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REVIEW

Activation and Inhibition of ATM by Phytochemicals: Awakening and Sleeping the Guardian Angel Naturally

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Abstract Double-stranded breaks (DSBs) are cytotoxic DNA lesions caused by oxygen radicals, ionizing radiation, and radiomimetic chemicals. Increasing understanding of DNA damage signaling has provided an ever-expanding list of modulators reported to orchestrate DNA damage repair and ataxia telangiectasia mutated (ATM) is the master regulator and main transducer of the DSB response. Increasingly, it is being realized that DNA damage response is a synchronized and branched network that functionalizes different molecular cascades to activate special checkpoints, thus temporarily arresting progression of the cell cycle while damage is being assessed and processed. It is noteworthy that both nutrigenetics and nutrigenomics have revolutionized the field of molecular biology and rapidly accumulating experimental evidence has started to shed light on biological activities of a wide range of phytochemicals reported to modulate cell cycle, DNA repair, cell growth, differentiation and apoptosis as evidenced by cell-based studies. In this review, we have attempted to provide an overview of DNA damage signaling, how ATM signaling regulates tumor necrosis factors-related apoptosis inducing ligand (TRAIL)-induced intracellular network. We also illuminate on how resveratrol, epigallocatechin gallate, curcumin, jaceosidin, cucurbitacin, apigenin, genistein, and others trigger activation of ATM in different cancer cells as well as agents for ATM inactivation. Understanding the interplay of TRAIL-induced intracellular signaling and ATM modulation of downstream effectors is very important. This holds particularly for a reconceptualization of the apparently paradoxical roles and therapeutically targetable for enhancing the response to DNA damage-inducing therapy.

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Introduction

It became evident that DNA damage mediates the activation of the phosphoinositide-3-kinase-related protein kinase (PIKK) family members ataxia telangiectasia mutated (ATM), ataxia telangiectasia and Rad3-related (ATR) serine/threonine kinase, and DNA-dependent protein kinase, catalytic subunit (Falck et al. 2005) is further systematically categorized into modes of repair including homologous recombination and non-homologous end joining (NHEJ) (Shrivastav et al. 2008). Each member of the PIKK family can function through a network of proteins to initiate a hallmark repair mode (Hiom 2005). Unsolved as yet is, in case homologous recombination is initiated how then is NHEJ inhibited. Initial evidence suggests that a pathway-specific protein machinery is regulated by wide ranging natural anticancer agents.

DNA damage signaling has emerged as a recently extensively and deeply studied molecular phenomenon. This allowed us to develop a sharper landscape after putting together different jig saw puzzles. Laboratory methodologies have revealed the multifaceted biological mechanisms where double-stranded breaks (DSBs) are induced. Mechanistically, following DSB induction, there is a redistribution of ATM spatially and a fraction of nuclear ATM shuttles to the DSBs and gets positioned on the damaged site (Alvarez-Quilon et al. 2014). We now know that only a few DSBs can effectively induce ATM activation. There are some exciting pieces of information which highlight divergent mechanisms of ATM activation suggesting that ATM can be activated in the absence and the presence of damaged DNA. It has been shown that positioning of ATM to undamaged DNA induced activation. However, there are some other studies substantiating the fact that damaged DNA is essential for ATM activation (Stracker et al. 2013). Increasing experimental evidence has considerably deepened our understanding regarding DNA damage signaling and it is now evident that ATM-dependent phosphorylation of chromatin-associated proteins and mediators at damaged sites initiates intricate process of local nucleosomal ubiquitylation to transduce signals for recruitment of repair complexes to the damage site.

There is a rapidly growing body of experimental studies demonstrating ATM regulation by different natural anticancer agents. Accordingly, we aim to discuss a list of phytonutrients reported to be involved in the induction of cell cycle arrest. Following certain natural agents, normal ATM function commonly triggers G1 arrest (Costantino et al. 2013; Neumann et al. 2014) via p53. ATM is also involved in inducing S phase (Tyagi et al. 2005) and G2/M phase arrest (Guo et al. 2014b; Tyagi et al. 2014b).

In this review, we mainly focus on ATM activation and inactivation by phytochemicals (Table 1). They were described in detail as follows.

