Cytoplasmic ATM protein kinase: an emerging therapeutic target for diabetes, cancer and neuronal degeneration

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Ataxia–telangiectasia (A–T) is an autosomal recessive disorder characterized by cerebellar ataxia and oculocutaneous telangiectasias. The gene mutated in this disease, Atm (A–T mutated), encodes a serine/threonine protein kinase that has been traditionally considered to be a nuclear protein controlling cell-cycle progression. However, many of the growth abnormalities observed in patients with A–T, including neuronal degeneration and insulin resistance, remain difficult to explain with nuclear localization of ATM. Here, recent advances in elucidating the cytoplasmic localization and function of ATM are reviewed. Particular attention is given to the role of ATM in insulin signaling and Akt activation. The potential for cytoplasmic ATM protein kinase to be an emerging therapeutic target for treating diabetes, cancer and neuronal degeneration is discussed.

Introduction

Ataxia–telangiectasia (A–T) is an autosomal, recessive disorder that progressively affects multiple organs. The most noticeable characteristics of A–T are cerebellar ataxia and oculocutaneous telangiectasia [1]. Ataxia is the loss of muscular coordination, whereas telangiectasia describes the appearance of red spider veins that are caused by dilated peripheral blood vessels in the corners of the eyes.

A–T symptoms are first noticed in children who appear to have an unsteady gait, caused by neuronal degeneration in the cerebellar cortex, which eventually confines afflicted children to wheelchairs. Patients with A–T are also accompanied by a predisposition for cancer, multiple immune deficiencies, growth retardation, premature aging, insulin resistance and glucose intolerance [1]. Cell lines obtained from A–T patients show signs of hypersensitivity to ionizing radiation, defective cell cycle arrest, increased serum growth factor requirements and early senescence [2–6].

A–T is caused by mutations in the Atm gene – resulting in lack or inactivation of the ATM protein it encodes [1]. ATM is a 370 kDa serine/threonine protein kinase containing an open reading frame of 3056 amino acids [7]. The ATM kinase domain displays homologies to that of the large protein family of phosphotidylinositol 3-kinases (PI3Ks). The kinases in the PI3K super family play major parts in signaling pathways that are responsive to various types of stimuli related to cellular growth [1]. Other sequences identified within ATM include several nuclear localization signals, a leucine zipper and a HEAT repeat sequence [7], a motif found in many nuclear and cytoplasmic proteins involved in protein trafficking. Although many functions of ATM have been deduced from its amino acid sequence, corresponding laboratory studies have not yet identified functions for >90% of the remaining sequence. This indicates that ATM could have many, yet unknown, additional functions [1].

Nuclear ATM responds to a specific type of DNA damage (i.e. DNA double strand breaks [7]). In response to DNA double strand breaks ATM phosphorylates multiple substrates including p53 [6,8], a major player in the G_1/S checkpoint, and Chk2 [9], which is crucial at the G_2/M checkpoint of the cell cycle [7]. The function of ATM in controlling cell-cycle progression following DNA damage can readily explain why A–T patients are cancer prone. However, many other physiologically relevant symptoms associated with A–T, such as insulin resistance and neuronal degeneration, are difficult to explain by the lack of DNA damage control.

Although ATM has been traditionally considered a nuclear protein that functions in response to genotoxic stress, there is

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increasing evidence suggesting it also has separate cytoplasmic functions [7]. In fact, in neuronal or neuron-like cells ATM localization was found to be predominantly cytoplasmic [10–12]. Another study revealed that a fraction of ATM is found in the cytoplasmic compartments of proliferating cells where it associates with β-adaptin, a cytoplasmic protein involved in vesicle trafficking [13]. More importantly, clues about the cytoplasmic function of ATM have come from the discovery of its involvement in insulin signaling pathways [14–16].

In the first report demonstrating a role of ATM in insulin signaling, ATM kinase activity was found to increase 3-fold in response to insulin in rat 3T3-L1 cells that had differentiated into adipocytes [14]. In addition, insulin leads to phosphorylation of 4E-BP1 (also called PHAS-I), an insulin-responsive cytoplasmic protein, in an ATM-dependent manner. Phosphorylation of 4E-BP1 at Ser111 by ATM promotes initiation of mRNA translation [14]. More recently, it was discovered that ATM stimulates insulin-induced Akt phosphorylation at Ser473 and mediates the full activation of Akt activity [15,16]. Akt participates in multiple physiological processes, including protein translation, glucose uptake, cell proliferation and cell survival, in response to insulin and many other growth factors. Therefore, these findings open the door for exploring the unknown functions of ATM and could provide explanations for many of the clinical phenotypes of A–T that are difficult to explain by the nuclear localization and functions of ATM.

