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Review: Glycosaminoglycans (GAGs) versus Cancer

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HISTORY

Received: 20st July 2014
Received in revised form: 1st of September 2014
Accepted: 4th of November 2014

KEYWORDS

cancer
tumor
glycosaminoglycans (GAGS)
seafood
marine

ABSTRACT

Cancer or tumor is a killer disease that brings mortality worldwide. Extracellular matrix (ECM) constituents involve in the potential growth, invasive and metastasis of the tumor cell through its interaction with cell-surface receptors, growth factors and cytokines. Thus, previous researchers came with a discovery of a potential anticancer compound known as glycosaminoglycans (GAGs). GAG is a polysachharide that plays an important role in physiological and pathological conditions by affecting the cell properties and its functions. GAGs are majored from chondroitin sulfate (CS), dermatan sulfate (DS), keratan sulfate, heparin and heparan sulfate (HS), and hyaluronan which have their own important roles in cancer progression and cell signalling. Many researchers have reported the finding of GAGs in animal but there were least research of GAGs extraction from seafood and marine fauna. There are a few researches on extraction and analysis of GAGs from seafood wastes and marine lives such as white shrimp heads, mollusks and cuttlefish that showed the potential of GAGs as anticancer. Therefore, more researches on extraction of GAGs from seafoods need to be carried out as it can be anticancer therapeutic approaches for future prospective.

INTRODUCTION

Cancer is known as a killer disease that leads to mortality worldwide [1]. Within the tumor microenvironment, there are stromal cells that will secrete the stimulus which influences the interaction between various molecules expressed by cancer cell, thus leads to invasion and metastasis. The gene expression profile and the functions of macromolecules are affected by the signal transmitted to the cell. The extracellular matrix (ECM) components interact with cell-surface receptors, growth factors and cytokines, and this leads to the involving of the functional macromolecules of extracellular matrix (ECM) in the function and regulation of cell properties, as well as tissue support provider. The adhesion and migration of cancer cell, their invasiveness and metastasis potential were affected from the involving of ECM constituents in specific mechanism of tumor cells [1].

Glycosaminoglycans are polysaccharides that naturally unbranched. It composed of repeating disaccharide units either sulfated or non-sulfated monosaccharides of uronic acids and amino sugars which are structured alternately[2, 19]. The differences in tissue and their state make up their molecular size and sulfation type. Their state can be either as free chains or as part of proteoglycan. Proteoglycans are formed when most GAGs are covalently attached to core proteins [20]. GAGs take a main role in physiological and pathological conditions where it affects the cell properties and functions. It binds to various ligands then regulates the cellular behavior, inflammation, proteolytic natural environment, angiogenesis, and the signalling of growth factor. From the previous study, [2] claimed that the regulated expression of GAGs within cancer malignancy that correlates with medical treatment in numerous malignant neoplasms has contributed the advancement of pharmacological focusing on cancer. This pharmaceutical approach included the altered structure of GAGs such as chemically modified heparins and some defined structures of GAGs.

Categories of GAGs are majored from chondroitin sulfate (CS), dermatan sulfate (DS), keratan sulfate, heparin and heparan sulfate (HS), and hyaluronan (HA) [2]. All of this class of GAGs play their important roles in cancer progression and

cell signalling. For an example,the non-sulfated HA which is synthesized at exterior surface of plasma membrane is viewed as an important participant in inflammatory condition and tissue homeostasis. On the other hand Golgi apparatus synthesized the particular sulfated GAGs which are as well as altered by specific biosynthesis enzymes which contribute to different steps of tumor progression [1]. The most important sulfated class of GAG which is HS works as regulating compound in various standard and pathological circumstances as it contained in almost of tissues and cells. HS tend to be covalently bond with protein core in order to create HS proteoglycans (HSPGs). These HSPGs regulate various features of cancer cells by promoting the key alteration in cell phenotype, thus leading to invasion, metastasis and the growth of tumor [3, 4, 5]. The growth factors, cytokines, chemokines, morphogens and enzymes will interact with HSPGs through HS moieties [6]. HS is functions in arrangement of the ECM through attachment to matrix compounds. It also involved in structural advancement as well as reliability of the ECM and its basement. Other than that, it modulates the interaction between cell-cell and cell-ECM. HS chains stimulate cell adhesion on its presence but on the other side of its absence, it will promote migration and intrusion of malignant cells [7, 8]. GAGs are important as modulator in adhesion and anti-adhesion balancing in order to prevent the malignant cells invasion in surrounding tissues. Thus, the interaction between HSPGs with the growth factors creates the protected reservoirs that are introduced in some circumstances, either by promoting or controlling the cancerous growth.

