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ATM in DNA repair in cancer

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ABSTRACT

Alterations in DNA damage response (DDR) pathways are hallmarks of cancer. Incorrect repair of DNA lesions often leads to genomic instability. Ataxia telangiectasia mutated (ATM), a core component of the DNA repair system, is activated to enhance the homologous recombination (HR) repair pathway upon DNA double-strand breaks. Although ATM signaling has been widely studied in different types of cancer, its research is still lacking compared with other DDR-involved molecules such as PARP and ATR. There is still a vast research opportunity for the development of ATM inhibitors as anticancer agents. Here, we focus on the recent findings of ATM signaling in DNA repair of cancer. Previous studies have identified several partners of ATM, some of which promote ATM signaling, while others have the opposite effect. ATM inhibitors, including KU-55933, KU-60019, KU-59403, CP-466722, AZ31, AZ32, AZD0156, and AZD1390, have been evaluated for their antitumor effects. It has been revealed that ATM inhibition increases a cancer cell's sensitivity to radiotherapy. Moreover, the combination with PARP or ATR inhibitors has synergistic lethality in some cancers. Of note, among these ATM inhibitors, AZD0156 and AZD1390 achieve potent and highly selective ATM kinase inhibition and have an excellent ability to penetrate the blood-brain barrier. Currently, AZD0156 and AZD1390 are under investigation in phase I clinical trials. Taken together, targeting ATM may be a promising strategy for cancer treatment. Hence, further development of ATM inhibitors is urgently needed in cancer research.

Contents

1. Introduction: an overview of the DNA repair signaling network

Numerous DNA damage events occur each day in the human body by exposure to various conditions (Jackson & Bartek, 2009). These DNA lesions include simple base modifications, base mismatches, bulky DNA adducts, inter-strand and intra-strand crosslinks, protein-DNA crosslinks, DNA single-strand break (SSB) and double-strand break (DSB) (Roos, Thomas, & Kaina, 2016). When normal cells are

Abbreviations: DDR, DNA Damage Response; ATM, Ataxia Telangiectasia Mutated; PARP, Poly (Adp-Ribose) Polymerase; ATR, Ataxia Telangiectasia and Rad3 Related; Chk1, Checkpoint Kinase 1; DNA-PKcs, DNA-dependent Protein Kinase catalytic subunit; SSB, Single-Strand Break; DSB, Double-Strand Break; RPA, Replication Protein A; PCNA, Proliferating Cell Nuclear Antigen; NHEJ, Non-Homologous End Joining; HR, Homologous Recombination; MRN, MRE11-Rad50-NBS1; BRCA1, Breast Cancer Type 1 Susceptibility Protein; Skp2, S-Phase Kinase-Associated Protein 2; TRAX, Translin-Associated Factor x; ING3, Inhibitor of Growth Protein 3; UBR5, Ubiquitin Protein Ligase E3 Component N-Recognin 5; IR, Ionizing Radiation; PPARγ, Peroxisome Proliferator Activated Receptor γ; INPP4B, Inositol Polyphosphate-4-Phosphatase Type II; DAB2IP, Disabled Homolog 2-Interacting Protein; GBM, Glioblastoma; BBB, Blood-Brain Barrier..

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subjected to stress that induces DNA damage, they can repair the damage through intact DNA repair pathways unless the stress is extensive, which leads to cell death or senescence (O'Connor, 2015). Specific defective DNA damage response (DDR) signals are a hallmark of cancer (Helleday, Petermann, Lundin, Hodgson, & Sharma, 2008; Jennifer Ma, Setton, Lee, Riaz, & Powell, 2018). Considering this property of cancer, targeting DNA repair pathways has been identified as a promising area for anticancer treatment research (Gavande et al., 2016).

A previous study revealed about 450 DDR-related molecules that may be potential therapeutic targets in cancer (Pearl, Schierz, Ward, Al-Lazikani, & Pearl, 2015). Among these candidates, owing to the critical roles of the multicomplex DDR network, some DDR-related components have been extensively studied, such as poly (ADP-ribose) polymerase (PARP), ataxia telangiectasia, mutated (ATM), ataxia telangiectasia and Rad3 related (ATR), nuclear kinase WEE1, checkpoint kinase 1 (Chk1), and DNA-dependent protein kinase catalytic subunit (DNA-PKcs) (Pilie, Tang, Mills, & Yap, 2019).