ATM Activation

Reynoutria japonica

Resveratrol (3,4′,5-trihydroxystilbene) is a polyphenolic phytoalexin isolated from *Reynoutria japonica*. Interestingly, resveratrol treatment displayed cell cycle arrest in several types of cancer cells. There was a notable apoptosis in cancer cells and re-sensitization of cancer cells to ionizing radiation. For example, resveratrol was reported to inhibit cell proliferation of prostate cancer PC3 and 22RV1 cells but was less harmful to normal prostate PNT1A cells (Rashid et al. 2011). Caspase-3 was noted to be activated in resveratrol-treated prostate cancer cells. Recently, a novel resveratrol analog (digalloylresveratrol)-treated pancreatic cancer AsPC-1 and BxPC-3 cell lines showed antiproliferative effects and it also enhanced the phosphorylation of proto-oncogene-encoded cell division cycle 25A (CDC25A) (Ray and Kiyokawa 2008) by ATM (Saiko et al. 2013). Subsequently, phosphorylated CDC25A was proteasomally degraded resulting in S phase arrest of pancreatic cancer AsPC-1 and BxPC-3 cells. Moreover, ATM also reportedly mediated phosphorylation of CDC25A at tyrosine-15 and caused S phase arrest in resveratrol-treated ovarian cancer Ovcar-3 cells (Tyagi et al. 2005).

The responses of ATM to resveratrol treatment in normal and transformed cells may display differently. For example, resveratrol can lead to an autophosphorylation of ATM on Ser1981 and a phosphorylation of p53 on Ser15 in transformed cells (HEK293T and HCT116) involving reactive oxygen species (ROS) but this is largely unchanged in human normal fibroblasts (GM08399) (Lee et al. 2014). The resveratrol-induced ATM signaling effect was inhibited by the disulfide-specific reducing agent Tris(2-carboxyethyl)phosphine and the antioxidant N-acetyl cysteine, suggesting that high oxidative stress was involved in ATM signaling of resveratrol in transformed cells to block cancer cell proliferation (Lee et al. 2014).

Green Tea

Epigallocatechin gallate (EGCG)-treated head and neck squamous cell carcinoma (HNSCC) cells displayed an increase in apoptotic rate as evidenced by the transcriptional upregulation of pro-apoptotic genes such as

