Phlorotannins in Cancer

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Mitochondrial dysfunction is an interesting therapeutic target to help reduce cancer deaths, and the use of bioactive compounds has emerged as a novel and safe approach to solve this problem. Phlorotannins, a type of polyphenol present in brown seaweeds that reportedly functions as antioxidants/pro-oxidants and anti-inflammatory and anti-tumorigenic agents. Specifically, available evidence indicates that dieckol and phloroglucinol promote mitochondrial membrane depolarization and mitochondria-dependent apoptosis. Phlorotannins also reduce pro-tumorigenic, -inflammatory, and -angiogenic signaling mechanisms involving RAS/MAPK/ERK, PI3K/Akt/mTOR, NF-κB, and VEGF. In doing so, they inhibit pathways that favor cancer development and progression.

phloroglucinol metabolism

1. Introduction

Cancer cells acquire capabilities that enable tumor growth and metastatic dissemination. Metabolic reprogramming is one of the hallmarks of cancer. The increased cell proliferation observed in neoplastic disease is associated with adjustments in the energy metabolism in order to permit accelerated cell growth and division. Cancer cells metabolize glucose to lactate instead of processing the molecule via mitochondrial respiration [1][2]. Although less efficient, this allows cancer cells to obtain energy, as well as intermediate metabolites required to proliferate and metastasize. Specifically, glycolytic metabolites fuel the biosynthesis of nucleosides and amino acids, essential for the synthesis of macromolecules required during proliferation. Moreover, glycolysis has been associated with the activation of signaling pathways involving proteins such as RAS (rat sarcoma virus oncogene), Myc (Myc proto-oncogene), TP53 (tumor protein suppressor p53), and HIF-1α (hypoxia inducible factor 1 subunit alpha), thereby promoting cancer development and progression [1][3][4][5][6][7][8][9][10][11]. Furthermore, cancer cells display mitochondrial DNA mutations which induce mitochondrial dysfunction associated with tumor development, progression, and chemo-resistance. For instance, mutations in mitochondrial NADH dehydrogenase result in reduced activity of the mitochondrial respiratory Complex I and increased formation of reactive oxygen species (ROS), which increase the metastatic potential of murine Lewis lung carcinoma cells [12]. In addition, some mitochondrial DNA mutations increase ROS levels, resulting in increased Akt (also known as protein kinase B, PKB), MAPK (mitogen-activated protein kinase), and HIF-1α-dependent signaling pathways, thereby promoting cancer progression [13][14][15]. Meanwhile, partial depletion of mitochondrial DNA increases anti-apoptotic Bcl-2 (B-cell lymphoma 2) and Bcl-X(L) (B-cell lymphoma-extra-large) protein levels and induces the sequestration of the proapoptotic factors Bid (BH3-interacting domain death agonist), Bax (Bcl-2-like protein 4) and Bad (Bcl-2 associated agonist of cell death) in the inner mitochondrial membrane, thus preventing cell death through apoptosis, which again favors cancer development [16][17].

ROS are generated as byproducts of the mitochondrial electron transport chain and NADPH oxidases. In addition, peroxisomes and endoplasmic reticulum (ER) membranes generate ROS. Mitochondrial ROS are mainly produced by complexes I and III, and while 50% is retained within the mitochondrial matrix, the other 50% is released to the cytoplasm [18]. Subsequently, ROS inhibit the phosphatases PTEN (phosphatase and tensin homolog) and PTP1B (protein tyrosine phosphatase non-receptor type 1), negative regulators of the PI3K/Akt/mTOR and MAPK/ERK mitogenic signaling cascades, thereby driving the survival and proliferation of cancer cells [19][20][21]. Furthermore, ROS promote the epithelial-to-mesenchymal (EMT) transition of cancer cells through cytoskeleton rearrangement induced by Rac1 (Rac family small GTPase 1), RhoA (Ras homolog family member A) and FAK (focal adhesion kinase) [22][23][24]. Moreover, ROS induce NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) phosphorylation, increase matrix metalloproteinase (MMP) expression, and enhance extracellular matrix degradation [25][26]. Also, ROS suppress HIF-1α degradation and induce angiogenesis [27][28][29]. Therefore, ROS increase the metastatic potential of cancer cells. On the other hand, excessive ROS increments have antitumoral effects by inducing cancer cell death [27][30][31][32][33]. In this sense, cancer treatment could be possible by reducing or increasing ROS levels, in order to prevent early neoplasia or to kill cancer cells, respectively [27].