Many DDR-related studies have focused on direct targeting of SSB and DSB in DNA (Pilie et al., 2019) or indirect suppression of SSB and DSB repair by targeting cell cycle checkpoints (Branzei & Foiani, 2008). In general, SSB recruit multiple DDR sensors, such as replication protein A (RPA), ATR, ChK1, and PARP, to damaged sites and activate their substrate molecules to repair the lesions (Burgess & Misteli, 2015; Lord & Ashworth, 2017). However, if the SSB is not repaired in a timely manner, it may become a DSB during replication, which is severely detrimental to cells (Abbotts & Wilson, 2017; Pilie et al., 2019). Specifically, once the replication fork stalls, replication protein A (RPA) is first recruited to the SSB site when cells enter S phase (Ruff, Donnianni, Glancy, Oh, & Symington, 2016). Accumulated RPA directly activates SMARCAL1 that acts as a fork reversal mediator, and this interaction enhances the fork regression activity. This event facilitates loading of BRCA2 and RAD51 to the single-stranded DNA and replaces the RPA position. Because RAD51 is a fork reversal enzyme with a crucial role in the homologous recombination (HR; also known as homology-directed repair) repair pathway, recruited RAD51 promotes SSB repair. During this process, if there is a problem with the SSB repair, the fork can be restored slowly, and then proliferating cell nuclear antigen (PCNA) and polymerase III cooperate to initiate leading and lagging strand synthesis. Finally, the SSB may become a double-strand break (Bhat & Cortez, 2018; Kuzminov, 2001; Malkova & Ira, 2013; Ruff et al., 2016). The predominant pathways of DSB repair include classical non-homologous end joining (NHEJ), HR, alternative end joining, and single strand annealing (Ceccaldi, Rondinelli, & D'Andrea, 2016; Samadder, Aithal, Belan, & Krejci, 2016). Among them, HR and NHEJ repair signaling pathways have been considered to be crucial, but HR performs relatively more accurate DSB repair than NHEJ (Ceccaldi et al., 2016; Chang, Pannunzio, Adachi, & Lieber, 2017; Chen, Feng, Lim, Kass, & Jasin, 2018; Woodbine, Gennery, & Jeggo, 2014). Recent pan-cancer analysis of HR-related gene alterations frequently detected both germline and somatic mutations (Riaz et al., 2017). More specifically, BRCA1, BRCA2, ATM, BAP1, CHEK2, and PALB2 mutations were more commonly observed in breast, ovarian, and prostate cancers. Deficiency in NHEJ factors can also drive genomic instability. For example, loss of DNA ligase IV and X-ray repair cross-complementing protein 4 results in embryonic lethality (Chang et al., 2017; Woodbine et al., 2014). High levels of thymocyte selection-associated high mobility group box protein inhibits the NHEJ repair pathway to confer genomic instability (Lobbardi et al., 2017). Thus, targeting DNA repair pathways has become an attractive concept for the treatment of HR- or NHEJ-deficient cancers (Carrassa & Damia, 2017; Curtin, 2012).

The crosstalk between DDR pathways and other systems such as immune signaling networks is much more complicated (Bednarski & Sleckman, 2019; Chatzinikolaou, Karakasilioti, & Garinis, 2014; Mouw, Goldberg, Konstantinopoulos, & D'Andrea, 2017).

To date, ATM deficiency or low expression has been identified as a biomarker of sensitivity to PARP or ATR inhibitors in cancers (Min et al., 2017; Perkhofer et al., 2017; Schmitt et al., 2017; Weston et al., 2010). However, among the current DDR-targeted drugs, research on ATM inhibitors is limited (Gavande et al., 2016). Although the ATM status has been found to be pivotal for DNA repair signaling, the role of ATM in DNA repair pathways is not fully known. Thus, the unmet medical need for the development of ATM inhibitors for cancer therapy prompted us to focus on ATM studies. In this review, we discuss both preclinical and clinical studies of the role of ATM in the DNA repair network of cancer.

2. ATM signaling pathways in DNA repair

Ataxia telangiectasia is an inherited recessive disease. Patients with ataxia telangiectasia exhibit multiple clinical manifestations such as cerebellar degeneration, immunodeficiency, susceptibility to malignancies, increased radiosensitivity, and metabolic diseases (Amirifar, Ranjouri, Yazdani, Abolhassani, & Aghamohammadi, 2019). Ataxia telangiectasia mutated, named ATM, belongs to the phosphatidylinositol 3-kinase-related kinase family. It has multiple functions in cancer development such as cell cycle checkpoints, DNA DSB repair, metabolic regulation, migration, and chromatin remodeling (Stracker, Roig, Knobel, & Marjanovic, 2013). ATM acts as a cell cycle checkpoint following exposure to stress. ATM-p53-p21/ATM-Chk2-CDC25A pathways control G1/S arrest, and ATM-BRCA1/FANCD2/NBS1/SMC1 and ATM-Chk2-CDC25C/ATM-BRCA1-cyclin B/ATM-p53-CDC2-cyclin B1 pathways regulate S phase and G2-M arrest, respectively (Guleria & Chandna, 2016). ATM deficiency can potentiate insulin resistance through upregulation of JNK-IRS1 and AKT/4E-BP1 signals (Guleria & Chandna, 2016). ATM-dependent cell migration has also been identified in diverse cancer types. In response to oxidative stress, ATM facilitates interleukin-8 release to enhance breast and lung cancer cell migration (Chen et al., 2015). In colon cancer cells, ATM deficiency leads to inhibition of B56γ2 ubiquitination and degradation, which further downregulates Chk1-p53-p21 signals to reduce cell migration (Liu et al., 2017). Chromatin remodeling is highly associated with the DDR process because the chromatin relax can increase sensitivity to DDR-targeting agents (Sulli, Di Micco, & d'Adda di Fagagna, 2012). Well-known histone modifiers, including the SW1/SNF complex, TIP60, and HDAC, correlate with H2AX and ATM activities (Ji et al., 2017; Sulli et al., 2012; Thurn, Thomas, Raha, Qureshi, & Munster, 2013). Overall, most of the abovementioned proteins participate in DNA repair processes, and the interplay between DNA repair pathways and other systems is tightly regulated. In this review, we focus on the ATM signaling pathway in the DNA repair network of cancer.