GAGS FROM SEAFOODS AND MARINE LIVES

GAGs have been reported found in animals in previous researches. But there were least research of GAGs extraction from seafood and marine fauna. In the previous research where chitin, protein, carotenoids and glycosaminoglycans were recovered from processing waste of Pacific white shrimp by [9], the GAGs were extracted from white shrimp heads. The amount of sulphated GAG recovered from 1 kg shrimp heads is about 79 ± 2 mg kg^{-2}. GAG content from the extraction obtained after centrifugation of the hydrolyzed sample and ethanol precipitation. The dried agarose gel as well as PDA buffer was used in this method. The sulfated GAG relative was distinguished by propylenediamine acetate and pH 9.00 buffers. Chondroitin sulfate was separated from heparin, heparan sulfate and dermatan sulfate due to their charge densities, structures and migration length. Heparin was separated from heparan sulfate and dermatan sulfate by barium acetate and diaminopropane acetate. On the other hand, GAG was separated by Tris acetate buffer based on their charge respectively. From this finding, it shown that sulfated GAG was presence in some invertebrates and heparan sulfate is the most extracted GAG from the dried shrimp sediment. Heparan sulfate has been characterized as anticoagulant from previous research [2].

Other than shrimps, mollusks also have been used in GAG extraction. From previous researches, mollusks are identified abundant in lipid, amino acid, polysaccharides and proteins. The extraction polysaccharides were optimized through the use of exterior technique. In previous research of antioxidant and anticancer activities found in polysachharides from *Cyclinasinensis* by [10], the differences of pharmacological effects on the crude and purified was studied. The crude and the purified polysaccharide extract were characterized in order to study its antioxidant and anticancer properties. The purification was done by using chromatography of DEAE-52 and SephadexG-100, thus lyophilization of polysaccharides then performed to further study. The crude extract contained most of sulfate and uronic acid. The crude and purified extract of polysachharide then tested on human gastric cancer line to study the cell proliferation and its scavenging results on hydroxyl and superoxide radical to study the antioxidation. The inhibitory activity of compound on cell proliferation and hydroxyl radical scavenging activity assay and are referred to the method by [10]. The crude shows that it has high scavenging activities on hydroxyl and superoxide radical, thus it also shows strong inhibitory effects on human gastric cell line growth.

The strong and higher activities of polysaccharide compound was found contributed by high content of protein, sulfate and uronic acid. The transformation of the cancer cell is related with the reactive oxygen species and antioxygen level. Thus, the higher scavenging activity of GAGs extracted from mollusks on free radicals indicates its higher anticancer activity as it inhibit the growth factor. In other research on GAGs extracted from mollusks by [11], the anticancer activity of sulfated GAG was performed in mice treated with Lewis lung carcinoma tumor. The size and volume of tumor induced in the mice was measured. Evaluations of tumor weight, volume and percentage before and after the sulfated GAG treatment determine the effects of sulfated GAG on host survival and growth of tumor. At the end of the remedy period, the tumor tissues were removed and weighed, thus it shown the reduction in tumor weigh.

Cuttlefish or squid also have been used in the extraction of uronic compound from GAGs to study its anticancer properties. This research was carried out by [12]. The ink from cuttlefish was isolated, purified and characterized through specific methods. Tris-HCl used to extract the ink and then fractionated using ion exchange and gel chromatography. Cervical cancer line HeLa and Caski were used to study the anticancer properties of the fractionated compound, thus it demonstrates the high content of uronic acid peptidoglycan. Typical morphological features of apoptosis such as apoptotic bodies, membrane blebbing, DNA fragmentation and chromatin condensation on the cervical cancer lines were determined as if it can be induced by the purified cuttlefish compound. From the morphological assay and staining, the compound found can induces the cervical cancer cell death and its alteration. Light microscopy was used to show the anti-proliferative effect on human cervical cancer based on respective concentration of the purified fraction compound. The increasing of the purified compound will increase the cytotoxicity activity. The purified fraction demonstrated the inducing of the chromatin condensation, membrane blebbing and cancer cell DNA damage by using Giemsa staining, Ethidium Bromide staining and Comet assay. Thus, this study shown that apoptosis was mediated by antiproliferative effects of the purified fraction.

