Ataxia-telangiectasia mutated (ATM) kinase

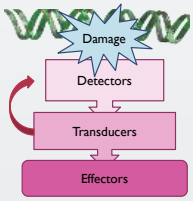
Its role in DNA damage repair

Daniel Adell Gracia, Biochemistry

UAB Universitat Autònoma de Barcelona

Objectives and introduction

- Understand the role of ATM kinase in the DNA damage repair mechanism.
- Know all the steps that drive to the activation of the kinase and the function of its substrates.
- Relate primary structure mutations with ataxia-telangiectasia and its symptoms.



The ATM protein kinase is one of the first proteins to be activated in response to double-stranded break (DSB) in DNA. It regulates three cell-cycle checkpoints, intercedes in the DNA repair mechanism, apoptosis and oxidative stress.
The DNA repair mechanism consists of a signalling network formed by **detectors** of the damage, **transducers** and **effectors**. The last ones will decide which repair mechanism will be activated. There are two main paths to repair the DNA, nonhomologous end joining (NHEJ), which is the predominant one, and homologous recombination (HR), which needs a homologous chain. ATM can activate both of them.

Ataxia-telangiectasia

The main disease associated with the loss of function of ATM is ataxia-telangiectasia, an autosomal recessive disease caused in the 71% of cases by the **premature termination of the protein kinase synthesis**.
The incidence is very low, although it is thought that the heterozygous population might be much greater. There are two type of the disease, classical, which appears mainly during the early age, and mild, which appears once the patient is already adult and the symptoms are less severe. The main symptoms are in the figure.
The patients also present sensitivity to ionizing radiation and predisposition to cancer of lymphoid origin due to the inability to repair the DNA.
Patients with residual activity of the kinase show less severity of the symptoms.

ATM activation

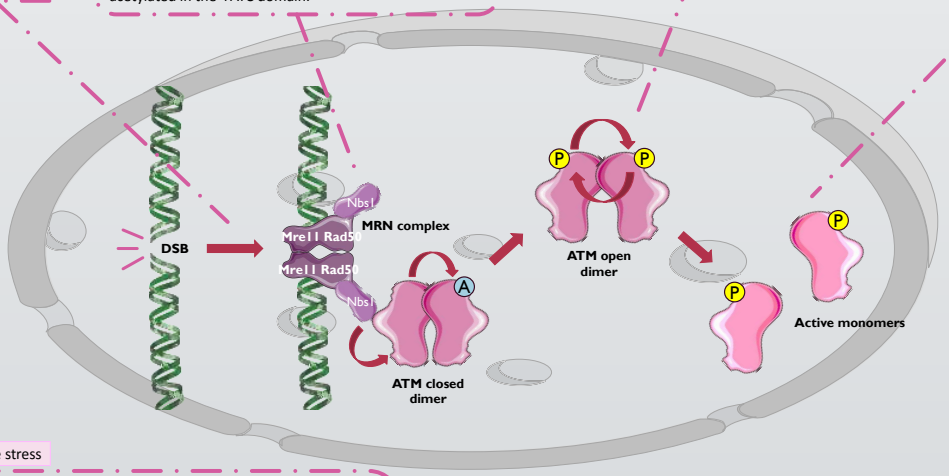
Activation by DNA damage

The induction of a DSB results in the recruitment of MRN to the site of the damage. MRN recruit ATM by interacting with the C-terminus of Nbs1.

Mre11 of the MRN complex has exonuclease activity, which would allow the resection of the DNA in the site of the damage. It is very probable that this, driven by the union of ATP, causes a conformational change in Nbs1 protein that will allow the inactive ATM dimer to be acetylated in the FATC domain.

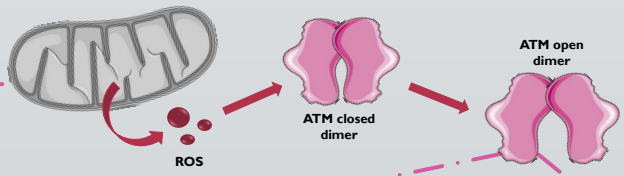
The acetylation allows the dimer to become a more relaxed open inactive dimer. This state undergoes an autophosphorylation in trans in Ser1981 of the FAT domain.

The autophosphorylation allows the dimer to become two active monomers that are capable of phosphorylate different substrates.



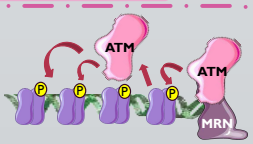
Activation by oxidative stress

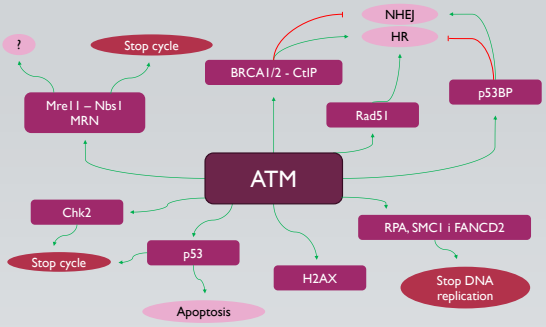
The MRN complex does not intervene in the activation of ATM by oxidative stress. The inactive dimmer of ATM does not become autophosphorylated nor monomerize, as opposed to what happen in response to DNA damage. The dimer increases its affinity for ATP in response to ROS, which indicates that there is a conformational change of the protein. Some of the substrates activated by oxidative stress are the same as for DNA damage response, even though some of them are not, which indicates that there is different substrate preferences depending on the activation path
It helps the cell to maintain homeostasis.

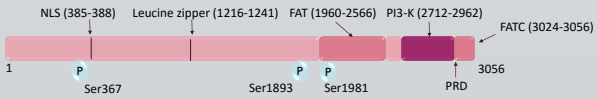


Substrates

The ATM phosphorylates Ser or Thr that are in the S/TQ motifs. The ATM substrates have this motif or a set of S/TQ motifs very close to space, what is called S/TQ cluster domains (SCDs).
One of the first substrates to be phosphorylated is histone H2AX that will allow the recruitment of more ATM. They will continue phosphorylating the histones to amplify the signal and mark the DNA position where the injury has occurred. The created platform is of great help for the subsequent recruitment of other ATM substrates involved in the damage signalling pathway, cell-cycle arrest and DNA repair mechanism, such as p53, Chk1 and Chk2, BRCA 1, and more. Therefore, ATM acts as a central activator of a big network of proteins involved in many processes.







The serine-threonine ATM kinase has 3056 amino acids, a molecular weight of 350.6 kDa and it is member of the PIKK family. Nuclear localization signal (NLS), leucine zipper (LZ), FRP/ATM/TRRAP (FAT) domain, which is necessary for the dimerization, kinase domain (PI3-K) and FAT C-terminus domain (FATC).

Relation with cancer

Patients with ataxia-telangiectasia develop tumours of lymphoid origin. ATM is essential for repairing the DNA lesions caused by the V(D)J recombination that B/T cells do. Loss of function of the protein lead to the malfunction of these cells and the increase risk of developing tumours. Also, patients have more risk of developing breast cancer due to the inability to activate BRCA1 by ATM. It has been seen that the expression of the protein in heterozygosis has a protective role against lymphomas but not breast cancer.

Conclusions

- ATM participates in marking the DNA injury by phosphorylating the histone H2AX and activates substrates related to the DNA repair mechanism and cell-cycle arrest.
- MRN complex is essential for ATM optimal activation even though it can be activated by other cell signals.
- The different mutations of the gene are related with the different degree of affectation of ataxia-telangiectasia and its increased risk of developing cancer.

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