ATM has five major autophosphorylation sites: Ser367, Ser1893, Ser1981, Ser2996, and Thr1885. Once ATM is stimulated by DNA damage, its dimerized form dissociates and converts to monomers, leading to phosphorylation of the abovementioned residues (Kozlov et al., 2011; Stracker et al., 2013). In contrast to other sites, phosphorylation of ATM at Ser1981 does not indicate ATM activity (Lau et al., 2016). There are two major conformations of dimeric ATM, closed and open forms. In the closed form, the phosphatidylinositol 3-kinase-related protein kinase domain is blocked, whereas the open form of dimeric ATM has a limited contact interface. The open structure may be more active than the closed structure, even though both forms have enzymatic activity (Baretic et al., 2017). How the change between ATM's dimers and monomers occurs is still unknown.

Various proteins cooperating with ATM to participate in DNA repair have been identified in numerous studies (Fig. 1). The MRE11-NBS1-RAD50 (MRN) complex is recruited to damaged sites by DSB and activates ATM, which also phosphorylates the MRN complex, resulting in phosphorylation of hundreds of ATM substrates (Blackford & Jackson, 2017; Lavin, Kozlov, Gatei, & Kijas, 2015). DNA damage-induced MRE11 UFMylation on K282 is required for MRN complex formation to activate ATM and enhance HR repair signals (Wang et al., 2019). Because alterations in UFMylation factors have been found in malignant

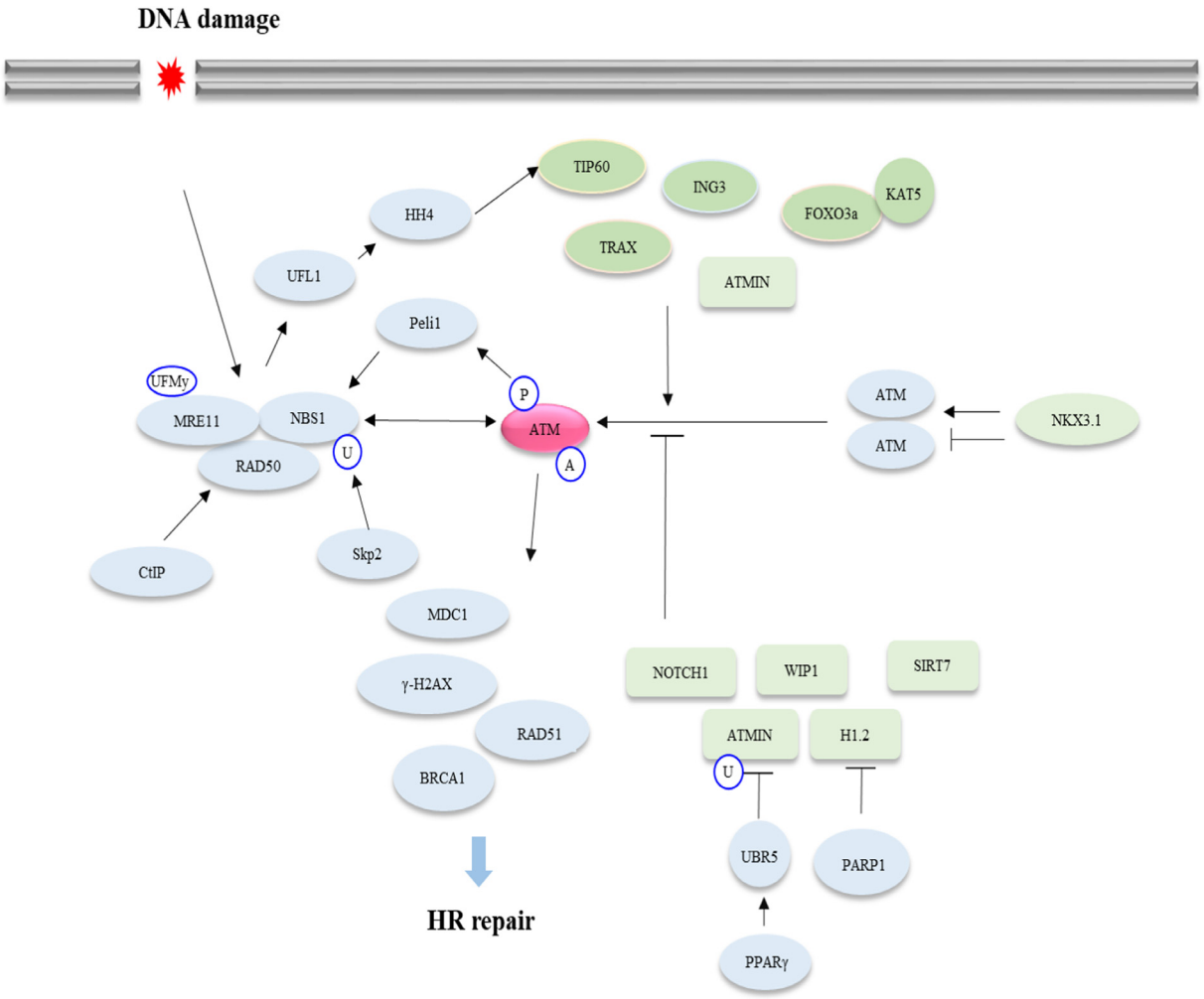

Fig. 1. Overview of the ATM signaling pathway in DNA repair In response to DNA DSB, ATM cooperates with the MRN complex to regulate DNA repair signals. During the repair, ATM activation is controlled by various partners that can be divided into two groups. Both positive and negative ATM mediators affect HR repair signals and ultimately regulate cell fate. P, phosphorylation; U, ubiquitination; UFMy, UFMylation.