GAGS AND PGS BASED IN ANTICANCER THERAPEUTIC APPROACHES

From some of the researches doing, the compound extracted from the marine lives was shown to be having anticancer properties and it's demonstrated to come from the polysaccharides. As the sulfated GAGs and uronic acid content in GAG are found to be the suppressor of tumor growth, the GAG based approaches was developed, for example is the chemically modified heparin and GAGs. [13]demonstrated that heparin is a sulfated GAG and it has natural ability in anticancer as well as anticoagulant. Anti-metastatic activity based on heparin anticoagulant activity decrease thrombin generation and fibrin formation, thus affects the tumor progression. Combination of heparin with conventional chemotherapy is suggested could prolong the survival of cancer patient [14].

Besides heparin, the altered chondroitin sulfate and heparan sulfate have been studied as probable therapeutics for cancer. Breast tumor cancer nude mice have been abolished by the modified chondroitin sulfate, and on the other hand, the tumor cell adhesion, migration, growth and invasion can be inhibited by heparan sulfate mimetics with its anticancer properties. [2] demonstrated another approach is the inhibition of GAG biosynthesis. The deficiency of GAG compounds in cell can reduce seeding and growth of tumor cells. For example, 4-methylumbelliferone can inhibit hyaluronan biosynthesis in murine melanoma cells, thus inhibit cancer adhesion and invasion of tumor [16]. The next approach is the inhibitors from GAG-biodegrading enzymes. GAG-biodegrading enzymes could be one of anticancer approach for GAG degradation is important in cancer. Heparanase is involved in several stages in tumor progression and its expression increased through the respective stages. Heparanase activity can be inhibited by substrate analog, sulfated oligosachharide phosphomannopentose sulfate (PI-88), which prevents heparan sulfate degradation [15]. It also inhibits cancer growth at late stages thus reducing tumor cell invasion, metastasis, and angiogenesis. On the other hand, heparan sulfate/heparin can be transformed into heparanase inhibitor through selective chemical modification. The potent inhibitor known as Glycol-split N-acetyl heparins, they tend not togenerate fibroblast growth factor-2 from ECM, the other one is polysulfonatednaphthylurea, Suramin and its derivatives. It reduces cancel proliferation and angiogenesis by interfering with GAG catabolism and inhibiting several growth factors to the receptors. The use of inhibitory GAG-binding peptides also is one of another therapeutic anticancer approach. For example, a peptide (P4) which binds to hyaluronanstrongly can reduce angiogenesis and thus inhibits cell growth [17]. On the other hand, as another therapeutic anticancer approach, some of GAG plays an important role as tumor-specific aimed towards chemotherapeutics and toxins. Hyaluronan was assigned to play the major role because it is internalized efficiently by variety of cells via its hyaluronan-mediated motility receptor. Furthermore, as many tumors overexpress the receptor, coupling of the hyaluronan with cytotoxic drugs such as butyric acid, will reduce primary tumor growth and metastasis including of prolonged survival [18].

CONCLUSION

Both of GAGs and proteoglycans (PGs) are responsible in inhibition of angiogenesis. Most of the compounds in GAG classes and PGs such as heparin, chondroitin sulfate, heparan sulfate and matrix and cell-surface proteoglycans involved in angiogenesis. They have their diagnostic and prognostic values in some cancers and that make them as targeted therapeutic anticancer. Major of GAGs either sulfated or non-sulfated and PGs itself acts in tumor growth and progression when they are interacted with cytokines, growth factors, and its receptors. GAGs become valuable in novel therapeutic approaches as it have the specific biological roles in invasion and metastasis of malignant cells, signaling cascades and also regulating angiogenesis. Thus, this promising targeted therapy in cancer leads to the extraction and characterization of GAG compounds from various sources such as from marine lives. Seafood and marine lives can be a potential source of anticancer compounds but they are least explored. From the previous researches, extraction of GAGs from white shrimp heads, mollusks, cuttlefish and squids, resulted in finding of function of GAGS as anticoagulant and anticancer. Inducing of extracted GAG compounds into the cancer infected mice or cancer cell lines clearly indicate that the extracted GAG compounds may inhibit angiogenesis thus act as an antitumor agent. Most of the results show that GAGs inhibit the growth of cancer cells while some prolong the survival time for cancer infected mice. As the seafood or marine lives are cheap and readily available, they have a great promise for providing the potential and safer anticancer drugs. Further research and study on GAGs as anticancer should be carried out for new future prospective of GAGs in therapeutics.

ACKNOWLEDGEMENT

The authors would like to gratefully acknowledge Universiti Malaysia Pahang for an operation research grant (UMP-RDU130308) and Ministry of Higher Education for Research Acculturation Grant Scheme (RAGSRDU 131406) and Fundamental Research Grant (FRGS RDU 140131)

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