

Gene Section

Review

ATM (ataxia telangiectasia mutated)

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Abstract

Review on ATM, with data on DNA, on the protein encoded, and where the gene is implicated.

Keywords

Ataxia telangiectasia; Cerebellar ataxia; Telangiectasia; Immunodeficiency; T- cell malignancies; B-cell malignancies; Carcinomas; Senescence; Chromosome instability syndrome; DNA double-strand breaks; Translocation; Oxidative stress; Homeostasis; ATM; chromosome.

Identity

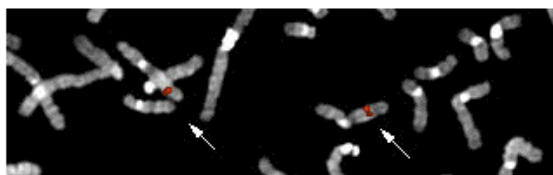
HGNC (Hugo): ATM

Location: 11q22.3

Note

See also, in Deep Insight section: Ataxia-Telangiectasia and variants.

DNA/RNA



ATM (11q22.3) in normal cells: PAC 1053F10 - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics.

Description

The ATM gene extends over 184 kb and contains 66 exons producing a 13 kb mRNA (Uziel T et al., 1996; Platzer M et al., 1997); numerous Alu and Lime sequences.

Transcription

Alternative exons 1a and 1b; initiation codon lies within exon 4; 12 kb transcript with a 9.2 kb of coding sequence.

The ATM promotor is bi-directional and also directs the transcription of the NPAT gene.

Protein

Description

ATM is a homeostatic protein kinase with an extremely broad range of roles in various cellular circuits (Shiloh Y et al., 2013; Guleria A et al., 2016; Shiloh Y, 2014; Cremona CA et al., 2014; Ambrose M et al., 2013; Espach Y et al., 2015; Awasthi P et al., 2016). This large polypeptide of 350 kDa and 3,056 residues bears a PI3 kinase signature within its carboxy-terminal catalytic site, but has the catalytic activity of a serine-threonine protein kinase. This motif is characteristic of a protein family of which ATM is a member - the PI-3 kinase-like protein kinases (PIKKs; Lovejoy CA et al., 2009; Bareti+ACY-cacute; D et al., 2014).

This family also contains the MTOR protein, which regulates many signaling pathways in response to nutrient levels, growth factors and energy balance (Alayev A et al., 2013; Cornu M et al., 2013); the catalytic subunit of the DNA-dependent protein kinase (DNA-PKcs), which is involved in the NHEJ pathway of double strand breaks (DSB) repair and other genotoxic stress responses (Davis AJ et al., 2014; Jette N et al., 2015), SMG1, which plays a key role in nonsense-mediated mRNA decay (Yamashita A, 2013); and ATR, which responds to stalled replication forks and a variety of DNA lesions that lead to the formation of single-stranded DNA, including deeply resected DSBs (Errico A et al., 2012; Mar+ACY-eacute;chal A et al., 2013; Awasthi P et al., 2016). The redundancy, crosstalk and collaboration between the latter three PIKKs, which collectively respond to a broad spectrum of genotoxic stresses, are being extensively investigated (Lovejoy CA et al., 2009; Mar+ACY-eacute;chal A et al., 2013; Sirbu BM et al., 2013; Thompson LH, 2012; Gobbini E et al., 2013; Chen BP et al., 2012).

It should be noted that in A-T patients, the two PIKKs that converse and cooperate with ATM in the response to genotoxic stress, ATR and DNA-PK, remain active. In view of the functional relationships between the three protein kinases, some of ATM's duties are probably carried out to a certain extent by ATR and/or DNA-PK, in A-T cells. On the other hand, the lack of a very versatile member of this trio may lead to some suboptimal responses of the other two, if they depend on the crosstalk with ATM. This interesting question is a subject of intensive research.

Expression

ATM is expressed in all tissues.

Localisation

Mostly in the nucleus throughout all stages of the cell cycle.