Table 1 A list of phytochemicals that act as ATM inducers and inhibitors

Source	Chemical	Target[a]	References
ATM inducers			
Reynoutria japonica (Kimura et al. 1995)	Resveratrol	ATM/ATR↑; CHEK1/2↑; CDK1↑; AMPK↑	Rashid et al. (2011); Tyagi et al. (2005)
Resveratrol analog	Digalloylresveratrol	ATM↑; CHEK2↑; CDC25A↓	Lee et al. (2014)
Green tea (Gensler et al. 1996)	Epigallocatechin gallate	ATM↑; CDKN1A↑	Amin et al. (2010); Kang et al. (2013)
Curcuma longa	Curcumin	ATM↑; p53↑; CHEK1↑ mTOR↓; NF-κB↓	Lu et al. (2011); Qiao et al. (2013); Sahu et al. (2009)
Emilia sonchifolia (L.)	γ-humulene	ATM↑; p53↑; Fas↑; FADD↑; DR4↑; DR5↑	Lan et al. (2011, 2012)
Artemisia douglasiana (Priestap et al. 2011)	Dehydroleucodine	ATM↑; p53↑; CDKN1A↑	Costantino et al. (2013)
Artemisia princeps	Eupatilin	ATM↑; CHEK1/2↑; CDK1↑; CDC25C↑	Cho et al. (2011)
Taiwania cryptomerioides	Taiwanin A	ATM↑; p53↑; FasL↑; PARP↑; caspases7/10↑	Shyur et al. (2010)
Glycyrrhiza uralensis (Wang et al. 2013b)	Isoliquiritigenin	ATM↑; p53↑; CDKN1A↑ Bcl-2↓	Hsu et al. (2009a)
Eucalyptus honey (Martos et al. 2000)	Tricetin	ATM↑ CDK1↓; CDC25C↓; cyclins B/A↓	Hsu et al. (2009b)
Cinnamomum kotoense (Chen et al. 2006)	Kotomolide A	ATM↑; p53 ↑	Chen et al. (2008)
Whole-grain cereals, legumes, fruits, and vegetables	Pinoresinol	ATM↑; p53↑ CDK1↓; cyclin B↓	Fini et al. (2008)
Cucurbitaceous species (Lavie and Glotter 1971)	Cucurbitacin	ATM↑; p53↑; γ-H2AX↑	Guo et al. (2014a, b)
Artemisia sp.	Jaceosidin	ATM↑; p53↑; CDKN1A↑; γ-H2AX↑ CDK1↓; cyclin B1↓	Khan et al. (2011); Lee et al. (2013)
Aglaia sp.	Rocaglamide	ATM↑; p38↑; JNK↑; γ-H2AX↑ CDC25A↓; caspase-8↓	Li-Weber (2014); Luan et al. (2015); Neumann et al. (2014)
Fruits and vegetables	Apigenin	ATM↑; p53↑; NAG-1↑; γ-H2AX↑ CDKN1A↓	Arango et al. (2012); Zhong et al. (2010)
Genista tinctoria	Genistein	ATM↑; p53↑; PTEN↑; GADD45A↑ CDK1↓; CDC25A↓	Xie et al. (2014); Zhang et al. (2013)
Myristica malabarica	Malabaricone C	ATM↑; CHEK1↑; p38↑; γ-H2AX↑; cyclins E/A↑ BAX↓	Tyagi et al. (2014a, b)
Silybum marianum	Silibinin	ATM↑; p53↑; CHEK2↑; γ-H2AX↑ cleaved-PARP↑; cleaved-caspases 3/8/9↑	(Tyagi et al. 2006)
ATM inhibitors			
Persimmon leaf	2″-galloyl moiety (PLEg)	ATM↓; p53↓; CHEK1↓	Kawakami et al. (2011)
Gynostemma pentaphyllum Makino	Gypenoside	*ATM/ATR*↓[a]; *p53*↓; *DNA-PK*↓; *BRCA1*↓	Lu et al. (2010)
Rheum palmatum L.	Emodin[b]; Aloe-emodin[c]; Rhein[d]	*ATM/ATR*↓[a]; *DNA-PK*↓; *BRCA1*↓; *MGMT*↓	Chen et al. (2010)
Chocolate, tea and coffee	Caffeine	ATM↓	Blasina et al. (1999); Cortez (2003); Sarkaria et al. (1999)
Marine-derived oligosaccharide (Zhao et al. 2006)	JG3	ATM↓; NF-κB↓	Zhang et al. (2012)

[a] mRNA expressions are marked in italic fonts

[b] Emodin = 1,3,8-trihydroxy-6-methylanthraquinone

[c] Aloe-emodin = 1,8-dihydroxy-3-(hydroxymethyl)-anthra-quinone

[d] Rhein = 4,5-dihydroxyanthraquinone-2-carboxylic acid

phosphorylated p53 and the nonsteroidal anti-inflammatory drug-activated gene-1 (NAG-1) in a time- and dose-dependent manner (Kang et al. 2013). NAG-1 depleted cells by NAG-1 small interfering RNA (siRNA) and NAG-1 competent cells by mock siRNA were treated with EGCG and it was verified that there was a decrease in apoptotic rate in NAG-1 depleted HNSCC cells under EGCG treatment. It is noted that NAG-1 is triggered by ATM in EGCG-treated HNSCC cells. Moreover, EGCG can induce NAG-1 and p-p53 expression to suppress tumor growth in EGCG-treated murine SCC VII/SF cells-xenografted mice compared to the control group (Kang et al. 2013).

Curcuma longa

Curcumin-treated pancreatic cancer cells demonstrated that activated ATM, induced G2/M arrest and increased phosphorylation of γ-H2AX and CHEK1 proteins leading to apoptosis of pancreatic cancer cells (Sahu et al. 2009). Using RNA interference strategies against ATM, the curcumin-mediated cell cycle arrest of pancreatic cancer BxPC-3 cells was recovered. Recently, it has been reported that non-Hodgkin's lymphoma cells treated with curcumin at a low dose of 2 μM were arrested at G2/M phase and induced p53 and CDKN1A expressions upon exposure to ionizing radiation (Qiao et al. 2013). This curcumin-mediated cell cycle arrest was impaired upon interfering with ATM by KU55933, a specific inhibitor of ATM. However, widely acclaimed mechanism of cell cycle arrest by ATM was contradicted in a recent report that suggested curcumin-induced S and G2/M arrest in colorectal carcinoma HCT116 cells was unable to be reverted by the ATM inhibitor caffeine. This result suggests that curcumin-mediated cell cycle arrest was independent of ATM activation although the DNA damage was inducible (Lu et al. 2011).

