Ataxia-telangiectasia mutated (ATM) kinase
Its role in DNA damage repair

Daniel Adell Gracia, Biochemistry

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, intermediates 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.

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, classic, 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 ionising radiation and predisposition to cancer of lymphoid origin due to inability to repair the DNA. Patients with residual activity of the kinase show less severity of the symptoms.

Ataxia-telangiectasia

Ataxia-telangiectasia is a genetic disorder that affects the development of the lymphatic system and the immune system. It is caused by a mutation in the ATM gene, which is located on chromosome 11. The ATM gene encodes a protein kinase called ATM, which is involved in the repair of DNA damage caused by radiation and other environmental factors.

The ATM kinase phosphorylates Ser or Thr that are in the S/TQ motifs. The ATM substrates have this motif or a S/TQ cluster domains (SCDs). Therefore, ATM acts as a central activator of a big network of proteins involved in many processes. The ATM phosphorylates Ser or Thr that are in the S/TQ motifs. The ATM substrates have this motif or a S/TQ cluster domains (SCDs).

Substrates

The ATM phosphorylates Ser or Thr that are in the S/TQ motifs. The ATM substrates have this motif or a S/TQ motif very close to space, what is called S/TQ cluster domains (SCDs).

Relation with cancer

Patients with ataxia-telangiectasia develop tumours of lymphoid origin. ATM is essential for repairing the DNA lesions caused by the VDJ 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 stimulates substrate recruitment to the DNA repair mechanism and cell-cycle arrest.
- ATM kinase 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 degrees of afection of ataxia-telangiectasia and its increased risk of developing cancer.