IONIZING RADIATION-INDUCED DNA DAMAGE AND ITS REPAIR

Malgorzata Z. Zdzienicka

Department of Radiation Genetics and Chemical Mutagenesis, MGC, Leiden University, 2333 AL Leiden, Wassenaarseweg 72, and J.A. Cohen Institute, Interuniversity Research Institute for Radiopathology and Radiation Protection, Leiden The Netherlands.

The deposition of energy in the cell by ionizing radiation results in damage to DNA, both directly and indirectly, as a effect of free radical formation. As a consequence, a variety of DNA lesion are induced, including single- and double-strand breaks (SSB and DSB, respectively), and base damages. All organisms have highly efficient mechanisms for the recognition and repair of DNA damage. The cellular response to ionizing radiation, in addition to DNA repair, includes other safeguards such as cell cycle regulation and mechanisms involved in scavenging of free radicals which are produced by ionizing radiation. Therefore, a tremendous complexity of the cellular defense mechanisms against ionizing radiation can be expected.

To dissect and elucidate these mechanisms, X-ray-sensitive mutants have been investigated in a wide variety of organisms. In humans only two hereditary disorders are shown to have clearly an increased sensitivity to ionizing radiation: ataxia telangiectasia (AT) and Nijmegen Breakage Syndrome (NBS) (reviewed in ref. 1 and 2). The recent isolation of the *ATM* (*AT Mutated*) gene for several previously established complementation groups indicate that one gene is responsible for AT (3). The existence of patients with characteristics of both, AT and NBS indicate that these two disorders are closely related, although recent studies suggest that they are distinct, since the gene(s) defective in NBS is not located at the site of the *ATM* gene (4 and 5).

As a genetic approach to analyze the mammalian cellular response to ionizing radiation, in addition to the human mutants, many X-ray-sensitive mutants have been isolated in cultured rodent cells, and at least eleven complementation groups have been identified (reviewed in ref. 6). Amongst these groups, one group has been suggested to be defective in the gene homologous to the AT gene (7).

Recently, a fruitful interaction between researchers working in different fields, such as radiobiology, biochemistry, immunology and somatic cell genetics has led to the discovery that V(D)J recombination, the process responsible for the formation of the immunoglobulin and T-receptor genes, utilize elements of the DSB repair machinery. Studies with four groups of X-ray-sensitive rodent cell mutants (groups 4, 5, 6, and 7), have led to the identification of the *XRCC4* (8), *Ku86, Ku70*, and *DNA-PK*$_{cs}$ genes (reviewed in ref. 9 and 10). Recently, mutations in XRCC4 and Ku86, have been identified in the hamster mutants of group 4 and 5, respectively, providing the direct evidence that the *XRCC4* (8) and *Ku86* (11) genes, are responsible for the observed phenotype of these groups of mutants. Sofar, mutations in DNA-PK$_{cs}$ which are responsible for the defect in *scid* mouse cells, have not been identified.

Rodent mutants have served as a tool for the isolation of the *XRCC1* and *XRCC3* genes (12 and 13) which are involved in DNA single-strand break repair. The *XRCC1* gene product is required for normal activity of DNA ligase III (14), and the *XRCC3* gene function remains unknown.

In addition to the defective repair of DNA lesions induced by ionizing radiation, defects in cell cycle progression might lead to the increased X-ray sensitivity. The phenomenon of radioresistant DNA synthesis (RDS) after γ-irradiation was the first sign of a defect in cell cycle control in AT cells. A major insight into the nature of the product of the *ATM* gene is indicated by the observation that the carboxyl terminus of this protein is similar to the catalytic subunit of phosphoinositide 3-kinase (PI 3-kinase) (3). This protein is implicated in the response to DNA damage. The ATM protein shows the functional homology to the products of several genes such as, MEC1, rad3, mei-41, TEL1 and DNA-PK$_{cs}$ which play a role in cell-cycle control in the presence of DNA damage (reviewed in ref. 15 and 16).

A recent finding that a gene located on human chromosome 4q enhances the level of inhibition of DNA synthesis after gamma-irradiation (17), indicates that the rate of DNA synthesis is regulated by numerous genes, including *ATM, NBS*, and the gene localized on chromosome 4q. The identification of hamster mutants showing RDS (18) should be helpful in the identification of these genes. Since the gene on chromosome 4q inhibits DNA synthesis after ionizing radiation without correcting the X-ray sensitivity, in terms of cell killing or chromosomal aberrations, it is indicated that RDS is not responsible for these biological consequences of RDS (19).

The isolation of the genes involved in NBS, as well as in the remaining complementation groups of rodent X-ray-sensitive mutants, and the recognition of their precise role, should further elucidate the mechanism of the cellular response to ionizing radiation and its involvement in cancer.

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