Susceptibility of Fanconi’s Anemia Lymphoblasts to DNA-cross-linking and Alkylating Agents

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ABSTRACT

In order to develop the usefulness of Fanconi’s anemia (FA) lymphoblast lines for biochemical and genetic studies, we have determined their sensitivity to a variety of DNA-damaging chemicals. We have adapted a growth inhibition protocol in which the sensitivity of a cell line is characterized by the drug concentration yielding a 50% inhibition of growth (EC50). The DNA-cross-linking agents, mitomycin C, nitrogen mustard, melphan, 1,3-butanediene diepoxide, cis-diaminedichloroplatinum(II), and cyclophosphamide, were all more toxic to four FA cell lines than to five normal lines. Three lines, HSC 72 (FA), 99 (FA), and 230 (FA), had EC50s that were 10 to 20 times lower than that of controls while the fourth line, HSC 62 (FA), had an intermediate EC50. Three nitrosourea compounds were also more toxic to FA cells than to controls. However, 2 normal cell lines (HSC 92 and 93) had nitrosourea EC50s 4 to 7 times lower than the other nine controls and overlapped the sensitivity of the intermediate [HSC 62 (FA)] cell line. The same 2 normal cell lines were also more sensitive than 12 other controls, including FA heterozygotes, xeroderma pigmentosum, and ataxia telangiectasia, to the monofunctional alkylating agents, ethyl methane sulfonate, methyl methane sulfonate, and N-methyl-N-nitro-N-nitrosoguanidine. Heterogeneity was also found with FA lines. Two FA cell lines (HSC 72 and 230) had EC50s lower than all control lines while one FA line (HSC 99) had an EC50 similar to that of the resistant normal lines. FA and normal cells had nearly the same sensitivity to 4-nitroquinoline-1-oxide and bleomycin. These results demonstrate that FA lymphoblast lines are more sensitive than normal cell lines to all DNA-cross-linking agents examined. These cell lines should therefore be useful for the analysis of DNA cross-link repair and the biochemical defect in FA. We have also found an unexpected sensitivity of some FA and normal lines to monofunctional alkylating agents.

INTRODUCTION

FA3 is a human genetic condition which falls within a group of ‘DNA repair’ disorders that include XP, AT, Bloom’s syn-

1 This work was supported by a grant from the Medical Research Council of Canada (MT 7220).
2 To whom requests for reprints should be addressed.
3 The abbreviations used are: FA; Fanconi’s anemia; XP, xeroderma pigmentosum; AT, ataxia telangiectasia; MMC, mitomycin C; DEB, 1,3-butanediene diepoxide; PBS, phosphate-buffered saline (137 mM NaCl, 2.7 mM KCI, 81 mM NaH2PO4, 1.5 mM KH2PO4, 0.9 mM CaCl2, and 0.5 mM MgCl2); MMS, methyl methane sulfonate; EMS, ethyl methane sulfonate; MNNG, N-methyl-N-nitro-N-nitrosoguanidine; cis-platinum, cis-diaminedichloroplatinum(II); BONU, 1,3-bis(2-chloroethyl)-1-nitrosourea; CCNU, 1-(2-chloroethyl)-3-cyclohexylyl-1-nitrosourea; TMZ, temozolomide; EC50, effective concentration of drug that gives a 50% inhibition of growth relative to untreated cells.

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purchased from the Human Genetic Mutant Cell Repository (Camden, N. J.). Cells were grown in α-medium (41) supplemented with 10% fetal calf serum without antibiotics. The cultures were maintained at 37° in a humidified atmosphere containing 5% CO₂ and the culture medium was changed twice a week. The list of cell lines used is given in Table 1.

Drugs. All drugs with the exception of MMC were stored frozen as concentrated solutions. An aliquot was thawed shortly before use, diluted, and added to the cells. The following drugs were dissolved in PBS: MMC, MMS, bleomycin sulfate, melphalan, and EMS (all from Sigma Chemical Company, St. Louis, Mo.); nitrogen mustard (The Boots Company Ltd., Nottingham, England); DEB and MNNG (Aldrich Chemical Company, Inc., Montreal, Canada); and cis-platinum and cyclophosphamide (Drug Synthesis and Chemistry Branch of the Division of Cancer Treatment, National Cancer Institute, Bethesda, Md.). BCNU, CCNU, and MeCCNU (National Cancer Institute) were dissolved in ethanol and diluted with PBS prior to use. 4NQO (Sigma) was dissolved in dimethyl sulfoxide. A 2-mg vial of MMC (Sigma) was dissolved in PBS in the dark immediately before dilution and use.