A–T and growth retardation

Growth retardation is a classic hallmark of A–T, well documented in clinical cases [17] and in Atm-deficient mice [18–20]. It is estimated that the frequency of somatic growth retardation in A–T patients is as high as 75%, and is often associated with loss of subcutaneous fat [17]. Dysfunction of ATM also results in higher requirements of serum growth factors in cells derived from A–T patients [1]. However, the exact cause of growth retardation in A–T is unknown.

Peretz *et al.* found that A–T cells contain a lower number of insulin-like growth factor (IGF)-1 receptors as compared with control cells derived from patients without A–T [21]. Consistent with this finding, an earlier study involving 12 A–T patients found significantly increased serum IGF-1 levels and slightly increased serum IGF-binding protein (IGFBP)-3 levels [22]. They also reported a significant increase in serum insulin levels, which is consistent with insulin resistance typically observed in A–T patients.

Insulin and IGF-1 are by far the best characterized growth factors that regulate protein translation [23,24]. The insulin-stimulated phosphorylation of 4E-BP1 by ATM represents an important link between the signaling of growth factor receptors, protein synthesis and cell growth [14]. In its hypophosphorylated state 4E-BP1 binds tightly to eIF-4E, a translation initiation factor bound to the N^7-methylguanosine cap of eukaryotic mRNA. Addition of insulin or IGF-1 induces phosphorylation of 4E-BP1 at multiple sites [25]. eIF-4E can then dissociate from 4E-BP1, thereby facilitating the formation of the large translation initiation complex eIF-4F.

Furthermore, a recent large-scale proteomic screen of ATM substrates not only confirmed Ser111 of 4E-BP1 as a phosphorylation site of ATM but also identified p70S6 kinase as a potential ATM target [26]. p70S6 kinase is a protein translation factor known to be involved in regulating cell growth and cell size [27,28]. Akt, like ATM, is also involved in the regulation of multiple protein translation factors [23,24]. For example, mTOR, a downstream target of Akt, phosphorylates p70S6 kinase and 4E-BP1 in response to growth factor stimulation [29–32]. Akt also regulates the activity of other protein translation factors such as eIF-2B [23,24].

Taken together, these recent discoveries suggest that ATM, in addition to phosphorylation of 4E-BP1, could have a broader role in regulating protein translation and cell growth. Unraveling the molecular details of ATM-mediated protein translation can shed more light on our understanding of the growth retardation symptoms associated with A–T.

A–T and type 2 diabetes mellitus

An increased incidence of insulin resistance and type 2 diabetes is observed in A–T patients. In one study, 59% of A–T patients were reported to develop type 2 diabetes [33]. Using an oral glucose tolerance test (OGTT), it was found that A–T patients with diabetes displayed classical symptoms of insulin resistance including hyperinsulinemia, hyperglycemia and glucose intolerance. In another case study, two siblings with A–T were found to have severe insulin resistance, because endogenous and exogenous insulin did not result in a substantial decrease of glucose levels [34]. A–T patients usually die within the third decade of life, well before type 2 diabetes is typically diagnosed. Thus, the number of A–T patients that develop diabetes might be significantly underestimated.

Although symptoms of insulin resistance and increased incidence of type 2 diabetes have been noted in A–T patients for the past four decades, only very recently have the mechanisms underlying these clinical observations been investigated. The discovery of cytoplasmic ATM as an insulin-responsive protein provides the first indication that a defective response to insulin could be related to the development of insulin resistance and type 2 diabetes in A–T patients [14]. A recent study investigated the effect of ATM deficiency on insulin resistance in mice with an apolipoprotein E (ApoE) null background. $Atm^{-/-}$ mice were bred with ApoE null mice, a mouse model for atherosclerosis, to generate $Atm^{-/-}$/$ApoE^{-/-}$ and $Atm^{+/-}$/$ApoE^{-/-}$ mice. After feeding the mice a Western high-fat diet it was found that insulin resistance, atherosclerosis and glucose intolerance increased in $Atm^{+/-}$/$ApoE^{-/-}$ as compared with $Atm^{+/+}$/$ApoE^{-/-}$ mice [35].

