THE GENE (A-T) AND ITS GENE PRODUCT (ATM)

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Proteins and genes

Proteins are large molecules made of amino acid building blocks that control the structure, function and life cycle of the cell. Generally, each protein plays a specific role in cellular physiology and structure. Together, proteins govern the development and function of every cell in the body.

Each protein is produced in the cell according to a set of instructions contained in its gene. The gene, which is a specific segment of our DNA, determines the structure of the protein, as well as the timing and rate at which it is produced. Each cell has its own copies of the approximately 100,000 genes that make up the human blueprint. These genes are strung together along the DNA molecule. During cell division this molecule is condensed into structures called chromosomes. The genes and chromosomes are inherited, which means that copies are passed down from parent to child.

When the gene is structurally normal, the protein is made in the correct form and at the right time, and the corresponding physiological function is carried out properly. When a gene is distorted by an error (mutation), the protein is either not produced at all or is produced in an abnormal version that cannot carry out its specified function. The consequence of mutation may be a congenital malformation, a metabolic defect or a developmental abnormality. A-T is such a genetic disorder.

The A-T gene

The gene causing A-T was identified in 1995 and designated *ATM* (A-T mutated). It is a large gene on chromosome 11 that comprises more than 150,000 bases of DNA and is organized in 66 segments (exons) that contain the information for the structure of its product, the ATM protein. Mutations have been found in all parts of the ATM gene in the DNA of A-T patients. The majority of mutations that cause A-T prevent any production of the ATM protein. A very few mild cases of A-T have been caused by mutations that allow production of small amounts of otherwise normal ATM protein.

A-T GENE

- Located on chromosome 11
- Made of 150,000 DNA bases (nucleotides) and organized in 66 segments (exons)
- Encodes a protein that
  - is very large, consisting of 3,056 amino acids
  - detects damaged DNA (and perhaps other cellular stress or damage)
  - regulates cellular repair mechanisms and the life cycle of the cell

A single protein such as ATM can control the activity of many "target proteins," each one responsible for a different function.

What does the ATM protein do?

The discovery of the ATM gene opened the way for research groups to study the protein that it encodes. This was not possible before the gene was isolated, since the information contained in the gene was essential for the identification of the ATM protein. For example, one of the key ways to identify a protein is to develop antibodies that bind to it specifically. Production of such antibodies is much easier when the gene sequence is known. Another benefit of knowing the gene sequence is the ability to make an artificial ATM gene in the test tube that then can be introduced into cells where it produces large amounts of the ATM protein. No less important are "knockout mice" in which the mouse gene corresponding to the human ATM gene is mutated, producing an animal model of A-T. All these tools are now available for the study of the ATM protein and its functions.

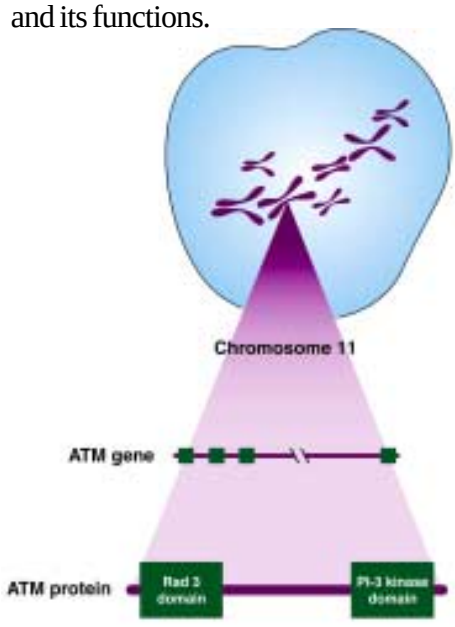

Fig. 2-1: The ATM gene on chromosome 11 encodes a large, multifunctional protein, ATM.

Extensive investigation of the ATM protein revealed a large protein of 3,056 amino acid building blocks. The ATM protein is capable of physically interacting with many other proteins in the cell, producing critical chemical modifications that alter their activity. In this way, a single protein such as ATM can control the activity of many "target proteins," each one responsible for a different function. Thus, this "Master Controller of Physiological Processes" has the power to affect multiple functions in the cell at one time.

The ATM protein is found in the nucleus of cells near the DNA. It is also found outside the nucleus, in the cytoplasm, where it is attached to various cellular structures such as vesicles. The ATM protein has two parts (domains) that have similarity to other proteins with known function. One part of the ATM protein (Rad3 domain) is characteristic of several proteins that respond to radiation damage and control cell division. The other part of the ATM protein, called the PI3-kinase-like domain, is characteristic of proteins that control the cell's response to growth signals. The enzymatic activity of ATM resides in that domain.

One of the key tasks of the ATM protein is to activate cellular responses to DNA damage caused by radiation, certain chemicals or normal cellular metabolism. This is why chromosomes of A-T patients show multiple breaks, and their cells are so sensitive to radiation. When ATM senses such DNA damage, it responds by increasing its biochemical activity, which modifies other proteins, each one responsible for a particular response. One obvious response is DNA repair. Another response is to temporarily stop the cell from dividing and allow time for repair. In normal cells, these responses usually lead to cellular recovery and continued survival following DNA damage. But if DNA damage is too extensive or ATM is not there to direct proper repair, some cells may opt to undergo a process called "programmed cell death." As a result, A-T cells are much more sensitive to radiation, and they may die or develop multiple unrepaired breaks in chromosomes. ATM functions at this important point where it is decided whether the cell will try to repair damage and survive, or instead will die.

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Sitting at this critically important junction and controlling other proteins in the area - by "talking" to some, receiving signals from others, and modifying the structure of still others - ATM controls not only DNA damage responses, but numerous processes that control cell division. Not all of these processes are understood. Thus, one of the main goals of A-T research is to identify other jobs that the ATM protein might do, and other proteins with which it physically interacts. By understanding the functions of ATM and how it performs these functions, it may be possible to design drugs that will boost those very activities that are dependent on ATM and are eclipsed in its absence. We hope it will be possible to compensate for the loss of ATM, at least in part, by augmenting in A-T patients the functions normally under ATM control.

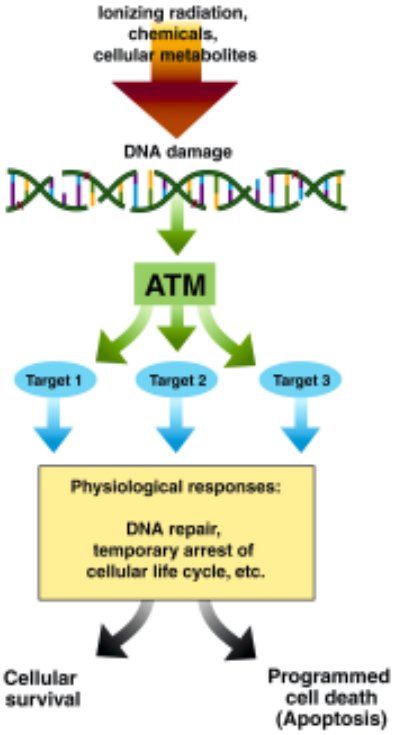

Fig. 2-2: ATM senses DNA damage and in response modifies other "target" proteins. These proteins alter the function of the cell, leading either to survival or death (apoptosis).