tumors, they may be candidate biomarkers for the efficacy of DDR-targeted drugs in the treatment of cancer. MRN complex-dependent ATM activation requires S-phase kinase-associated protein 2 (Skp2) E3 ligase to ubiquitinate NBS1 and stimulate the HR repair pathway (Wu et al., 2012). Skp2 loss abrogates the HR repair pathway, but does not affect NHEJ repair. A positive interaction between Skp2 and ATM phosphorylation has been observed in osteosarcoma and prostate cancer cells. These results partially illustrated the mechanism of MRN-dependent ATM activation. Another study reported that activated ATM facilitates Pellino1 phosphorylation to regulate NBS1 ubiquitination (Ha et al., 2019). The positive feedback loop of MRN and ATM signals leads to enhanced HR repair.

DNA damage-induced ATM activation is controlled by multiple factors in addition to the MRN complex. For example, nuclear Translin-associated factor X (TRAX) plays a critical role in ATM activation during DNA repair (Wang, Chen, Sun, Chien, & Chern, 2015). Binding of TRAX to ATM leads to ATM phosphorylation at Ser1981 and stabilization of the MRN complex, which further phosphorylates downstream proteins such as H2AX and MDM2. Both ATM phosphorylation and DNA repair signals are impaired in TRAX null cells. Another candidate for the mechanism of ATM activation is the homeodomain-containing transcription factor NKX3.1 (Bowen, Ju, Lee, Paull, & Gelmann, 2013; Johnson et al., 2018). It has been determined that rapid phosphorylation of Tyr222 in NKX3.1 promotes ATM activation by Ser1981 phosphorylation within a few minutes of DNA damage, which in turn induces NKX3.1 phosphorylation at Thr166 and Thr134, causing NKX3.1 degradation (Bowen et al., 2013). To date, six homeodomain proteins, including NKX3.1, NKX2.2, TTF1, NKX2.5, HOXB7 and CDX2, have been shown to interact with ATM and the MRN complex (Johnson et al., 2018). However, homeodomain proteins enhance ATM signaling pathways only under low levels of MRN in vitro. In contrast, homeodomain proteins bound to ATM inhibit ATM signals upon their overexpression or high expression levels of the MRN complex. These results indicate that the association between homeodomain proteins and ATM kinase activity may depend on MRN levels. For ATM activation, inhibitor of growth protein 3 (ING3) is considered to be a very important facilitating factor (Mouche et al., 2019). When cells undergo a DSB, ING3 is recruited to the damaged site. This event enhances ATM signals, and then the NHEJ and HR repair pathways operate through p53-binding protein 1 and breast cancer type 1 susceptibility protein (BRCA1) pathways. ATM kinase activity can also be enhanced by acetylation of itself (Blackford & Jackson, 2017; Sun, Xu, Roy, & Price, 2007). Tip60 directly acetylates ATM on Lys3016 to further activate its kinase. Interestingly, the MRN complex-dependent UFM1 specific ligase 1-histone H4 signaling pathway promotes ATM activation by Tip60 recruitment (Qin et al., 2019). In addition, ATM-dependent p53 and Chk2 phosphorylation are interrupted by suppression of Tip60 histone acetyltransferase (Sun, Jiang, Chen, Fernandes, & Price, 2005).

Considering that ATR and ATM share numerous factors involved in DNA repair, the crosstalk between ATM and ATR signaling pathways

has been studied by many investigators (Awasthi, Foiani, & Kumar, 2015; Weber & Ryan, 2015). In response to DSBs, the MRN complex and C-terminal-binding protein-interacting protein cooperate for DNA end resection, leading to single-stranded DNA accumulation, which activates the ATR pathway (Cremona & Behrens, 2013; Sartori et al., 2007). ATR can also enhance ATM-Chk2 signals following replication fork stalling (Stiff et al., 2006). These data suggest that ATM and ATR regulate each other in the presence of DNA damage. A growing body of evidence has indicated that ATM deficiency is a biomarker of ATR inhibition sensitivity through caspase-3-dependent apoptosis and DNA repair failure in cancer (Min et al., 2017; Schmitt et al., 2017). Therefore, ATR activity might have a crucial role in response to ATM inhibition.

ATMIN, an ATM partner, competes with NBS1 for ATM binding to inhibit ATM's functions until it is ubiquitinated by ubiquitin protein ligase E3 component n-recognin 5 (UBR5), which is stimulated by ionizing radiation (IR) (Zhang, Cronshaw, Kanu, Snijders, & Behrens, 2014). Importantly, the molecule upstream of UBR5, peroxisome proliferator activated receptor γ (PPARγ), enhances UBR5-dependent ATMIN degradation to promote DNA repair (Li et al., 2019). However, the interaction between PPARγ and UBR5 is interrupted when cells incur loss of PPARγ functions, leading to persistent DNA damage. Generally, except for NHEJ repair, DSB repair pathways require end resection at the first step by C-terminal-binding protein-interacting protein and the MRN complex (Ceccaldi et al., 2016). Then, molecules such as PCNA, RAD18, and RPA are recruited for single-stranded DNA replication (Kanu et al., 2016). PCNA ubiquitination is induced by association with ATMIN, WRN-interacting protein 1, RAD18, and E3 ligase, promoting ATM signals in response to replication stress (Kanu et al., 2016). Notably, WRN-interacting protein 1 is not involved in IR-induced ATM activation. Currently, there is controversy regarding ATMIN functions. As a non-canonical ATM signaling pathway, ATMIN promotes ATM activation after hypotonic stress. It is well known that, in the absence of DSB, ATMIN-dependent ATM activation phosphorylates downstream signals to facilitate chromatin remodeling (Cremona & Behrens, 2013; Schmidt et al., 2014; Stracker et al., 2013). A recent study has revealed that, under hypoxia-induced replication stress, ATM signaling is not always enhanced by ATMIN. Some studies have shown that phosphorylation of ATM substrates, such as KAP1, p53 and H2AX, is not mediated by ATMIN expression in response to replication stress (Liu et al., 2017). Moreover, even repressed ATMIN and expression of its transcriptional target gene DYNLL1 have been observed, which were negatively regulated by p53 and HIF-1α under hypoxic stimulation (Leszczynska et al., 2016). Based on these data, ATM/ATMIN cooperation may be controlled by different proteins in diverse microenvironments.