Insulin resistance in rats can be induced by feeding them a high-fat diet [16]. It was found that these rats had dramatically reduced ATM levels and decreased phosphorylation of Akt at Ser473 in muscle tissue when compared with regular chow-fed rats [16]. These results suggest that reduced expression of ATM is involved in the development of insulin resistance through its downregulation of Akt activity. In addition, the role of ATM in the activation of Akt (by effecting its phosphorylation at Ser473 and Thr308) was demonstrated in mouse embryonic fibroblast (MEF) A29 ($Atm^{+/+}$) and A38 ($Atm^{-/-}$) cells [16]. Similarly, ATM deficiency also resulted in decreased Akt phosphorylation at Ser473 and Thr308 in insulin-stimulated ApoE null mice [35].

Several studies have shown that disruption of insulin-mediated glucose transport is a major underlying cause of insulin resistance,

a hallmark of type 2 diabetes. Akt is a central regulator of insulin-mediated glucose uptake in muscle cells. Glucose transporter 4 (GLUT4) is responsible for insulin-mediated glucose uptake in skeletal muscle. It was found that muscle-tissue-specific disruption of GLUT4 in mice led to increased insulin resistance and glucose intolerance [36].

Further results by Halaby *et al*. [16] show that ATM inhibition by its specific inhibitor, KU55933, in L6 myoblasts resulted in an abrogation of Akt phosphorylation at Ser473 and Thr308, as well as a dramatic reduction of insulin-mediated glucose uptake [16]. Moreover, it was demonstrated that ATM participates in the insulin-regulated GLUT4 translocation process in L6 muscle cells. An immunofluorescence experiment showed that in L6 cells transfected with wild type (WT)-ATM insulin caused a dramatic increase of the cell surface GLUT4, whereas in cells transfected with kinase dead (KD)-ATM translocation of GLUT4 to the cell surface in response to insulin was markedly inhibited [16].

It is known that GLUT4 translocation in response to insulin is regulated by the PI3K/Akt pathway [37]. Although some components of the PI3K/Akt pathway regulating insulin-mediated GLUT4 translocation have been identified, a detailed molecular description of this process is still lacking [38]. These findings place ATM as a novel signal transducer in the insulin signaling pathway regulating glucose uptake and GLUT4 translocation in muscle cells.

In another recent report, $Atm^{-/-}$ mice were used to study the effect of ATM deficiency on insulin sensitivity and glucose tolerance. $Atm^{-/-}$ mice developed diabetes with age, demonstrated by elevated blood glucose and decreased plasma-insulin concentration [39]. Serum C-peptide levels, an indicator of insulin secretion, were also significantly decreased in aging A–T mice (27 weeks or older) compared with wild type mice, suggesting that the β cells of the pancreas were unable to secrete insulin following glucose uptake [39]. It was hypothesized that $Atm^{-/-}$ mice could exhibit increased β-cell apoptosis and reduced β-cell mass as they age [39].

It should be emphasized that the current model of type 2 diabetes mellitus is defined by an initial symptom of insulin resistance and/or reduced glucose uptake and a subsequent decrease in insulin secretion caused by reduced pancreatic β-cell mass [40]. Therefore, it is not surprising that ATM could participate in signaling pathways that promote insulin-mediated glucose uptake as well as β-cell survival.

A–T and neuronal degeneration

The most prevalent feature in A–T patients is ataxia. Autopsy results indicate cerebellar neurodegeneration in the cerebellar cortex where Purkinje and granular cells are selectively lost, whereas basket cells remain intact [1]. Although extensive effort has been made to understand how ATM deficiency could result in neuronal degeneration, the mechanisms behind neuronal degeneration of A–T are still poorly understood. It has been speculated that defective responses of ATM to DNA damage could be the cause of neuronal degeneration in A–T. However, $Atm^{-/-}$ mice show compromised function in DNA repair but fail to develop significant neuronal degeneration or exhibit symptoms of ataxia [19,41], suggesting a lack of correlation between dysfunction in DNA repair and neuronal degeneration of the A–T disease.