Emilia sonchifolia

γ-Humulene, isolated from the extracts of a herbaceous plant *Emilia sonchifolia*, was reported to induce apoptosis in colorectal cancer HT29 cells mediated by death receptor 5 (DR5) and caspases-8/3 signaling (Lan et al. 2011). γ-humulene also dramatically induced overexpression of ATM, p-ATM, p53 and p-p53 Ser15 in cancer cells. More surprisingly, p53 mediated transcriptional upregulation of the cluster of differentiation 95 (CD95/Fas) and DR5 was essential to induce apoptosis (Lan et al. 2012).

Artemisia douglasiana

Dehydroleucodine is a sesquiterpene lactone isolated from *Artemisia douglasiana*. It was reported that dehydroleucodine inhibited the degranulation of human leukemic LAD2 mast cells, thus acting as mast cell stabilizers (Vera et al. 2012). Interestingly, it was reported that dehydroleucodine-treated cervical cancer HeLa cells became apoptotic, where the greater accumulation of DNA lesions that triggered the activation of ATM were consequently leading to transient G2/M arrest and permanent G1 arrest of HeLa cells (Costantino et al. 2013).

Artemisia princeps

Eupatilin is a flavonoid isolated from *Artemisia princeps* and it has been reported to counteract cell growth of endometrial cancer cell lines (Hec1A and KLE) (Cho et al. 2011). Eupatilin overexpressed the cyclin-dependent kinase inhibitor 1A (p21; Cip1; CDKN1A) and consequently resulted in G2/M arrest. It is surprising to note that the mutant p53 is a target of this natural compound and endometrial cancer cells treated with eupatilin displayed an increase in CDKN1A after inhibition of mutant p53 (Cho et al. 2011).

Taiwania cryptomerioides

Taiwanin A is a main lignan compound isolated from *Taiwania cryptomerioides* and it was reported to have antiproliferative effects on several cancer cells (Chang et al. 2000; Ho et al. 2007). For example, Taiwanin A arrested cell cycle at G2/M phase and induced p53 and caspase 3-dependent apoptosis in human liver cancer HepG2 cells (Ho et al. 2007). Moreover, Taiwanin A was reported to induce ROS generation and DNA damage in breast cancer MCF-7 cells in a time dependent manner (Shyur et al. 2010). It also induced ATM/p53 and checkpoint kinase (CHEK; Chk) mediated G2/M arrest by upregulating p53, phosphorylating p53, CDKN1A, and cyclin-dependent kinase inhibitor 1B (p27; Kip1; CDKN1B), and downregulating the G2/M checkpoint CDK1 (CDC2)-cyclin A/B.

Glycyrrhiza uralensis

Shallot and licorice constituent isoliquiritigenin, isolated from *Glycyrrhiza uralensis*, was reported to be involved in inducing G2/M arrest and apoptosis in human cervical cancer HeLa cells by activation of the ATM/p53 pathway (Hsu et al. 2009a). In addition, there was considerably enhanced increase in phosphorylated contents of CDC25C and CDK1 in isoliquiritigenin-treated cancer cells. Isoangustone A, a licorice-derived compound, was demonstrated to antiproliferation of colon cancer SW480 cells (Huang et al. 2014). Several active polyphenols such as liquiritin and isoliquiritin were also isolated from *G. uralensis* and showed the antiproliferation of lung cancer A549 cells in a

p53-dependent manner (Zhou and Ho 2014). *G. uralensis* also contained a coumestan namely glycyrol which was reported to be antitumor against colon cancer HCT 116 cells (Xu and Kim 2014). The role of ATM in these compounds was warranted for further investigation in future.

Eucalyptus Honey

Tricetin flavonoid, isolated from Eucalyptus honey, was reported to inhibit cell proliferation, induce G2/M arrest, and lead to apoptosis in human breast adenocarcinoma MCF-7 cells (Hsu et al. 2009b). After tricetin treatment, both ATM and p53 were activated and the apoptosis signaling proteins were overexpressed in MCF-7 cells. Furthermore, tricetin also inhibited proliferation of two liver cancer cells (Hep G2 and PLC/PRF/5) through ROS generation-mediated intrinsic and extrinsic apoptosis (Hsu et al. 2010).

