## Phylogeny

ATM is a serine/threonine kinase of the phosphatidylinositol-3-kinase-related kinase (PIKK) family, which also includes ATR, DNA-PKcs, mTOR, SMG1 and TRRAP. Orthologues occur in all metazoans and in yeast (Tel1), with conservation of the FAT, kinase and FATC domains, indicating an ancient eukaryotic origin (Bhatti et al., 2011; Lee & Paull, 2021; Pavletich & Warren, 2022; Shiloh & Ziv, 2013; Ueno et al., 2022).

## Reaction Catalyzed

ATP + [L-seryl/threonyl-protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-protein (Putti et al., 2021; Shiloh & Ziv, 2013).

## Cofactor Requirements

Mg²⁺ is essential for ATP binding and phosphoryl-transfer activity (Bhatti et al., 2011; Pavletich & Warren, 2022).

## Substrate Specificity

ATM preferentially phosphorylates serine or threonine residues immediately followed by glutamine (SQ/TQ motifs). Key substrates include H2AX (Ser139 → γH2AX), p53, Chk2 and components of the MRN complex (Bhatti et al., 2011; Putti et al., 2021; Shiloh & Ziv, 2013).

## Structure

• N-terminal HEAT repeats form a solenoid scaffold for partner binding.  
• C-terminal FAT, kinase and FATC domains compose the catalytic core; the kinase cleft resembles class I PI3Ks.  
• In resting cells, ATM exists as an inactive homodimer; DNA double-strand breaks induce autophosphorylation (Ser1981) and dissociation into active monomers.  
• The FAT domain contributes to autoinhibition, whereas the FATC tail is required for folding and full catalytic activity.  
(Pavletich & Warren, 2022; Bhatti et al., 2011; Lau et al., 2016; Wang et al., 2016; Shiloh & Ziv, 2013)

## Regulation

• Recruitment by the MRN complex to DNA breaks triggers Ser1981 autophosphorylation and activation.  
• Tip60 acetylates ATM (e.g., Lys3016) to achieve maximal activity.  
• PP2A and PP5 dephosphorylate ATM to terminate signalling.  
• Oxidative stress activates ATM through disulfide-bond formation.  
(Bhatti et al., 2011; Oberle & Blattner, 2010; Putti et al., 2021; Shiloh & Ziv, 2013; Ueno et al., 2022)

## Function

ATM is a master regulator of the DNA damage response, coordinating checkpoint control, homologous recombination, non-homologous end-joining and apoptosis via phosphorylation of γH2AX, p53, Chk2, BRCA1 and other effectors. Additional roles include immune development, vesicle/protein trafficking, metabolic and redox regulation. Expression is ubiquitous but highest in brain, immune tissues and proliferative cells (Amirifar et al., 2019; Bhatti et al., 2011; Lee & Paull, 2021; Putti et al., 2021; Shiloh & Ziv, 2013; Ueno et al., 2022).

## Inhibitors

Multiple experimental ATP-competitive ATM inhibitors are under pre-clinical and early clinical evaluation to potentiate radiotherapy or DNA-damaging chemotherapy, although achieving kinase selectivity remains challenging (Putti et al., 2021; Shiloh & Ziv, 2013; Williams et al., 2020).

## Other Comments

Germline loss-of-function mutations in ATM cause the recessive disorder ataxia-telangiectasia, characterised by neurodegeneration, immunodeficiency, cancer predisposition and radiosensitivity. Somatic or heterozygous “kinase-dead” mutations promote genomic instability and influence therapy responses, underscoring ATM’s tumour-suppressor role (Amirifar et al., 2019; Bhatti et al., 2011; Putti et al., 2021).

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