Recently, interesting data have shown how linker histone H1.2 regulates ATM activity in DNA damage repair (Li, Li, et al., 2018). According to earlier data, linker histone H1.2 has a critical role in chromatin structure modulation. Furthermore, it has been shown that H1.2-deficient cancer cells are resistant to X-ray irradiation or etoposide (Konishi et al., 2003). Another study indicated that DNA DSB linker histone H1.2 inhibits ATM recruitment and activation by binding to the ATM HEAT repeat domain, and this interaction is blocked via PARP1-dependent linker histone H1.2 degradation (Li, Li, et al., 2018). This study also revealed that ATM or PARP1 inhibition reverses the resistance of H1.2-knockout cells to etoposide. Destabilization of linker histone H1.2 plays crucial roles in DNA repair signaling. This finding illustrates the specific interaction between PARP and ATM activity, and provides a rationale for combination therapy. A novel mechanism of ATM regulation has been clearly described (Adamowicz, Vermezovic, & d'Adda di Fagagna, F., 2016; Vermezovic et al., 2015). NOTCH1 targets the ATM-MRN complex by directly suppressing ATM's FATC domain to impair ATM signals (Vermezovic et al., 2015). However, the NOTCH1-ATM interaction does not affect ATM recruitment or NBS1 activity (Adamowicz et al., 2016). Highly expressed NOTCH1 has strong affinity for ATM. However, under low NOTCH1 expression, FOXO3a and KAT5, instead of NOTCH1, cooperate with ATM to further promote DDR signals (Adamowicz et al., 2016). These results suggest that FOXO3a may be a good candidate target in combination with DDR-targeted agents. Very recently, a novel ATM negative regulator of DNA repair has been discovered. Sirtuin 7 (SIRT7) directly deacetylates ATM to inhibit HR repair signals (Tang et al., 2019). SIRT7-knockout human colon cancer cells exhibit enhanced ATM-γ-H2AX levels and delayed DSB repair compared with wildtype cells.

As discussed above, growing data support the idea that ATM has a key function in DNA repair pathways, and that various factors participate in ATM signaling pathways to control ATM's activity. Although many studies have discovered novel and important findings about the ATM status upon DNA damage, further research is still needed.

3. ATM alterations in cancers

Cytotoxic chemotherapeutic agents induce DNA damage in cancer cells that engage numerous factors to repair the lesions for survival (Hosoya & Miyagawa, 2014; Matt & Hofmann, 2016). Activation of ATM signaling is one of the barriers to chemotherapeutic activity and radiation resistance (Matt & Hofmann, 2016). Currently, several transcription factors have been identified to facilitate ATM activation in response to chemotherapeutic agents (Palmieri et al., 2011). To improve a patients' response to anti-cancer therapy, inhibition of ATM activity is important.

Germline and somatic mutations of ATM have been assessed in many tumor types. Approximately 45% of cases of mantle cell lymphoma and T-cell prolymphocytic leukemia harbored an ATM mutation. In colorectal cancer, gastric cancer, and lung adenocarcinoma, 10%–20% of cases had an ATM mutation. In pancreatic ductal adenocarcinoma, breast cancer, head and neck squamous cell carcinoma, and gall bladder cancer, the frequency of ATM mutation was less than 10% (Choi, Kipps, & Kurzrock, 2016).

Although these data show a relatively high mutation frequency in cancers, the limitation of these studies is that the number of cases is small. Compared with mutations, ATM deficiency is more frequently observed in many cancers. Low ATM expression has been observed in about 21.4%–63.9% of gastric cancer cases, 11%–24.5% of pancreatic cancer cases, and 31% of breast cancers (Kim, Saka, et al., 2013; Kim et al., 2013; Kim et al., 2014; Suh et al., 2016).

The main mechanism of ATM deficiency is hypermethylation of the ATM promoter region (Begam, Jamil, & Raju, 2017). Of note, ATM promoter region hypermethylation has been reported in about 50%–70% of brain tumors and advanced breast cancers, as well as in head and neck squamous cell carcinoma and early stage non-small cell lung cancer (Bolt et al., 2005; Mehdipour, Karami, Javan, & Mehrazin, 2015; Safar et al., 2005; Vo et al., 2004).

Because impaired DNA repair supported by low ATM activity is observed in diverse tumor types, several ATM inhibitors have been under investigation (Choi et al., 2016; Stracker et al., 2013; Weber & Ryan, 2015).

