## Phylogeny

ATM belongs to the phosphatidylinositol-3-kinase-related kinase (PIKK/PI3KK) family, which also comprises ATR, DNA-PKcs and mTOR (Choy & Watters, 2018; Shiloh & Ziv, 2013). All PIKKs share a conserved domain layout—N-terminal HEAT repeats followed by FAT, kinase and FATC domains—forming a distinct clade within the protein-kinase superfamily (Paull, 2015). Orthologues are present throughout eukaryotes, e.g., Tel1p in Saccharomyces cerevisiae, Rad3 in Schizosaccharomyces pombe, mei-41 in Drosophila melanogaster and Atm in mouse, underscoring a conserved role in DNA-damage signalling (Choy & Watters, 2018; Hoekstra, 1997; Lee & Paull, 2021).

## Reaction Catalyzed

ATP + protein → ADP + phosphoprotein (Choy & Watters, 2018; Paull, 2015).

## Cofactor Requirements

Requires divalent metal ions; Mn²⁺ supports optimal activity, while Mg²⁺ can substitute in some assays (Kim et al., 1999; Putti et al., 2021).

## Substrate Specificity

ATM is a Ser/Thr kinase that preferentially phosphorylates [S/T]-Q motifs, with hydrophobic residues immediately N-terminal to the SQ/TQ enhancing recognition and basic residues disfavoured (Johnson et al., 2023; Kim et al., 1999; Shiloh & Ziv, 2013). Motif analyses cluster ATM with other +1 Gln-selecting kinases, and the enzyme targets classic substrates such as p53 Ser15 (Johnson et al., 2023).

## Structure

The ~350–370 kDa polypeptide forms an inactive, non-covalent homodimer. Each protomer contains extensive N-terminal HEAT repeats, a central FAT domain, a bi-lobed C-terminal kinase domain and a terminal FATC segment (Paull, 2015; Ueno et al., 2022). In the dimer, the catalytic cleft is autoinhibited by the FAT domain; cryo-EM has revealed “closed” inactive and “open” partially active conformers (Lee & Paull, 2021; Ueno et al., 2022). The kinase fold resembles class I PI3-kinases and retains the conserved catalytic and activation loops required for ATP binding and phosphotransfer (Paull, 2015).

## Regulation

DNA double-strand breaks activate ATM through recruitment by the MRN complex (Mre11-Rad50-NBS1), promoting dimer dissociation into active monomers (Choy & Watters, 2018; Paull, 2015). Activation involves autophosphorylation on Ser1981, with additional sites Ser367 and Ser1893, and is further stimulated by acetylation of Lys3016 (Guleria & Chandna, 2016; Lee & Paull, 2021). An MRN-independent pathway activates ATM on oxidative stress via cysteine oxidation (Lee & Paull, 2021; Paull, 2015).

## Function

ATM is an apical kinase in the DNA-damage response, coordinating cell-cycle checkpoints, DNA repair and apoptosis (Shiloh & Ziv, 2013; Jin & Oh, 2019). Although predominantly nuclear, ATM also functions in cytoplasm, mitochondria and peroxisomes (Choy & Watters, 2018). Downstream substrates include p53, CHK2 and histone H2AX (Ser139) (Lee & Paull, 2021; McKinnon, 2004). Through these targets ATM regulates genomic stability, oxidative-stress responses and mitochondrial homeostasis (Guleria & Chandna, 2016).

## Inhibitors

Experimental inhibitors: KU-55933, KU-60019, KU-59403 and CP-466722.  
Clinical candidates: AZD0156 and the blood–brain-barrier-permeable AZD1390.  
Additional inhibitor: wortmannin (Jin & Oh, 2019; Hoekstra, 1997).

## Other Comments

Loss-of-function mutations in ATM cause the autosomal-recessive disorder ataxia-telangiectasia, characterised by neurodegeneration, immunodeficiency, radiosensitivity and cancer predisposition. Approximately 70 % of pathogenic variants create protein truncations; kinase-dead missense alleles also confer genomic instability and malignancy risk (Guleria & Chandna, 2016; Putti et al., 2021).

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