Function

Homeostatic protein kinase involved in many cellular circuits. A primary role in the DNA damage response. Activated vigorously by DNA double-strand breaks and activates a broad network of responses. ATM initiates cell cycle checkpoints in response to double-strand DNA breaks by phosphorylating TP53, BRCA1, H2AFX, ABL1, NFKBIA and CHEK1, as well as other targets; in certain types of tissues ATM inhibits radiation-induced, TP53-dependent apoptosis.

Double strand breaks The most widely documented function of ATM, and the one associated with its most vigorous activation, is the mobilization of the complex signaling network that responds to DSBs in the DNA (Shiloh Y et al., 2013; Cremona CA et al., 2014; Awasthi P et al., 2016;

Thompson LH, 2012; McKinnon PJ, 2012). DSBs are induced by exogenous DNA breaking agents or endogenous reactive oxygen species (Schieber M et al., 2014), and are an integral part of physiological processes including meiotic recombination (Borde V et al., 2013; Lange J et al., 2011) and the rearrangement of antigen receptor genes in the adaptive immune system (Alt FW et al., 2013). DSBs are repaired via nonhomologous end-joining (NHEJ), or homologous recombination repair (HRR; Shibata A et al., 2014; Chapman JR et al., 2012; Jasin M et al., 2013; Radhakrishnan SK et al., 2014). DSBs also activates the DDR, a vast signaling network that mobilizes special cell cycle checkpoints, extensively alters the cellular transcriptome, and changes the turnover, activity and function of numerous proteins that ultimately leads to modulation of numerous cellular circuits. This network is based on a core of dedicated DDR players and the ad-hoc recruitment of proteins from many other arenas of cellular metabolism, which typically undergo special, damage-induced post-translational modifications (PTMs; Shiloh Y et al., 2013; Sirbu BM et al., 2013; Thompson LH, 2012) (Goodarzi AA et al., 2013; Panier S et al., 2013; Polo SE et al., 2011).

Once ATM mobilizes the vast DDR network in response to a DSB (McKinnon PJ, 2012; Shiloh Y et al., 2013; Bhatti S et al., 2011), its protein kinase activity is rapidly enhanced, and PTMs on the ATM molecule are induced, including several autophosphorylations and an acetylation (Shiloh Y et al., 2013; Bhatti S et al., 2011; Bakkenist CJ et al., 2003; Kozlov SV et al., 2006; Bensimon A et al., 2010; Sun Y et al., 2007; Kaidi A et al., 2013; Paull TT, 2015).

ATM subsequently phosphorylates key players in various arms of the DSB response network (Shiloh Y et al., 2013; Bensimon A et al., 2010; Matsuoka S et al., 2007; Mu JJ et al., 2007; Bensimon A et al., 2011), including other protein kinases that in turn phosphorylate still other targets (Bensimon A et al., 2011).

Single-strand break repair and base excision repair

A broader, overarching role for ATM in maintaining genome stability was recently suggested in addition to mobilizing the DSB response (Shiloh Y, 2014). According to this conjecture, ATM supports other DNA repair pathways that respond to various genotoxic stresses, among them single-strand break repair (SSBR; Khoronenkova SV et al., 2015) and base excision repair (BER) - a cardinal pathway in dealing with the daily nuclear and mitochondrial DNA damage caused by endogenous agents (Wallace SS, 2014; Bauer NC et al., 2015).

ATM's involvement in these processes is based on its ability to phosphorylate proteins that function in these pathways. In this way ATM also takes part also in resolving non-canonical DNA structures that arise

in DNA metabolism, and in regulating other aspects of genome integrity such as nucleotide metabolism, the response to replication stress, and resolution of the occasional conflicts that arise between DNA damage and the transcription machinery. ATM is not critical for any of these processes in the same way it is for the DSB response, but rather contributes to their regulation (in most cases, their enhancement) when the need arises (Shiloh Y, 2014; Segal-Raz H et al., 2011; Zolner AE et al., 2011).