4. ATM inhibitors

The antitumor effects of various kinds of ATM inhibitors have been studied in both human cancer cells and mouse models (Weber & Ryan, 2015). In this review, we outline the recent research advances in the effects of these ATM inhibitors on DNA repair pathways, including KU-55933, KU-60019, KU-59403, CP-466722, AZ31, AZ32, AZD0156, and AZD1390 (Table 1).

4.1. Early ATM inhibitors

KU-55933, the first selective ATM kinase inhibitor, is the most widely tested ATM inhibitor in various cancers (Hickson et al., 2004). In the presence of a DSB, KU-55933 significantly blocks HR repair signals by increasing γ-H2AX and RAD51 focal reduction in human melanoma

Table 1
Preclinical studies with ATM inhibitors

Compound	In vivo administration	IC50 of ATM kinase inhibition	Property	References
KU-55933	Not recommended	0.013 μmol/L	1. First selective ATM inhibitor. High expression of INPP4B or DAB2IP-deficient cancer cells are sensitive to ATM inhibitor 2. Following exposure to IR, KU-55933 significantly impairs HR repair.	Hickson et al., 2004; Wang et al., 2016; Zhang et al., 2015; Weber & Ryan, 2015
KU-60019	Intraperitoneally or orally	0.0063 μmol/L	1. Analogue of KU-55933 with improved pharmacokinetics and bio-availability. 2. PTEN-deficient cells are sensitive to KU-60019 when combined with cisplatin. 3. TP53 mutant GBM cells are also sensitive to KU-60019 under the IR	Golding et al., 2009; Weber & Ryan, 2015; Li, Yan, et al., 2018; Biddlestone-Thorpe et al., 2013
KU-59403	intraperitoneally	0.003 μmol/L	1. KU-59403 alone has no anti-tumor effect 2. Combination with chemotherapy or IR could kill the cancer cells independent of p53 status.	Batey et al., 2013
CP-466722	Orally	0.41 μmol/L	1. Reversible ATM inhibitor. 2. Has no effect on other PIKK family. 3. Transient inhibition of ATM also sensitive to IR treatment.	Rainey et al., 2008; Shen et al., 2019
AZ31 and AZ32	Orally	0.046 and 0.0062 μmol/L	1. Low BBB penetration	Karlin et al., 2018; Pike et al., 2018
AZD0156	Orally	0.00058 μmol/L	1. First potent and bioavailable inhibitor. 2. Low predicted in vivo dose. 3. suitable for in vivo study.	Pike et al., 2018 Morgado-Palacin et al., 2016
AZD1390	Orally	0.00078 μmol/L	1. Currently, is the most potent and highly selective ATM inhibitor. 2. Excellent BBB penetration. 3. In in vivo model, AZD1390 plus radiation repressed tumor growth.	Durant et al., 2018

cells (Herrero & Gutierrez, 2017). More specifically, inositol polyphosphate-4-phosphatase type II (INPP4B) expression positively correlates with the ATM level. KU-55933 potently impairs ATM-mediated repair signals under high expression of INPP4B in response to chemotherapy in human melanoma cells (Wang et al., 2016). Interestingly, INPP4B expression has the opposite roles in different cancer types. For example, INPP4B, as an oncogenic regulator, positively mediates AKT and glucocorticoid-regulated kinase 3 levels, thereby reducing the proliferation of colon cancer cells (Guo et al., 2016). In contrast, another study found that INPP4B is a tumor suppressor that reduces tumor migration, invasion, and angiogenesis of prostate cancer cells (Chen, Li, & Chen, 2017). However, INPP4B expression may not always correlate with ATM levels, although more evidence is required to prove this conjecture. Disabled homolog 2-interacting protein (DAB2IP) has been evaluated as a biomarker of KU-55933 treatment in bladder cancer cells. DAB2IP-deficient bladder cancer cells are resistant to radiotherapy, which is reversed by addition of KU-55933 (Zhang, Shen, Chen, Hsieh, & Kong, 2015). In glioblastoma (GBM) cancer stem cells, ATM-dependent DNA repair pathways activate following exposure to IR. However, KU-55933 efficiently abrogates repair pathways through γ-H2AX focal reduction (Carruthers et al., 2015). Although this compound is commonly used as an ATM kinase inhibitor, it has limited utility in vivo owing to its high lipophilicity (Weber & Ryan, 2015).

KU-60019, a KU-55933 analogue, is an ATP-competitive ATM inhibitor with improved pharmacokinetics and bioavailability compared with KU-55933 (Golding et al., 2009; Weber & Ryan, 2015). In GBM cells, KU-60019 efficiently blocks ATM activity to interrupt DDR signals, and it downregulates AKT phosphorylation to reduce cell survival (Golding et al., 2009). PTEN has been reported to be involved in the DNA repair process of various cancer cell types (Ma et al., 2019; Mansour et al., 2018). In PTEN-deficient breast cancer cells, the combination of KU-60019 and cisplatin results in synthetic lethality by increasing γ-H2AX foci and PARP cleavage, and reducing RAD51 foci (Li, Yan, et al., 2018). In line with this result, KU-60019 has also been tested in colorectal and prostate cancer cells. ATM inhibition is selectively toxic to PTEN-deficient cells both in vitro and in vivo (McCabe et al., 2015). Importantly, PTEN-deficient cells have enhanced sensitivity to PARP inhibitors following IR treatment (Mansour et al., 2018). Therefore, PTEN-deficiency may be a good biomarker for DDR-targeting agents.