Phytochemicals are secondary plant metabolites with antioxidant properties that play important roles in cancer chemoprevention by reversing oxidative stress-induced malignant transformation. Indeed, populations that consume high levels of plant-derived foods enriched in polyphenols have reduced cancer incidence [34]. In this way, curcumin, epigallocatechin gallate, and resveratrol inhibit cancer cell proliferation, survival, migration, invasion and thereby tumor growth and metastasis [27][35]. Hence, utilizing polyphenols as an orally administered therapeutic alternative represents a less invasive approach [36] to cancer prevention.

Phlorotannins are phenolic compounds produced by sea algae with elevated antioxidant capacity compared to polyphenols from terrestrial plants. They have demonstrated bioactive properties, including the reduction of oxidative stress, inflammation and tumorigenesis. Due to the potential of phlorotannins to reduce cancer development and progression, there is great interest in their biopharmaceutical application [34].

2. Mitochondrial Dysfunction and Oxidative Stress in Cancer

Cancer cells exhibit mitochondrial dysfunction due to defects in tricarboxylic acid (TCA) cycle enzymes and the mitochondrial electron transport chain, mitochondrial DNA mutations, oxidative stress, as well as aberrant oncogene and tumor suppressor signaling [37][38][39][40][41][42][43][44][45]. Subsequently, mitochondrial dysfunction can promote cancer progression to an apoptosis-resistant/chemo-resistant and/or invasive phenotype through various mechanisms involving KRAS, c-Myc, MAPK, AMPK (AMP-activated protein kinase), PI3K/Akt, HIF-1α and TP53 [15][37][46][47][48][49]. Furthermore, oxidative stress, generated as a consequence of the aberrant mitochondrial metabolism, plays a dual role in normal and cancer cells. For instance, the accumulation of ROS is detrimental in normal cells, but cancer cells maintain high levels of metabolism and generate ROS that facilitate the activation of several signaling pathways and promote cancer progression. However, the increase in ROS beyond a certain threshold level becomes toxic and promotes cancer cell death. For that reason, metabolic tumor reprogramming

favors glycolysis and mechanisms transforming pyruvate to lactate, which consumes and reduces ROS to non-toxic levels in cancer cells (reviewed in [50]).

3. Phlorotannins, a Group of Bioactive Compounds with Cancer-Preventing Potential

The ROS balance is highly relevant in cancer therapy. Some chemotherapies increase ROS to toxic levels, thereby promoting cancer cell death. Alternatively, antioxidants that reduce ROS content also serve to prevent signaling pathways related to cancer progression (reviewed in [50]). The metabolic reprogramming from oxidative phosphorylation to a glycolytic metabolism results in cells that generate fewer ROS. Consequently, glycolytic cancer cells are resistant to chemotherapeutic agents that rely on the production of ROS and induction of apoptosis [51]. Furthermore, the level of glycolysis correlates with tumor migration, invasion, and metastasis [2], making the targeting of glycolysis, mitochondria and ROS important approaches for the development of novel therapies.

Polyphenols are bioactive compounds widely present in terrestrial and marine plants that display antioxidant and anti-inflammatory properties [52][53][54]. In addition, they have been attributed anti-tumorigenic properties, whereby some bioactive compounds prevent cancer through metabolic control. For instance, novel polyphenols inhibit cell growth, glycolysis, and mitochondrial respiration in colorectal cancer cells. One proposed mechanism is the activation of AMPK signaling and induction of caspase-dependent apoptosis [55]. In addition, oleuropein, the main bioactive phenolic component present in olive leaves, prevents the aerobic glycolysis exploited by tumor cells. This reduction in activity is attributable to a significant decrease in glucose transporter-1, protein kinase isoform M2, and monocarboxylate transporter-4 expression in melanoma, colon carcinoma, breast cancer, as well as chronic myeloid leukemia cells [56].

Marine polyphenols are bioactive compounds obtained from seaweeds. These polyphenols are grouped as phlorotannins, simple phenolic acids, flavonoids, and bromophenols. Marine polyphenols indeed possess antioxidant capacity and have demonstrated enzyme inhibitory, antimicrobial, antiviral, anticancer, antidiabetic and anti-inflammatory activities [57][58][59][60][61][62][63][64][65]. Phlorotannins are a type of marine polyphenol found exclusively in high levels in brown seaweeds. They are phloroglucinol polymers and exhibit superior antioxidant capacity compared to the other families of phenolic compounds [66]. Phlorotannins are classified according to their chemical structure as fucols, phlorethols, fucophlorethols, fuhalols, carmalols and eckols [57][67].

