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Letters to the Editor

Correspondence re: M. Stephen Meyn, Ataxia Telangiectasia and Cellular Responses to DNA Damage. Cancer Res., *55:* 5991–6001, 1995

Letter

In his recent review (1) and in an earlier publication (2), Dr. Meyn has proposed that the radiosensitivity of cells from patients with the autosomal recessive disease AT[1] is the direct result of an increased level of apoptosis after irradiation. Others have proposed a similar mechanism for the radiosensitivity of AT cells (3). The hypothesis is based on the reduced extent to which AT cells respond to genotoxic stress (for example, by not increasing their levels of p53 and failing to block at multiple cell cycle checkpoints). It is also based on experimental data showing that apoptosis in SV40-transformed AT fibroblasts is greater than that in normal fibroblast cell lines and that transfection of a dominant negative construct of p53 can almost fully complement the radiosensitive phenotype of the AT cells (2).

The purpose of this letter is to point out that regardless of whether AT cells show an increased level of radiation-induced apoptosis [and there are recent data that it is only SV40-transformed AT cells that have a higher rate of radiation-induced apoptosis (4)], there is compelling evidence that apoptosis is *not* the primary reason for the radiosensitivity of AT cells. Rather, the data from several studies strongly suggest that the defect in AT cells that can account for their increased radiosensitivity is a reduced capacity to repair otherwise lethal chromosome breaks. Several years ago, in a classic study using premature chromosome condensation to determine the rate and extent of repair of chromosome breaks induced by ionizing radiation, Cornforth and Bedford (5) showed that although the initial level of chromosome breaks in fibroblasts from AT patients was the same as that in normal fibroblasts, repair of these breaks was less than in normal fibroblasts, so that the residual level of chromosome breaks was significantly higher than that in normal fibroblasts. This increased level of chromosome breaks (after repair) was also observed by Nagasawa *et al.* (6) We have also observed the same phenomenon using fluorescence *in situ* hybridization to quantitate the breaks in specific chromosomes in AT cells and in cells from normal fibroblasts and tumors (7). We found that: (*a*) the initial level of chromosome breaks was identical in all of the cell types; (*b*) the extent of repair of the radiation-induced chromosome breaks differed in the different cell lines; and (*c*) the level of chromosome breaks 24 h after irradiation could quantitatively account for the extent of cell killing determined by clonogenic assay in the different lines.

In other words, all four cell lines, including the AT fibroblast cells, had the same level of cell killing for the same level of final chromosome breaks (measured 24 h after irradiation). Because these studies were performed with cells maintained under nondividing conditions for 24 h after radiation, there were no differences in potential cell cycle arrest checkpoints between the lines, nor was there any evidence of apoptosis in the cells up to 24 h after irradiation.

Thus, although it would seem that the *AT* gene is involved in the response of cells to genotoxic stress, the defect responsible for the increased radiation sensitivity of the cells is likely to be a defect in the rejoining of chromosome breaks. This is very similar to the defect caused by a lack of the DNA-dependent protein kinase DNA-PK (8), although, in the latter case, the deficiency in chromosome break rejoining is also paralleled by a defect in double-strand break repair (9). Such is not the case with AT cells. Nonetheless, the radiation sensitivity of both mutations can be quantitatively accounted for by the increased level of chromosome aberrations after repair.

By what mechanism do chromosome breaks lead to cell killing? Although there is no definitive answer to this question, there are ample data to show that a single chromosome aberration involving an acentric fragment (caused either by a deletion or by a dicentric exchange) leads to cell death (10–12). It has been suggested that the reason for the death of cells with acentric fragments is the loss of a significant amount of genetic material (13), but it could also be that the cell, sensing misrepaired or missegregated chromosomes after one or more mitoses, undergoes apoptosis.

Thus, it seems clear that for the majority of cells of nonlymphoid origin, the primary mechanism for cell killing is the residual level of unrejoined or misrejoined chromosome breaks. Whether this death manifests itself as apoptosis or the more classic mitotically linked or necrotic cell death could depend on the genotype and cellular environment. An important feature of this model is that it can account for the fact that the level of apoptosis can be changed by manipulation of the environment or expression of certain genes without changing the overall radiation sensitivity, as has been observed (14, 15).

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[1] The abbreviation used is: AT, ataxia telangiectasia.