ATAXIA TELANGIECTASIA: AN INHERITED HUMAN DISEASE INVOLVING RADIOSENSITIVITY, MALIGNANCY AND DEFECTIVE DNA REPAIR

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SUMMARY

A unique feature of ataxia telangiectasia (AT), a hereditary multisystem disease, is extreme sensitivity to ionizing radiation, observed both clinically and in cell culture. Hence, we have measured the DNA repair capabilities of ten diploid fibroblast strains derived from unrelated AT donors, following anoxic $^{60}$Co γ-irradiation. Compared to two control strains, six of the ten mutant strains are markedly deficient in γ-induced repair replication. Two defective strains were defined further. While capable of rejoining single-strand breaks normally, both are impaired in the initial incision step in excision repair of base defects, assayed as γ-modified sites sensitive to a Micrococcus luteus endonuclease activity. Cell fusion studies assign three repair-deficient strains to two complementation groups; this result, coupled with a normal repair-replication ability in four of the ten AT strains, indicates genetic heterogeneity in the disease. AT strains appear otherwise normal, including their ability to repair UV damage. Aside from providing molecular insight into this complex disorder, our findings characterize AT as a γ-ray analogue of the UV-sensitive skin disease, xeroderma pigmentosum. Moreover, since AT patients are cancer-prone, faulty DNA repair is implicated in neoplastic transformation. Finally, given that (i) impaired embryonic differentiation best explains the clinical features of AT and (ii) defective DNA repair is of etiological relevance, we are led to conclude that DNA damage can lead to congenital malformations; thus, enzymatic DNA repair processes play a vital role in normal neonatal development.
INTRODUCTION

Ataxia telangiectasia (AT) (Louis-Bar syndrome) is an autosomal recessive, multisystem disorder in man clinically exhibiting progressive cerebellar ataxia, oculocutaneous telangiectasis and recurrent sinopulmonary infection (1-3). The infectious complication is associated with an immunodeficient state (4) often involving both immune systems, that is, humoral (e.g. diminished-to-absent levels of immunoglobulins IgA, IgE) and cellular (e.g. thymic hypoplasia, delayed skin-test reactivity) (3-5). Accessory manifestations typically include increased incidence of lymphoreticular malignancy (2-4), bronchiectasis (1,2), markedly elevated concentrations of serum-α-fetoprotein (6), and spontaneous chromosomal fragility (7).

Several reports (8-10) dealing with AT patients receiving standard radiotherapy for tumor treatment illustrate yet another feature of this complex disease: an unusually severe response to X-irradiation culminating in death of the patient. Laboratory studies indicate that radiosensitivity is also displayed at the cellular level. Ionizing irradiation induces chromosomal aberrations at elevated levels in leukocytes obtained from AT donors (11); in addition, diploid fibroblasts cultured from afflicted patients are deficient in their ability to form colonies following gamma (γ)-irradiation (12). In view of the well-known causal relationship between defective enzymatic repair of DNA lesions produced by an external agent and enhanced cell killing by that agent (13,14), these observations prompted us to determine the DNA repair properties of AT strains in response to 60Co γ-irradiation. Our results, summarized here, provide direct biochemical evidence that many AT strains are, in fact, deficient in enzymatic DNA repair — specifically, an excision-type repair process active on γ-ray-modified base residues. Moreover, we demonstrate the heterogeneous nature of the genetic defect in the disease, as indicated by (i) complementation between excision-deficient strains after cell fusion and (ii) the existence of strains which, although derived from patients clinically diagnosed as suffering from AT, have no apparent deficiency in their capacity to repair γ-ray-damaged DNA.

METHODS

Twelve human diploid strains, two normal and ten AT, were used: CRL 1141 and CRL 1147, established from healthy volunteers; and CRL 1312, CRL 1343, CRL 1347, AT3BI, AT4BI, AT5BI, AT7BI, AT81CTO, AT82CTO, and AT97CTO, derived from AT patients of unrelated kindred. The two normal and the first three AT strains were obtained from the American Type Culture Collection, Rockville, Maryland; the next four AT strains were kindly provided by