A clue to the role of ATM in neuronal cells comes from its cellular localization. ATM is predominantly localized in the nucleus of dividing cells, where it functions as a key signal transducer following DNA damage [42,43]. However, in post-mitotic Purkinje and granular cells ATM was localized exclusively in the cytoplasm [10]. Immunostaining for ATM in the brain of adult mice showed the protein is present in the cytoplasm of Purkinje cells and that of dorsal root ganglia neurons [11].

Moreover, it was found that levels of ATM protein dramatically decrease in differentiated mouse neural progenitor cells compared with proliferating cells [44]. Boehrs *et al*. compared the change in levels of ATM protein in rat PC12 cells and human SH-SY5Y cells following their differentiation into neuron-like cells [12]. Although ATM protein levels were greatly reduced in PC12 cells following differentiation, they remained the same following SH-SY5Y cell differentiation. These studies suggest that ATM might not be as important for neuronal survival in rodents as it is in humans, which could explain why $Atm^{-/-}$ mice do not display overt ataxia, whereas patients with A–T do. Further experiments indicate that ATM is predominantly nuclear in undifferentiated SH-SY5Y cells and then translocates to the cytoplasm following differentiation [12].

Taken together, these studies indicate that ATM has cytoplasmic functions in neuronal cells independent of its role as a DNA damage sensor. Recent results from Li *et al*. [45] showed that ATM not only is present in the cytoplasm of mouse brain tissues and cultured neuronal cells but also binds to vesicle-associated membrane protein VAMP2 and synapsin, two major components of synaptic vesicles, in cytoplasmic and synaptosomal fractions of mouse neuronal cells. These results indicate that cytoplasmic ATM could have important roles in neuronal synaptic functions. It should be noted that VAMP2 and synapsin are also components of the GLUT4-containing vesicles in muscle cells and therefore are also involved in insulin-mediated GLUT4 translocation to the plasma membrane [38].

In addition, insulin has recently been shown to be an important neurotrophic factor that enhances neuronal survival. The effect of insulin on neuronal cell survival is mediated by PI3K and its downstream target Akt [46]. Akt promotes cell survival in response to neurotrophic factors by inactivating many proapoptotic proteins [46]. Consistent with recent studies showing that ATM mediates Akt phosphorylation following insulin treatment [15,16], in differentiated SH-SY5Y cells transfected with WT-ATM, insulin was capable of mediating cell survival following serum-starvation. By contrast, insulin could not promote cell survival in serum-starved differentiated SH-SY5Y cells transfected with a dominant-negative KD-ATM [12]. Thus, ATM could act as an intracellular mediator of insulin which activates Akt in neurons, thereby leading to enhanced neuronal survival.

Targeting cytoplasmic ATM for the treatment of diabetes, cancer and neuronal degeneration

Type 2 and type 1 diabetes

Chloroquine is widely used as an antimalarial drug and has also been used in rheumatoid arthritis therapy [47]. Recently, it was shown that chloroquine activates ATM in the absence of DNA double strand breaks [48]. Because ATM deficiency has been correlated with increased insulin resistance, the effects of chloroquine were recently tested in several animal models of insulin resistance. Chloroquine treatment led to a decrease in fasting and

non-fasting glucose levels in ob/ob mice [35]. Chloroquine was also found to increase glucose tolerance in $Atm^{+/+}ApoE^{-/-}$ mice fed a Western fat diet, but not in $Atm^{-/-}ApoE^{-/-}$ mice fed the same diet [35].

In fact, an extensive literature search has indicated that the hypoglycemic effect of chloroquine was noted in the late 1980s. Chloroquine was tested in rat models of type 2 diabetes as well as in multiple pilot human clinical trials for type 2 diabetic patients. The results show significant improvement of insulin sensitivity and glucose tolerance in animal models and in human clinical trials [47,49–51].

Despite many studies performed, the mechanism underlying the hypoglycemic effect of chloroquine is still unclear. Results from Schneider *et al.* [35] suggest that chloroquine can decrease c-Jun N-terminal kinase (JNK) activity in an ATM-dependent manner. However, the Atm-deficient mice used in this study also had an ApoE-null background, which makes it difficult to determine whether increased JNK activity was caused by a deficiency in ATM or a deficiency in ApoE [35,52]. In a previous report, increased plasma cholesterol was only discovered in $Atm^{-/-}/ApoE^{-/-}$ mice but not in $Atm^{-/-}/LDLR^{-/-}$ mice (LDLR: low density lipoprotein receptor), which suggests a role of the secondary mutation in affecting lipid profiles of transgenic mice [52].

