Recent studies on the ATM gene

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Radiosensitivity is a universal characteristic of ataxia-telangiectasia (A-T), observed after exposure of patients and of cells in culture to radiation. This sensitivity is manifested as higher levels of radiation-induced chromosomal aberrations and reduced survival compared to controls. The gene for A-T was mapped to chromosome 11q 22-23 seven years ago and more recently we have been involved in the cloning of a single gene, ATM (ataxia-telangiectasia mutated), mutated in this syndrome. ATM is a large gene, approximately 150 kb in size, composed of 66 exons and codes for a major mRNA of 13 kb with a predicted open reading frame of 9.135 kb.

It is not yet known what activity the ATM gene product possesses, but the relatedness of this gene sequence to the phosphatidylinositol 3-kinase gene family supports a role for ATM in intracellular signalling. Considerable information is already available on defective signalling through the p53 damage-inducible pathway in A-T. This includes failure to arrest at either the G1/S or G2/M checkpoints as well as radioresistant DNA synthesis. A reduced and/or delayed response in the induction of p53 after exposure of A-T cells to ionizing radiation can account for the defective G1/S checkpoint. More recently we have demonstrated that the ATM gene product is involved in the control of multiple cell cycle checkpoints. Antibodies prepared against ATM peptides demonstrate the presence of a protein 350kDa in size, which is the predicted size for this protein based on open reading frame of 9 kb. This protein is present both in the nucleus and in the cytoplasm where it is present in vesicular structures. As expected from mutation data the ATM protein is absent in cells from some patients with A-T. The cloning of the ATM gene will allow for screening of radiosensitive patients for mutations in this gene and will provide a means of identifying interacting proteins and thus an understanding of how it functions.