For decades, researchers have extracted phlorotannins from brown seaweeds to study their biological properties. Indeed, the ability of phlorotannins to reduce the development and progression of cancer has been evaluated in different models.

For instance, extracts obtained from *Ecklonia stolonifera* have been probed in hepatocellular cancer cells. There, 100 µM dieckol, a type of phlorotannin enriched in *Ecklonia stolonifera* extracts, increases cytochrome c release and induces apoptosis in Hep3B and Sk-Hep1 liver cancer cells through Bid and caspase-3, 7, 8, and 9-dependent

mechanisms [68]. Commercially available dieckol (34 and 67 μM) promotes cell death through the activation of the caspases-3, 8, and 9 in A549 non-small-cell lung cancer cells. Moreover, dieckol reduces migration and invasion of lung cancer cells by decreasing matrix metalloproteinase-9 (MMP-9) and increasing E-cadherin levels. In addition, the PI3K/Akt signaling pathway is downregulated by dieckol, thereby affecting lung cancer cell survival, proliferation, and metastatic potential [69].

Another protein relevant to the migration and invasion of cancer cells is HIF-1α, which is increased in cancer and hypoxic conditions. In fact, hypoxia promotes HIF-1α expression, ROS generation, migration and invasion of HT29 colon cancer cells [70]. Like other phlorotannins that are known to be antioxidants [71], *Ecklonia cava*-isolated dieckol (34 mM) also reduces hypoxia-induced HIF-1α and ROS levels, as well as increases E-cadherin expression, thereby inhibiting migration and invasion [70]. Moreover, *Ecklonia cava*-isolated dieckol at a lower concentration (34 μM) attenuates ROS-induced increases in MMP-9 levels, as well as FAK and Rac1 activation, thereby preventing the ROS-enhanced migration and invasion of HT1080 fibrosarcoma [72], as well as B16F10 melanoma cells [73].

In a rat model of *N*-nitrosodiethylamine (NDEA)-induced hepatocarcinogenesis, the oral administration of *Ecklonia cava*-isolated dieckol prevents lipid peroxidation, as well as liver cell damage and promotes the enzymatic and non-enzymatic antioxidant defense system, thereby preventing hepatocarcinogenesis in vivo. In this rat model, *Ecklonia cava*-isolated dieckol and the carcinogenic drug NDEA were administrated simultaneously during 15 weeks. In these experiments, 10 and 20 mg/kg body weight of dieckol administrated orally were observed to have less cancer-preventive effects than 40 mg/kg b.w. of dieckol, revealing thereby dose- and concentration-dependent effects in preventing cancer initiation [74]. The mechanisms proposed are the induction of apoptosis via the intrinsic pathway by decreasing Bcl-2 expression and increasing the expression of Bax, favoring cytochrome c release and caspase-9/3 activation. Moreover, dieckol, present in extracts, reduces VEGF levels, thereby inhibiting angiogenesis. In addition, dieckol inhibits the pro-inflammatory transcription factor NF-κB, as well as reducing COX2 (cyclooxygenase 2) levels in a NDEA-induced hepatocarcinogenesis model [75].

Additionally, in vivo anticarcinogenic effects of eckol, another natural phlorotannin derived from marine brown algae, are reportedly linked to their ability to modulate the immune response in mice with sarcoma. In a mouse model of transplanted sarcoma, eckol derived from brown algae increases TUNEL-positive apoptotic cells via caspase-9/3 activation and down-regulates the expression of Bcl-2, Bax, and EGFR (epidermal growth factor receptor), as well as EGFR phosphorylation. In this xenograft-bearing mouse model, eckol was orally administrated as a pre-treatment for 7 days. Then, tumor cells were subcutaneously implanted and eckol was continuously administrated for another 10 days. Following this protocol, 0.25 and 0.50 mg/kg body weight of eckol administrated orally were found to have less cancer-preventive effects than 1 mg/kg b.w. of eckol, thereby revealing dose- and concentration-dependent effects in preventing cancer promotion [76].

As mentioned before, cancer cells undergo metabolic reprogramming by increasing glycolysis to replace mitochondrial metabolism. In this way, cancer cells control ROS levels, providing sufficient conditions to activate favorable signaling pathways without inducing apoptosis. A novel phloroglucinol quinone was identified that targets

both cancer cells that depend on glycolytic pathways or mitochondrial metabolism, albeit through different mechanisms. On the one hand, 50 µM phloroglucinol quinone induces mitochondrial membrane depolarization and loss of mitochondria electron transport, thereby reducing ATP synthesis and affecting HL-60 and HeLa cancer cells that maintain basal levels of mitochondrial metabolism. On the other hand, phloroglucinol prevents autophagy and reduces nutrient recycling, thereby affecting glycolytic cancer cells [51].