Cinnamomum kotoense

Kotomolide A effectively induced G2/M arrest and apoptosis in non-small cell lung cancer A549 cells utilizing similar ATM and P53 activation molecular machinery. There was a notable increase in apoptotic rate and mitochondrial depolarization via an intrinsic apoptosis pathway (Chen et al. 2008). Additionally, isoobtusilactone A also isolated from *Cinnamomum kotoense* and reportedly induced apoptosis in human liver cancer Hep G2 cells (Chen et al. 2007; Liu et al. 2008) and breast cancer cells (Kuo et al. 2008) through ROS. Isoobtusilactone A may function through the regulations of caspase (Liu et al. 2008), mitochondrial Lon protease (Wang et al. 2010), tumor necrosis factors-related apoptosis inducing ligand (TRAIL), C/-EBP homologous protein, and DR5 (Chen et al. 2012). The role of ATM in these compounds was warranted for further investigation in future.

Dietary Lignans

Pinoresinol (PIN) is the precursor of several dietary lignans and it is abundant in whole-grain cereals, legumes, fruits, and vegetables. PIN was reported to inhibit cell proliferation and induce the differentiation of leukemia HL60 cells by inducing mRNA and protein overexpression of the CDK inhibitor CDKN1A (Sepporta et al. 2013). PIN-rich olive oil has been tested in p53 depleted cancer cells (SW480 with p53 mutant) and p53 competent cancer cells (RKO and HCT116). Results provided convincing evidence that PIN-mediated G2/M arrest and apoptosis was significant in p53 proficient colon cancer cells by specifically activating the ATM-p53 signaling (Fini et al. 2008).

Cucurbitaceous Species

Cucurbitacins are a class of triterpenoids isolated from several cucurbitaceous species. Several anticancer effects have been reported from cucurbitacins. For example, cucurbitacin B was reported to induce oxidative stress (ROS generation and mitochondrial depolarization) and to increase cellular calcium ion concentration to mediate γH2AX-based DNA damage, G2/M arrest, and apoptosis in leukemia K562 cells (Guo et al. 2014b). Cucurbitacin B also induced DSBs in lung cancer A549 cells associated with ROS generation (Guo et al. 2014a). The underlying mechanism noted to be triggered by A549 cells was cucurbitacin B-mediated ATM activation that consequently resulted in CHEK1, CDC25C, and CDK1 activation.

Artemisia sp.

Jaceosidin, isolated from dietary mugwort (*Artemisia princeps*), was reported to induce G2/M arrest in glioblastoma U87 cells. This jaceosidin-induced arrest was associated with DNA fragmentation, upregulation of p53 and CDKN1A and subsequent downregulation of cyclin B1 and CDK1 expression at mRNA as well as at protein level (Khan et al. 2011). Moreover, studies conducted by Lee et al. (2013) showed jaceosidin exerted its inhibitory effects by increasing phosphorylation of CDC25C and ATM-CHEK1/2. It also modulated the extracellular-regulated protein kinases/ATM/CHEK1/2 signaling, inactivated the CDK1-cyclin B1 complex, and induced G2/M arrest in endometrial cancer Hec1A and KLE cells.

Aglaia sp.

Rocaglamides are potent natural anticancer compounds noted to enhance phosphorylation of CDC25A, thus promoting its degradation. Using in vitro assays, it was shown that degradation of CDC25A-triggered G1 arrest through the ATM/ATR-CHEK1/2 checkpoint pathway in several malignant cell lines but not for normal T lymphocytes (Neumann et al. 2014). Rocaglamide was reported to sensitize the TRAIL-resistant hepatocellular carcinoma Huh7 cells to TRAIL-mediated apoptosis by downregulation of cellular FADD-like IL-1β-converting enzyme like inhibitory protein and caspase 8 activation (Luan et al. 2015). Furthermore, rocaglamide also inhibited the Huh7 cells xenografting tumor growth, suggesting that apoptotic effect of rocaglamides also occurred in vivo.