TP53 is one of the most commonly mutated genes in cancer (Olivier, Hollstein, & Hainaut, 2010). In response to IR, TP53 mutant GBM cells are sensitive to KU-60019 treatment. Moreover, ATM inhibition plus IR significantly prolongs mouse survival (Biddlestone-Thorpe et al., 2013). However, upon intraperitoneal or oral administration, the plasma levels only maintain a low micromolar range owing to the blood-brain barrier (BBB) and blood-tumor barrier (Biddlestone-Thorpe et al., 2013).

KU-59403 is another selective ATM inhibitor. Compared with KU-55933 and KU-60019, KU-59403 has higher solubility and bioavailability (Batey et al., 2013). Although this compound has a higher potential for bioavailability in vivo compared with the other compounds, currently it is not widely used in cancer research. In 2013, it was reported that relatively low concentrations (1 μmol/L) of KU-59403 cause human cancer cells to become sensitive to chemotherapeutic agents or IR in a manner independent of the TP53 mutant status (Batey et al., 2013). However, KU-59403 alone has no antitumor effects in both in vitro and in vivo models. In this study, TP53 mutation showed no correlation with ATM inhibition sensitivity.

CP-466722 is a potent and reversible ATM inhibitor that also inhibits abl/src kinase, but has no effect on other phosphatidylinositol 3-kinase-related kinase family members (Rainey, Charlton, Stanton, & Kastan, 2008). Consistent with the previous data, CP-466722 enhances cell sensitivity to IR similarly to the other ATM inhibitors. Notably, upon transient inhibition of ATM by CP-466722 treatment for 4 h, the cells were sensitized to IR in a colony-forming assay, indicating that ATM has a critical role at an early stage of the DDR process (Rainey et al., 2008). Considering that CP-466722 is a reversible inhibitor, it is often used for a short time to evaluate ATM functions under various conditions. Cell metastasis studies showed that cisplatin resistance induces epithelial-mesenchymal transition in non-small cell lung cancer cells, which is reversed by CP-466722 treatment for 12 h. Thus, CP-466722 treatment reduces cell migration by inhibiting the JAK-STAT3-PD-L1 signaling pathway. These results were confirmed by ATM knockdown techniques (Shen et al., 2019). STAT3 has been reported to be involved in DDR signaling. It can transcriptionally regulate mediator of DNA damage checkpoint protein 1 to affect the ATM-Chk2 pathway or interrupt the ATR-Chk1 pathway to promote cell death (Barry et al., 2010; Koganti et al., 2014). Therefore, it is possible that ATM-STAT3-PD-L1-induced metastasis is also highly associated with DNA repair proteins.

Table 2
Clinical trials with ATM inhibitors

Compound	Phase	Disease	Intervention/ treatment	Status	Identification NO.
AZD0156	I	Advanced solid tumors	Olaparib, Irinotecan, Fluorouracil, Folinic Acid	Recruiting	NCT02588105
KU-60019	Not Applicable (Organotypic Cultures)	Kidney Cancer	Sunitinib, Pazopanib, Temsirolimus	Recruiting	NCT03571438
AZD1390	I	Recurrent Glioblastoma Multiforme, Primary Glioblastoma Multiforme, Brain Neoplasms Malignant, Leptomeningeal Disease (LMD)	Radiation Therapy	Recruiting	NCT03423628

4.2. AZ31, AZ32, AZD0156, and AZD1390

AZ31 and AZ32 are novel selective ATM inhibitors with IC_{50} values of 0.046 and 0.0062 μmol/L, respectively (Karlin et al., 2018; Pike et al., 2018). Comparison of these inhibitors with the other inhibitors revealed better BBB penetration. In a GBM mouse model, oral administration of AZ32 in combination with radiotherapy resulted in 6-fold more apoptosis than in the control group (Karlin et al., 2018). AZ32 also moderately inhibits ATR. Therefore, its ATM-specific inhibition is weaker than that of AZ31 (Karlin et al., 2018).

To better understand the effects of ATM inhibitors, AZD0156, which is a novel, potent, highly selective and orally available ATM inhibitor, was developed (Pike et al., 2018). AZD0156 inhibits ATM kinase with an IC_{50} value of 0.00058 μmol/L, and it has a long plasma half-life. (Jones et al., 2018; Pike et al., 2018). As a novel compound, there is limited data on AZD0156. Notably, in MLL-rearranged acute myeloid leukemia xenograft mouse models, AZD0156 prolongs survival (Morgado-Palacin et al., 2016). During the treatment, although toxicity was not seen in any of the mice, 20 mg/kg AZD0156 was a very high dose, which may have had off-target effects (Morgado-Palacin et al., 2016).

AZD1390 is an enhanced version of AZD0156 with an IC_{50} of 0.00078 μmol/L for ATM inhibition. AZD1390 has a stronger ability to cross the BBB than AZD0156, because AZD0156 is an efflux substrate for transporters (Durant et al., 2018). In a recent detailed study on AZD1390, the authors used glioma and lung cancer cells to evaluate its antitumor effect (Durant et al., 2018). This study revealed that AZD1390 has superior selective ATM kinase inhibition, and ATM phosphorylation begins to decrease after 4 h of treatment with AZD1390. In addition, AZD1390 combined with radiation exposure leads to dramatic G2 cell cycle arrest in TP53 mutant cells. This combination strategy also represses tumor growth in in vivo models.