Other synthetic phloroglucinols, hyperforin and myrtucommulone A acylphloroglucinols, have been shown to reduce HL-60 leukemia cell viability by directly affecting mitochondria at 0.03–0.9 µM. These phloroglucinols act as protonophores that dissipate the mitochondrial membrane potential, eliminate the mitochondrial proton motive force, and reduce ATP synthesis, which in turn activates AMPK and the intrinsic apoptosis pathway [77]. These effects were reviewed previously, showing that phloroglucinol has the ability to prevent cancer development and progression through the inhibition of mitochondrial metabolism and ROS production as well as inflammatory, angiogenic, and metastatic pathways [78][79][80][81].

Fucus vesiculosus-derived phlorotannin extracts exert specific cytotoxicity against Caco-2 and HT29 colon and MKN-28 gastric tumor cells without affecting the viability of HFF-1 normal cells. Specifically, eckstolonol and fucofurodiphlorethol, between 0.4 and 2.4 mM phloroglucinol equivalent, induce cell cycle arrest and apoptosis in cancer cells [82]. In addition, 1% phlorotannin-rich extracts derived from the brown algae *Ascophyllum nodosum* and *Fucus vesiculosus* have been shown to reduce ROS levels, thereby preventing cancer progression in A549 lung cancer cells [83].

On the other hand, phlorotannins have also been described as bioactive compounds that prevent cancer progression by increasing oxidative stress. Commercially available dieckol induces ROS generation and apoptosis in MG-63 human osteosarcoma cells through the activation of caspase-3 and the inhibition of the PI3K/Akt/mTOR signaling pathway. Also, 15 µM of commercially available dieckol reduces metalloproteinase levels and inflammatory markers (TNF (tumor necrosis factor), NF-κB, COX2, and IL-6 (interleukine-6)) [84], indicative of anti-metastatic and anti-inflammatory effects.

Moreover, 400 µg/mL *Ecklonia maxima* and *Ulva rigida* extracts induce apoptosis in HepG2 liver cancer cells through inhibition of the mitochondrial membrane potential and increasing ROS [85]. Also, *Ecklonia cava* extracts enriched in dieckol have cytotoxic effects in ovarian cancer cells and reduce tumor growth in xenograft mouse models when administrated orally at 100 mg/kg b.w. during 4 weeks. In vitro, 120 µM dieckol isolated from *Ecklonia cava* induces apoptosis in SKOV3 ovarian cancer cells through the activation of caspase-8,-9 and -3, as well as by inhibiting the Akt signaling pathway. At the mitochondrial level, dieckol induces mitochondrial membrane depolarization and cytochrome c release, as well as increases the expression of pro-apoptotic proteins. Additionally, dieckol downregulates the expression of anti-apoptotic proteins, such as XIAP (X-linked inhibitor of apoptosis protein), FLIP ((FADD-like IL-1β-converting enzyme)-inhibitor protein), and Bcl-2, thereby promoting apoptosis. These effects are associated with ROS increments. Indeed, the antioxidant *N*-acetyl-L-cysteine prevents caspase activation, cytochrome c release, Bcl-2 downregulation, and apoptosis that are caused by exposure to the seaweed extract [86].

Additionally, phlorotannins also improve the effects of chemotherapy by promoting apoptosis in cancer cells while protecting normal cells. Indeed, the combined administration of phlorotannin (dieckol)-rich extracts of *Ecklonia cava* and cisplatin potentiates the effects of each drug administrated alone by inducing apoptosis via the increase in ROS and inhibition of the Akt/NF-κB pathway. Moreover, dieckol-rich extracts suppress cisplatin-induced normal kidney cell damage [87].

Based on the aforementioned evidence, commercial and seaweed-isolated phlorotannins are effective at preventing cancer development and progression. In vitro results show potential anti-tumorigenic effects in a wide range of concentrations (15 µM–34 mM). Moreover, pre-clinical experiments demonstrate that dieckol isolated from *Ecklonia cava* reduces cancer initiation and development at 40 and 100 mg/kg b.w. in rats and mice, respectively. In addition, the pre-treatment with lower doses of eckol (1 mg/kg b.w.) prevents cancer promotion in xenograft-bearing mice.

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