Fruits and Vegetables

Apigenin, a flavonoid is involved in inducing protein kinase C delta (PKCδ)-dependent activation of ATM and

H2AX. Gene silencing strategy revealed that PKCδ inhibition repressed phosphorylation of ATM (Arango et al. 2012). Moreover, apigenin can inhibit cell proliferation and induce apoptosis of colon cancer HCT-116 cells. Apigenin also phosphorylated p53, and induced NAG-1, and CDKN1A overexpressions mediated by kinase pathways (PKCδ and ATM) in a dose response manner (Zhong et al. 2010). Using the mice model of adenomatous polyposis coli with multiple intestinal neoplasia (APC^{MIN+}), apigenin was able to decrease polyp numbers.

Genista tinctoria

It has recently reported that *Genista tinctoria*-derived genistein exerted its growth inhibitory, G2/M arrest and apoptosis effects by reducing CDK1/CDC25A expression and simultaneously enhancing ATM in $p53^{+/+}$ colon cancer HCT-116 cells (Zhang et al. 2013). Genistein also sensitized both bladder cancer and epithelial cell lines to a DNA topoisomerase I inhibitor (hydroxycamptothecin) both in vitro and in vivo by activation of ATM kinase and the anti-apoptotic NF-κB pathway (Wang et al. 2013a). Using estrogen receptor $(ER)^{+}$ and ER^{-} breast cancer cells, genistein was reported to enhance the radiosensitivity associated with G2/M arrest and the activation of the ATM/CHEK2/CDC25C/CDK1 checkpoint and apoptosis (Liu et al. 2013). Moreover, genistein also displayed methylation modulating effects. For example, genistein downregulated global DNA methylation in terms of DNA methyltransferase (DNMT) activity and DNMT1 expression in breast cancer MCF-7 and MDA-MB-231 cells (Xie et al. 2014).

Myristica malabarica

Malabaricone C, a phenolic compound isolated from *Myristica malabarica*, has recently been shown to be cytotoxic against human breast cancer MCF-7 cells, involving the early event of lysosomal membrane permeabilization. It has a caspase-independent, but cathepsin B and Bcl2 interacting protein (Bid)-dependent intrinsic mitochondrial apoptotic pathway (Tyagi et al. 2014a). Moreover, overexpression of cyclins E and A was found to induce subG1 accumulation, S or G2/M arrest, DNA damage (DSB), and apoptosis due to malabaricone C treatment. Malabaricone C-induced activation of ATM- and ATR further regulated CHEK1 phosphorylation in A549 cells (Tyagi et al. 2014b). It was shown that malabaricone C-induced p38-MAPK activation was partially abrogated upon ATM or ATR inhibition but was completely inhibited upon CHEK1 inhibition by siRNA silencing (Tyagi et al. 2014b).

Silybum marianum

Silibinin, a natural flavonolignan isolated from *Silybum marianum*, was reported to inhibit prosurvival protein survivin gene expression (mRNA and protein) and induce apoptosis in human bladder transitional cell carcinoma (TCC) RT4 cells (Tyagi et al. 2003). Silibinin also displayed growth inhibition, which was associated with G1 arrest at lower doses and G2/M arrest in bladder TCC-SUP cells (Tyagi et al. 2004). Silibinin can induce p53 activation involving the ATM-CHEK2 pathway and caspases 2-mediated apoptosis in RT4 cells (Tyagi et al. 2006). Silibinin also displayed in vivo effects of apoptosis inducible activity. For example, silibinin inhibited tobacco smoke carcinogen (OH-BBN)-induced urinary bladder tumor growth by inhibiting tumor cell proliferation (Tyagi et al. 2007). Oral silibinin intake also demonstrated the tumor growth inhibition and downregulation of survivin in terms of the human bladder tumor xenograft model (Singh et al. 2008).

Animal Model Studies

Riccardin D, a macrocyclicbisbibenzyl compound from the Chinese liverwort plant has been shown to initially enhance phosphorylation of ATM and CHEK2 in prostate cancer cells that then gradually decreased (Hu et al. 2013). Riccardin D exerted its tumor growth inhibitory effects in male nude mice xenografted with PC-3 cells. Glionitrin A, diketopiperazine disulfide has also been shown to activate ATM and ATR in prostate cancer DU145 cells (Kim et al. 2014). Results revealed that there was an increase in phosphorylated ATM and ATR protein levels, which further activated downstream effectors including CHEK1 and CHEK2, after 1 h of glionitrin A treatment. Tumor volume analysis in mice xenografted with DU145 cells indicated that treatment with 10 mg/kg glionitrin A considerably reduced the tumor burden (Kim et al. 2014).