Because ATM stimulates Akt activity, we recently tested the effect of chloroquine on Akt activity in L6 muscle cells. It was found that pre-treatment of L6 myoblasts with chloroquine resulted in an increase in Akt phosphorylation at Ser473 when compared with cells treated with insulin alone. Moreover, chloroquine also resulted in enhanced glucose uptake in L6 muscle cells treated with insulin (Yang, et al., 20th World Diabetes Congress, abstract #P-1728, 2009). These results not only confirm the role of ATM in controlling Akt activity but also suggest that chloroquine-mediated ATM activation can trigger the signaling cascades downstream of Akt.

Because chloroquine-mediated activation of ATM results in a dramatic increase in Akt activity, and Akt plays a crucial part in regulating both glucose uptake and pancreatic β-cell survival [39], ATM could be an attractive new therapeutic target to increase insulin sensitivity and enhance functional β-cell mass. Chloroquine has been successfully used in clinical settings for treating human diseases, such as malaria and rheumatoid arthritis [47]. Thus, chloroquine could lend itself to further investigations and clinical studies in patients with type 1 and type 2 diabetes.

Cancer

As a sensor of DNA damage, nuclear ATM has been used as a target for sensitizing cancer cells to DNA-damage-inducing agents [53]. Recent reports showing that ATM is also involved in the activation of Akt [15,16] have offered new avenues for using ATM as a therapeutic target for treating cancer.

The activation of the PI3K/Akt pathway is an early event in carcinogenesis, which promotes cancer progression through stimulating cell proliferation and cell survival [54]. Consistent with the finding that ATM activates Akt [15,16], Li *et al.* found that ATM inhibitor KU55933 [53] blocks phosphorylation of Akt and inhibits cell proliferation in cancer cell lines with over-activated Akt [55]. KU55933 arrests the cell cycle at the G1/S phase and downregulates cyclin D1, a protein crucial for G1/S cell cycle transition [55]. Recent results by Alao *et al.* [56] have confirmed these findings by showing that other inhibitors of ATM can reduce cyclin D1 levels as well.

It was further demonstrated that downregulation of cyclin D1 is caused by a reduced rate of cyclin D1 protein synthesis. The inhibition of 4E-BP1 phosphorylation by KU55933 could contribute to decreased synthesis of cyclin D1 [55]. This observation agrees with previous discoveries suggesting that ATM either plays a direct part in stimulating 4E-BP1 phosphorylation [14] or affects 4E-BP1 phosphorylation indirectly through its activation of Akt and mTOR [15,16]. In addition, KU55933 has the ability to induce apoptosis under conditions of serum deprivation [55]. This finding is significant because most cancer cells escape apoptotic mechanisms even during serum starvation.

Traditional PI3K or Akt inhibitors, such as LY294002 and perifosine, are either too toxic to be used clinically or have limited efficacy to treat cancer in a clinical setting [57–59]. By contrast, KU55933 is a specific inhibitor of ATM that has selectivity for ATM that is at least 100-fold greater than other related kinases, including PI3K [53]. Moreover, the inhibition of cell proliferation by KU55933 is positively correlated with phospho-Akt level. It appears that KU55933 inhibits cancer cell proliferation but spares normal cells with low Akt activity [55]. Therefore, the inhibition of ATM, as a strategy to treat cancer, could have advantages over the traditional inhibitors of PI3K or Akt.

Rapamycin, an inhibitor of mTOR, prevents the growth of cancer cells. However, a feedback activation of Akt caused by rapamycin treatment prohibits clinical application of rapamycin and its analogs [60,61]. KU55933 is able to inhibit the feedback activation of Akt induced by rapamycin. The combination of KU55933 and rapamycin not only induces apoptosis, which is not seen in cancer cells treated with rapamycin alone, but also shows significantly higher efficacy in inhibiting cancer cell proliferation than either drug alone [55]. Thus, these results provide a novel approach to improving mTOR-targeted anticancer therapy significantly through the combination of rapamycin and KU55933.