This function of ATM may explain the moderate, variable sensitivity of ATM-deficient cells to a broad range of DNA damaging agents. Among them are UV radiation, alkylating agents, crosslinking agents, hydrogen peroxide, 4-Nitroquinoline 1-oxide, phorbol-12-myristate-13-acetate and topoisomerase I poisons (Yi M et al., 1990; Ward AJ et al., 1994; Hoar DI et al., 1976; Paterson MC et al., 1976; Smith PJ et al., 1980; Mirzayans R et al., 1989; Henderson EE et al., 1980; Scudiero DA, 1980; Jaspers NG et al., 1982; Teo IA et al., 1982; Barfknecht TR et al., 1982; Fedier A et al., 2003; Leonard JC et al., 2004; Lee JH et al., 2006; Zhang N et al., 1996; Smith PJ et al., 1989; Alagoz M et al., 2013; Katyal S et al., 2014; Speit G et al., 2000; Shiloh Y et al., 1985; Hannan MA et al., 2002).

ATM-deficient cells also exhibit reduced efficiency in resolving TOP1 (Topoisomerase I) -DNA covalent intermediates (Alagoz M et al., 2013; Katyal S et al., 2014).

This ongoing role of ATM is its routine function in the daily maintenance of genome stability, while its powerful role in the DSB response is reserved for when this harmful lesion interferes with the daily life of a cell. Thus, when ATM is missing, not only is there markedly reduced response to DSBs, the ongoing modulation of numerous pathways in response to occasional stresses becomes suboptimal. All of these lesions are part of the daily wear and tear on the genome that contributes to ageing.

An additional role for ATM in genome dynamics was proposed following evidence that ATM is involved in shaping the epigenome in neurons by regulating the localization of the histone deacetylase 4 (HDAC4 Li J et al., 2012; Herrup K et al., 2013; Herrup K, 2013), targeting the EZH2 component of the polycomb repressive complex 2 (Li J et al., 2013), and regulating the levels of 5-hydroxymethylcytosine in Purkinje cells (Jiang D et al., 2015).

Oxidative stress/Cellular homeostasis.

Cytoplasmic fraction of ATM ATM's role in cellular homeostasis is further expanded by its cytoplasmic fraction. Specifically, cytoplasmic ATM was found to be associated with peroxisomes (Watters D et al., 1999; Tripathi DN et al., 2016; Zhang J et al., 2015) and mitochondria (Valentin-Vega YA et al., 2012). In view of the evidence of increased oxidative stress in ATM-deficient cells, it

has long been suspected that ATM senses and responds to oxidative stress (Gatei M et al., 2001; Rotman G et al., 1997; Rotman G et al., 1997; Barzilai A et al., 2002; Watters DJ, 2003; Takao N et al., 2000; Alexander A et al., 2010). This conjecture was validated by work from the Paull lab (Guo Z et al., 2010a), which identified an MRN-independent mode of ATM activation, differentiating it from DSB-induced activation, stimulated by reactive oxygen species (ROS) and leading to ATM oxidation (Paull TT, 2015; Guo Z et al., 2010a; Guo Z et al., 2010b; Lee JH et al., 2014). ATM was also found to be involved specifically in the protection against oxidative stress induced by oxidized low-density lipoprotein (Semlitsch M et al., 2011). It has thus assumed the role of a redox sensor (Ditch S et al., 2012; Tripathi DN et al., 2016; Kr+ACY-uuml;ger A et al., 2011). Recently, the first phospho-proteomic screen was carried out to identify substrates of ROS-activated ATM (Kozlov SV et al., 2016). An important arm of the ATM-mediated response to ROS extends to peroxisomes (Tripathi DN et al., 2016). Work from the Walker lab showed that ROS-mediated activation of peroxisomal ATM leads to ATM-mediated phosphorylation of LKB and subsequent activation of AMPK and TSC2, which dampens mTORC1-mediated signaling, eventually decreasing protein synthesis and enhancing autophagy (Alexander A et al., 2010; Tripathi DN et al., 2013; Zhang J et al., 2013; Alexander A et al., 2010; Alexander A et al., 2010).

