimes 3-O-methylxylose, 3-O-methylquinovose, 3-O-methylglucuronic acid and 6-O-acetylglucose. They may contain one, two or three sulfate groups [4,5].

During the last decade there have been several reviews of the published investigations of the cytotoxic activities of triterpene glycosides. These summaries have shown specific correlations between the structure of the triterpenoid saponins and their cytotoxicity and most common biological mechanisms of action [6]. At the milli- and micromolar concentrations sea cucumber glycosides show hemolytic, cytolytic, antifungal and other biological activities caused by membranotropic action. The basis of membranotropic action of the glycosides is their ability to attach to cell biomembranes and form nonselective ion-conducting complexes with 5(6)-nonsaturated sterol components of those cell membranes (Δ^5-sterols), preferably with cholesterol. Such sterol/saponin interaction results in an efflux of some ions, nucleotides and peptides, disrupting ion homeostasis and osmolarity, followed by lysis and cell death [3].

Cytotoxic activity of sea cucumber glycosides against different tumor cell types and cancer cell lines has been extensively studied. These studies have shown strong cytolytic effects upon tumor cells *in vitro* [6]. Some sea cucumber triterpene glycosides have pronounced anticancer effects by direct interaction with tumor cells in the subcytotoxic range of concentration, which reflects independence of cytotoxicity mechanisms of anticancer activity. At this moment, the detailed assembly of the anticancer action of these compounds still remains largely unclear. However, the general details of this mechanism may be reduced to the following points: induction of tumor cell apoptosis was shown to be one of the primary causative factors through the activation of intracellular caspase cell death pathways (caspases 3/7 and 9); arrest of the cell cycle at S or G2/M phases and increase of the sub-G0/G1 cell population which leads to the block of proliferation and apoptosis; regulation of nuclear factor NF-κB; regulation of certain cellular receptors and enzymes participating in cancerogenesis,

such as: EGFR, AKt, ERK, FAK, MMP-9 and some others. Finally, administration of some sea cucumber triterpene glycosides leads to reduction in cancer cell adhesion, suppression of cell migration and tube formation in those cells, suppression of angiogenesis, inhibition of cell proliferation, colony formation and tumor invasion, and marked growth inhibition of tumors *in vitro* and *in vivo*. Additionally, some holothurians' triterpene glycosides have the potential to be used as P-gp mediated MDR reversal agents in combined anticancer therapy with standard cytostatics [7].

By contrast, in low sub-toxic nanomolar concentrations marine triterpene glycosides induce cellular activation and potentiation of cellular functions of immune cells and show an immunostimulatory effect. Holothurian triterpene glycosides induces their activation resulting in an increase of immune cell adhesion on an extracellular matrix, enhancement of cell spreading and motility, increase of macrophage lysosomal activity, ROS formation and phagocytic activity, increase bactericidal activity of leucocytes and pathogenic microorganism killing, elevated synthesis of some (IL-6, TNF-α) cytokines induces an increase in the number of antibody-producing plaque-forming cells in mouse spleens, restore the level of some CD-markers of lymphocytes. Ultimately, an activation of cellular immunity and magnification of the organism resistance to various opportunistic infections is appeared under glycoside action [8].

Proteomic methods have demonstrated that the mechanism of immunomodulatory action of some sea cucumber glycosides on mouse splenocytes includes regulation of the expression of number of proteins involved in formation of the cellular immune response. These glycosides regulate the expression of proteins associated with lysosome maturation, activation and merging, phagocytosis, cytoskeletal reorganization, cell adhesion, mobility and proliferation of immune cells [9]. Using inhibitory analysis, confocal microscopy, flow cytometry, Ca^{2+}-imaging and patch-clamp on single macrophages, small interfering RNA technique, immunoblotting, SPR analysis, computer modeling and other methods, it was demonstrated that low doses of sea cucumber triterpene glycoside specifically to interact with purinergic P2X receptors (predominantly P2X4) on membranes of mature macrophages, enhancing the reversible ATP-dependent Ca^{2+} intake and recovering Ca^{2+} transport at inactivation of these receptors**.** Structural models of glycoside-mP2X4 complexes generated by *in silico* modeling disclosed that glycoside and ATP binding sites are localized at different areas of extracellular receptor domain. This action on the receptor turn those binding site residues connected through b-strands by H-bonds network. These findings and experimental data suggest that holothurians triterpene glycosides can act as an allosteric regulator which able to withdraw purine receptor inactivation by extracellular ATP and provide a recovery of Ca^{2+} conductivity of macrophage membrane. Such type of glycoside interaction with receptors may trigger an activation of Ca^{2+}-signaling pathway that initiates the amplification of expression of certain intracellular target proteins involved in key stages of immune cell physiology [10].

In conclusion, we can say that holothurian's triterpene glycosides perform the role of modulators of cellular activity and functions. Depending on the concentrations used and the type of cells, these compounds can cause the opposite effects. In mili- and micromolar concentrations the glycosides of holothurians exhibit membranolytic activity and suppress the viability of any cell types without specificity by disrupting the selective permeability of biomembranes followed by subsequent cell lysis. In subtoxic micromolar concentrations, holothurian glycosides cause tumor cell death by disrupting the functioning of a number of key intracellular targets involved in carcinogenesis and by induction of apoptosis. At the same time, in the nanomolar concentrations, triterpene glycosides, interacting with a certain type of purinergic receptors, can significantly activate the immune cells and enhance the organism immune responses.

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