Mutations in the PI3K pathway occur frequently in human cancers, and the resulting activation of Akt [62] accounts for the resistance of many types of cancer to chemo- and immunotherapy [22]. KU55933 inhibits proliferation of various cancer cell lines with overactivated Akt, including estrogen-receptor-negative/herceptin-resistant breast cancer and androgen-independent prostate cancer [55], thereby offering a highly effective approach for treating many types of aggressive cancers for which current chemo- or immuno-therapy has limited efficacy [55].

Cerebellar ataxia and neuronal degeneration

To date, there is no effective treatment for neuronal degeneration of A–T. Current strategies for treating A–T are largely based on relieving pain and discomfort associated with the symptoms of A–T patients. A recent study by Schubert *et al.* [63] found that the levels of IGF-1 and its interacting protein IGFBP-3 were significantly decreased in blood samples obtained from patients with A–T. To determine whether A–T patients benefit from treatment with growth factors, such as IGF-1, a clinical trial is currently underway with the support of the A–T Children's Project (ATCP, March 2009 Newsletter). The observation by Schubert *et al.*, however, disagrees

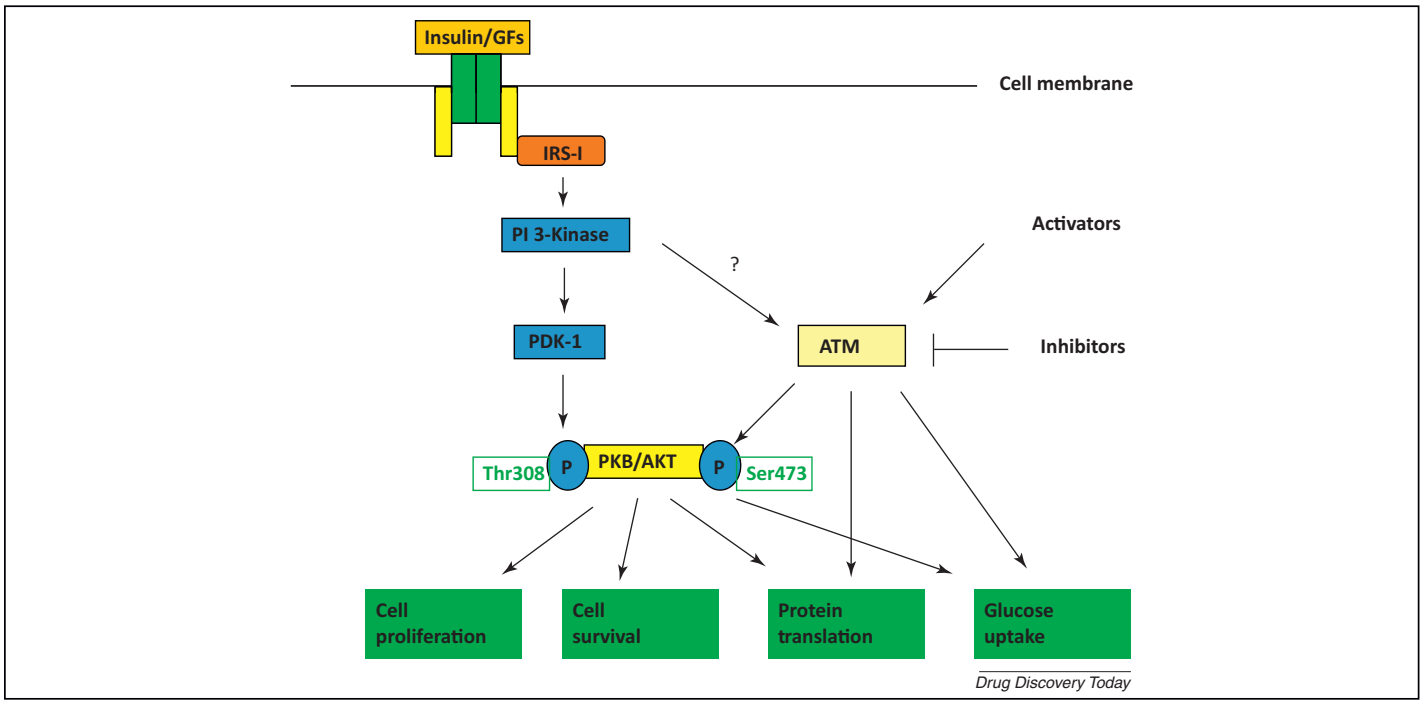

FIGURE 1

Role of cytoplasmic ATM in mediating insulin signaling and Akt phosphorylation. This figure summarizes the current knowledge about the role of ATM in physiological events mediated by insulin and other growth factors. ATM participates in these processes either through activation of Akt or by directly phosphorylating and/or interacting with key component proteins involved in the events. As implicated in the figure, ATM can be a potential therapeutic target for a number of human diseases. These include type 2 diabetes (enhancing glucose uptake and insulin sensitivity), type 1 diabetes (promoting beta cell proliferation and survival), cancer (inhibiting cancer cell proliferation and survival) and neuronal degeneration (promoting neuronal cell survival).

with an earlier study by Busiguina *et al.* [22] who found significantly increased serum IGF-1 levels and slightly increased serum IGFBP-3 levels in A–T patients.

Aside from the discrepancies in literature regarding concentrations of IGF-1 in A–T patients, studies have revealed that many growth-promoting factors, including IGF-1, might be associated with the development of cancer. This raises a serious concern because A–T patients already possess a much higher risk of developing cancer. Therefore, a safer approach to treat neuronal degeneration of A–T could lie in the effort to discover the downstream substrates that cytoplasmic ATM regulates. This could also include targeting Akt and its various downstream substrates.