ATM Inactivation

Persimmon Leaf

Characterization of persimmon leaf extract (PLE) identified flavonols with the 2”-galloyl moiety (PLEg). PLEg-treated lung adenocarcinoma A549 cells displayed an increase in sensitivity to doxorubicin (Kawakami et al. 2011). Mechanistically, it enhanced the sensitivity to doxorubicin and repressed the doxorubicin-mediated DNA damage and G2/M checkpoint by inhibiting the activation of ATM and p53.

Gynostemma pentaphyllum Makino

Gypenoside is a bioactive ingredient of *Gynostemma pentaphyllum* Makino. Gypenoside pretreatment of oral cancer SAS cells displayed a notable downregulation of DNA repair genes including ATM, p53, and DNA-PK (Lu et al. 2010). Furthermore, flavonoid like kaempferol rhamnohexoside derivatives (Tsui et al. 2014), gypenosides, and gynogenin (Chen et al. 2014a) were isolated from *G. pentaphyllum* and reportedly inhibited proliferation of lung cancer cells. *G. pentaphyllum*-derived dammarane saponins were found to be cytotoxic against liver cancer HepG2 cells (Piao et al. 2014). The role of ATM in these compounds was warranted for further investigation in future.

Rheum palmatum L.

In the human tongue cancer SCC-4 cells, *Rheum palmatum*-derived emodin, aloe-emodin and rhein have also been shown to induce DNA damage by suppressing the expression of DNA repair genes such as ATM/ATR and DNA-PK (Chen et al. 2010). Emodin also induced apoptosis in leukemia cells (Chen et al. 2014b), pancreatic cancer (Liu et al. 2011), cervical cancer (Yaoxian et al. 2013). Aloe-emodin was reported to induce apoptosis to nasopharyngeal (Lin et al. 2010) and liver (Lu et al. 2007) cancer cells.

Chocolate, Tea and Coffee

Caffeine is a common compound existing in chocolate, tea and coffee (Barone and Roberts 1996). Caffeine was reported to inhibit radiation-induced CHEK2 activation in vivo and ATM activity in vitro (Blasina et al. 1999), and repressing the DNA-damage checkpoint and increasing the radiosensitivity. Additionally, both ATM and ATR activities were reported to be inhibited by caffeine but the DNA-PK was not affected (Sarkaria et al. 1999). However, a recent report questioned the in vivo relationship between ATM-ATR activation and the checkpoint response. They found that caffeine can inhibit the checkpoint without inactivating ATM/ATR in vivo (Cortez 2003).

Marine-Derived Carbohydrates

By screening the marine-derived carbohydrate library, a newly semisynthesized compound JG3, which is a sulfated oligosaccharide derived from oligomannurarate, was identified to inhibit doxorubicin-triggered ATM signaling (Zhang et al. 2012). Recently, the algae-derived polysaccharide fucoidan was reported to demonstrate the anticancer effects (Jeong et al. 2012). For example, fucoidan was reported to inhibit the cell proliferation and/or induce apoptosis of bladder cancer (Park et al. 2014), liver cancer cells (Yang et al. 2013), and leukemia cells (Park et al. 2013). The role of ATM in these compounds was warranted for further investigation in future.

Conclusion

Research over the years has added important pieces of information to the puzzle of DNA damage signaling and apoptosis. There is a particular progress related to how different phytochemicals trigger activation and inactivation of ATM in cancer cells, addressing regulation of new proteins, context-dependent and cell type-specific responses of ATM. In most cases of ATM inducers listed in Table 1, the ATM seems to cooperate with CDKN1 to suppress proliferation of many cancer cells as literature reported (Crescenzi et al. 2008; Shen et al. 2005). However, the ATM and CDKN1 may have different tendencies sometimes like apigenin as shown in Table 1. Accordingly, it is still needed for further investigation to evaluate the combined ATM/CDKN1 expression for tumor stage markers.

Despite progresses were made in unraveling various facets of ATM biology in different cancer cells, it will be important to gather and re-interpret the ideas by testing for efficacy of different phytochemicals in preclinical models. Low bioavailability of phytochemicals is another stumbling block that requires detailed research and it needs to be determined which application strategy is most useful (intravenous administration or oral intake) for the evaluation of efficacy of phytochemicals in cancer models.

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