Further work from this lab (Zhang J et al., 2015) showed that ATM also phosphorylates the peroxisomal protein PEX5, flagging it for ubiquitylation and subsequent binding to the autophagy adapter, SQSTM1 (p62), in the process of autophagy-associated peroxisome degradation (pexophagy) - a critical process in peroxisome homeostasis (Till A et al., 2012).

Mitochondrial fraction of ATM. Still another arm of the ATM-mediated response to oxidative stress operates in the mitochondrial fraction of ATM. ATM is thus emerging also as a regulator of mitochondrial homeostasis. Evidence is accumulating of its involvement in mitochondrial function, mitophagy, and the integrity of mitochondrial DNA (Valentin-Vega YA et al., 2012; Ambrose M et al., 2007; Eaton JS et al., 2007; Fu X et al., 2008; Valentin-Vega YA et al., 2012; D'Souza AD et al., 2013; Sharma NK et al., 2014) and further work is needed to identify its substrates in mitochondria and the mechanistic aspects of its action in this arena.

Links between ATM and the SASP (senescence-associated secretory phenotype). Several laboratories recently described direct links between ATM and the SASP - a cardinal feature of cell senescence. Work from the Gamble lab (Chen H et al., 2015) showed that the histone variant

macroH2A.1 is required for full transcriptional activation of SASP-promoting genes, driving a positive feedback loop that enhances cell senescence. This response is countered by a negative feedback loop that involves ATM activation by endoplasmic reticulum stress, elevated ROS levels or DNA damage. ATM's activity is required for the removal of macroH2A.1 from sites of SASP genes, thus leading to SASP gene repression. The Elledge lab identified a major SASP activator - the transcription factor GATA4 ID, whose stabilization drives this process (Kang C et al., 2015). Importantly, the activation of this pathway was dependent on both ATM and ATR, as was senescence-associated activation of TP53 and CDKN2A (p16INK4a). On the other hand, the Zhang lab (Aird KM et al., 2015) recently showed that when cell senescence is induced by replication stress (e.g., following nucleotide deficiency), ATM inactivation allows the cell to bypass senescence by shifting cellular metabolism: upon ATM loss, dNTP levels rise due to up-regulation of the pentose phosphate pathway, whose key regulator, glucose-6-phosphate dehydrogenase (G6PD) is under functional regulation by ATM (Aird KM et al., 2015; Cosentino C et al., 2011).

Insulin response and lipoprotein metabolism. Other metabolic arenas in which ATM involvement is gaining attention are insulin response and lipoprotein metabolism, clinically represented by the metabolic syndrome. This role of ATM in cellular physiology was recently thoroughly and convincingly reviewed (Espach Y et al., 2015). Briefly, ATM was found to participate in several signaling pathways mediated by insulin (Yang DQ et al., 2000; Miles PD et al., 2007; Viniegra JG et al., 2005; Halaby MJ et al., 2008; Jeong I et al., 2010); and heterozygosity for *Atm* null allele in ApoE-deficient mice was found to aggravate their metabolic syndrome (Wu D et al., 2005; Schneider JG et al., 2006; Mercer JR et al., 2010), an effect that was partly relieved by the mitochondria-targeted antioxidant MitQ (Mercer JR et al., 2012).

IGF-1 receptor. Another pathway by which ATM may impact on cellular senescence is the dependence of IGF1R (IGF-1 receptor) expression on ATM (Peretz S et al., 2001; Goetz EM et al., 2011; Ching JK et al., 2013); the mechanism remains to be elucidated, but ATM impacts on IGF-1-mediated pathways, including those that affect cellular senescence (Luo X et al., 2014).