It is interesting to note that studies from two recent reports suggest that FOXO proteins are also potential downstream targets of ATM [15,26]. The FOXO family consists of proapoptotic transcriptional factors downstream of Akt. Phosphorylation of FOXOs by Akt leads to the abrogation of FOXO transcriptional activity. Activation of FOXO proteins has been linked to neuronal cell death [46]. By mediating Akt activation in neuronal cells ATM could lead to an inhibition of FOXO activity, thereby promoting cell survival. It is conceivable that FOXO proteins or their downstream targets could become attractive therapeutic targets for neuronal degeneration of A–T.

Decreased rates of translation are correlated with decreased cell survival and neurodegenerative diseases [64,65]. Although it is not clear whether ATM potentially regulates neuronal survival by affecting phosphorylation of 4E-BP1, another possible direct target of ATM, p70S6 kinase is known to be involved in the regulation of neuronal survival [66]. In addition, by mediating Akt activation, ATM could also regulate protein synthesis by modulating activities of several protein translation factors that are downstream of Akt, including eIF-2B. Previous studies showed that mutations in the genes coding for eIF-2B subunits result in the neurodegenerative disease VWM (leukoencephalopathy with vanishing white matter), which displays similar symptoms to those observed in A–T, such as ataxia [64,65]. It remains to be seen whether any translational factors such as p70S6 kinase and eIF-2B, or their immediate downstream targets, can be used as potential therapeutic targets for the treatment of A–T.

Concluding remarks

Despite intensive research efforts, the molecular basis of A–T disease is still poorly understood. To date, the majority of studies on ATM have focused on its nuclear function, which is to trigger the DNA damage response by causing cell cycle arrest. Although this area of study is crucial for defining the mechanisms of ATM in response to DNA double strand breaks, many of the symptoms of A–T simply cannot be explained by this role alone. The discoveries of the cytoplasmic functions of ATM in mediating insulin signaling and activating Akt (Fig. 1) have provided novel insights into the connections between a lack of ATM and the various growth abnormalities observed in A–T patients.

Currently, there is no cure for A–T nor is there a way to slow its progression. A more in-depth understanding of the cellular functions of ATM, including its role in the cytoplasm, could greatly assist with the development of effective approaches to treat this

devastating disorder. By contrast, recent progress in understanding the molecular details in the cytoplasmic actions of ATM, followed by its identification as a potential drug target, could lead to promising new avenues for the treatment of diabetes and cancer. Known pharmaceutical agents that specifically target ATM, such as chloroquine and KU55933, can be used in proof-of-concept studies to explore further their potential for targeting diabetes and cancer, respectively. Assuming successful outcomes, these studies could trigger the search for novel inhibitors and activators of ATM that can be explored further for their potential in the treatment of multiple diseases.

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