Taken together, ATM inhibitors as a monotherapy have shown few antitumor effects so far. In preclinical research, combination with cytotoxic chemotherapeutic agents, radiotherapy, DDR-targeting agents, anti-chromatin remodeling agents, or targeting oncogenes might be potential options to enhance DNA damage.

5. Clinical trials of ATM inhibitors

Among the diverse DDR-targeting agents, research on PARP inhibitors is the most advanced (Pilie et al., 2019; Sonnenblick, de Azambuja, Azim Jr., & Piccart, 2015). Olaparib and rucaparib are approved by the Food and Drug Administration for the treatment of advanced stage ovarian and breast cancers with BRCA1/2 mutation after chemotherapy (Pilie et al., 2019). In addition, there are hundreds of ongoing clinical trials evaluating PARP inhibitors.

Compared with PARP inhibitors, clinical development of ATM inhibitors is still at an early stage. So far, there are three ATM inhibitors in clinical trials for solid tumors (Table 2). The first ATM inhibitor selected for clinical trial was AZD0156 (ClinicalTrials.gov Identifier: NCT02588105). In this phase I trial, patients with advanced solid tumors were recruited to determine the tolerable dose of AZD0156 and further evaluate combination strategies with olaparib, irrinotecan, fluorouracil, or folinic acid. The second clinical trial evaluated KU-60019. The purpose of this study was to evaluate a combination strategy using organotypic cultures derived from patients with kidney cancers (ClinicalTrials.gov Identifier: NCT03571438). The combination regimen was KU-60019 plus sunitinib, pazopanib (VEGFR inhibitor), and temsirolimus (mTOR inhibitor). The third trial evaluated AZD1390 for various types of brain tumors (ClinicalTrials.gov Identifier: NCT03423628). This was also a phase I clinical trial that aimed to identify the maximum tolerated dose of AZD1390 alone and in combination with radiation therapy under three different settings. The results of these trials are expected to be released in the next 2 or 3 years.

Preclinical data showed that ATM deficiency is associated with increased sensitivity to DDR-targeted agents, chemotherapy, and radiotherapy in colorectal, gastric, lung, breast and pancreatic cancers (Ayars, Eshleman, & Goggins, 2017; Gilardini Montani et al., 2013; Min et al., 2017; Schmitt et al., 2017; Wang, Jette, Moussienko, Bebb, & Lees-Miller, 2017). Most recently, translational research has revealed that phosphorylation of RAD50 at Ser635 is a pharmacodynamics biomarker for AZD0156. It was also shown that combined effects with PARP inhibitors dramatically reduce RAD50 phosphorylation in triple-negative breast cancer patient-derived xenograft models (Jones et al., 2018). Identification of predictive biomarkers for ATM inhibitors is urgently needed. The standard therapy of many cancers is still cytotoxic chemotherapy, and growing positive clinical data of DDR-targeted agents are increasing. Thus, predictive biomarkers for combined therapy with chemotherapy or DDR-targeted agents need to be discovered. Further research on this issue is urgently needed to recruit suitable patients for clinical trials.

6. Conclusions and future directions

In whole DDR networks, ATM not only plays a critical role in DNA damage repair, but also controls cell cycle progression, apoptosis, chromatin remodeling, and transcriptional regulation (O'Connor, 2015; Weber & Ryan, 2015). Because PARP inhibitors have been approved for patients with breast and ovarian cancers, hundreds of preclinical and clinical trials are being performed to evaluate DDR-targeted agents for various cancer types. Several ATM cofactors have been identified, including the MRN complex, ATMIN, TRAX, TIP60, ING3, linker histone H1.2, NOTCH1, FOXO3a, and WIP1. Moreover, studies on several ATM kinase inhibitors alone or in combination treatments are ongoing. However, compared with other DDR-targeted agents, such as PARP, ATR, and WEE1 inhibitors, the development of ATM inhibitors is still at an early stage.

In the future, co-inhibition of ATM and immune checkpoints may be an ideal combined strategy. Growing evidence has revealed the relationship between DDR and the immune response. In particular, ATM not only mediates PD-L1 expression, but is also involved in the plasma cell genetic program, macrophage activation, and cytokine release (Bednarski & Sleckman, 2019; Chen et al., 2015; Mouw et al., 2017; Sato et al., 2017). The positive interaction between ATM and PD-L1 has been evaluated in preclinical studies of lung cancer and esophageal squamous cell carcinoma (Shen et al., 2019; Zhang, Jiang, Su, Xie, & Xu, 2019). Interestingly, tumor PD-L1 expression is negatively regulated by

ATM in gastric cancer (Angell et al., 2019; Buglioni et al., 2018). This issue is controversial based on the current evidence. ATM-enhanced interleukin-8 release may promote cancer cell metastasis and invasion. Interleukin-8 is a high affinity ligand for CXCR2, a marker of myeloid-derived suppressor cells (Katoh et al., 2013; Lee et al., 2012). To better understand the tumor microenvironment, the crosstalk between ATM and immune signaling pathways is worth exploring.

Declarations of Competing Interest

D-Y Oh is a consultant and advisory board member of AstraZeneca, Novartis, Genentech, Roche, Merck Serono, Bayer, Taiho, ASLAN, Halozyme, and Zymework. D-Y Oh has received research grants from AstraZeneca, Novartis, Array, Eli Lilly, and Green Cross. There is no conflict of interest to declare by MH Jin.

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