Beta-adrenergic receptor. Another series of observations assigned ATM a protective role in cardiac myocyte apoptosis stimulated by +ACY-beta; adrenergic receptor and myocardial remodeling. Loss of *Atm* in mice induced myocardial fibrosis and myocyte hypertrophy and interfered with cardiac remodeling following myocardial infarction (Foster CR et al., 2011; Foster

CR et al., 2012; Foster CR et al., 2013; Daniel LL et al., 2014). The mechanistic aspects of these effects are still unclear, but ATM's apparent involvement in myocardial homeostasis might be relevant to the observation of elevated arteriosclerosis in A-T carriers (Swift M et al., 1983; Su Y et al., 2000).

Homology

Phosphatidylinositol 3-kinase (PI3K)-like proteins, most closely related to ATR and the DNA-PK catalytic subunit.

Mutations

The cellular phenotype of A-T represents genome instability, deficient DNA damage response (DDR), and elevated oxidative stress, in addition to a premature senescence component (Shiloh Y et al., 1982).

Germinal

Various types of mutations have been described, dispersed throughout the gene, and therefore most patients are compound heterozygotes; most mutations appear to inactivate the ATM protein by truncation, large deletions, or annulation of initiation or termination, although missense mutations have been described in the PI3 kinase domain and the leucine zipper motif.

Patients with the severe form of A-T are homozygous or compound heterozygous for null ATM alleles. The corresponding mutations usually lead to truncation of the ATM protein and subsequently to its loss due to instability of the truncated derivatives; a smaller portion of the mutations create amino acid substitutions that abolish ATM's catalytic activity (Taylor AM et al., 2015; Gilad S et al., 1996; Sandoval N et al., 1999; Barone G et al., 2009).

Careful inspection of the neurological symptoms of A-T patients reveals variability in their age of onset and rate of progression among patients with different combinations of null ATM alleles (Taylor AM et al., 2015; Crawford TO et al., 2000; Alterman N et al., 2007). Thus, despite the identical outcome in terms of ATM function, additional genes may affect the most cardinal symptom of A-T. Other, milder types of ATM mutations further extend this variability, and account for forms of the disease with extremely variable severity and age of onset of symptoms. The corresponding ATM genotypes are combinations of hypomorphic alleles or combinations of null and hypomorphic ones. Many of the latter are leaky splicing mutations and others are missense mutations, eventually yielding low amounts of active ATM (Taylor AM et al., 2015; Alterman N et al., 2007; Soresina A et al., 2008; Verhagen MM et al., 2009; Silvestri G et al., 2010; Saunders-Pullman R et al., 2012; Verhagen MM et al., 2012; Worth PF et al., 2013; Claes K et al., 2013; M+ACY-eacute;neret

A et al., 2014; Nakamura K et al., 2014; Gilad S et al., 1998).

Somatic

B A variety of missense somatic, biallelic mutations were identified in hematologic malignancies, most notably mantle cell lymphoma and T-prolymphocytic leukaemia. Missense mutations outside of the PI3 kinase and leucine zipper domains have been described among breast cancer patients, although these mutations have not been found in A-T patients. Whether these mutations contribute to breast cancer though not to ataxia-telangiectasia remains controversial.

Implicated in

Ataxia telangiectasia

Note

Ataxia telangiectasia is a prototype genome instability syndrome (Perlman SL et al., 2012; Lavin MF, 2008; Crawford TO, 1998; Chun HH et al., 2004; Taylor AM et al., 1982; Taylor AM et al., 2015; Taylor AM, 1978; Butterworth SV et al., 1986; Kennaugh AA et al., 1986).

Disease

Ataxia telangiectasia is a progressive cerebellar degenerative disease with telangiectasia, immunodeficiency, premature aging, cancer risk, radiosensitivity, and chromosomal instability.

Prognosis

Prognosis is poor: median age at death: 17 years; survival rarely exceeds 30 years, though survival is increasing with improved medical care.

Cytogenetics

Spontaneous chromatid/chromosome breaks; non clonal stable chromosome rearrangements involving immunoglobulin superfamily genes e.g. inv(7)(p14q35); clonal rearrangements.

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