Growth Inhibition Experiments. Lymphoblasts (5 x 10⁵) were seeded in 1 ml into each well of a 24-well plate (Costar). The next day, the cell number in one of the wells was counted (the initial cell number), and the cells in the other wells were treated with various concentrations of drugs. Cells in untreated wells grew exponentially during the experiment, and both FA and control lines increased 8- to 16-fold in number. After 4 or 5 days, the cell number was counted in an electronic cell counter (Coulter Electronics, Hialeah, Fla.). The growth percentage was defined as follows:

\[
\text{Growth Percentage} = \frac{\text{number of drug-treated cells on the final day}}{\text{initial cell number}} \times 100.
\]

In the charts, the growth percentage was plotted against the logarithm of the drug concentration, and curves were fitted by eye through the points. The values in the tables are presented as EC₅₀.

RESULTS

Sensitivity of FA and Normal Lymphoblasts to DNA-cross-linking Agents. In previous studies with FA cells, survival was measured by the assay of colonies after 1 to 24 hr of drug treatment (16, 49). Since we wished to examine a wide spectrum of drugs, we developed a more practical rapid assay. This consisted of the measurement of growth with and without drugs over a period of 4 to 5 days. We have previously used such an assay effectively in other studies (6), and Moshell et al. (30) have used a slightly different method to study the sensitivity of XP lymphoblasts to UV. In Chart 1A, we show some typical results in which the effect of MMC on several strains was examined using this assay. The FA and control cells can be easily distinguished from each other. The EC₅₀ of 3 FA lines (HSC 72, 99, and 230) is in the range of 3 to 5 μM MMC, that of HSC 62 is approximately 11 μM, while those of the 5 control lines are 60 to 120 μM. The FA lines are 8 (HSC 62) or 20 (HSC 72, 99, and 230) times more sensitive than the control lines. These results are similar to those obtained when measuring the survival of fibroblasts derived from the same patients (49), thus demonstrating that the present assay is valid for the examination of sensitivity of FA cells to DNA-damaging agents.

We then proceeded to examine the effect of a variety of DNA-cross-linking agents on FA and control lines in order to establish whether sensitivity to these agents was a general characteristic of all FA lines and to see if any heterogeneity could be detected. Chart 1B illustrates the results of a typical experiment with DEB; the results are very similar to those seen with MMC. The results with the other cross-linking agents (not shown) are also very similar. The data for all drugs are presented as the average EC₅₀ in Table 2. These data are of interest in 2 respects: (a) in the comparison of the EC₅₀ of FA and control cells; and (b) in the comparison of the ability of the drugs to discriminate between FA and control lines. HSC 72 was arbitrarily taken as an index strain and its EC₅₀ was given a value of 1. The EC₅₀ of the other lines was then normalized (in parentheses in Table 2). With respect to the first parameter, it is apparent from the absolute as well as the normalized values that the increased sensitivity of FA cells is a common property for all the drugs. Furthermore, HSC 62 appears to be slightly less sensitive than the other FA lines for every drug tested. The EC₅₀ for the normal lines varies over a factor of about 2. In terms of the second parameter, DEB, MMC, and nitrogen mustard are the most toxic to cells and also result in the largest normal/FA ratios. Melphalan and cis-platinum are somewhat less toxic and give slightly lower normal/FA ratios. Cyclophosphamide is the least toxic and gives the lowest normal/FA ratio.

Table 1

<table>
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<th>Cell lines</th>
<th>Sex</th>
<th>Age of donor</th>
<th>Diagnosis of donor</th>
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<tr>
<td>HSC 3</td>
<td>M</td>
<td>Adult</td>
<td>Normal</td>
</tr>
<tr>
<td>HSC 14</td>
<td>M</td>
<td>22</td>
<td>Normal</td>
</tr>
<tr>
<td>HSC 15</td>
<td>M</td>
<td>3</td>
<td>Normal</td>
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<tr>
<td>HSC 20</td>
<td>F</td>
<td>10</td>
<td>AT</td>
</tr>
<tr>
<td>HSC 22</td>
<td>M</td>
<td>14</td>
<td>AT</td>
</tr>
<tr>
<td>HSC 49</td>
<td>F</td>
<td>9</td>
<td>Normal</td>
</tr>
<tr>
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<td>M</td>
<td>9</td>
<td>Normal</td>
</tr>
<tr>
<td>HSC 55</td>
<td>M</td>
<td>11</td>
<td>Normal</td>
</tr>
<tr>
<td>HSC 62</td>
<td>M</td>
<td>2</td>
<td>FA</td>
</tr>
<tr>
<td>HSC 71</td>
<td>F</td>
<td>Adult</td>
<td>FA heterozygote</td>
</tr>
<tr>
<td>HSC 72</td>
<td>F</td>
<td>10</td>
<td>FA</td>
</tr>
<tr>
<td>HSC 89</td>
<td>F</td>
<td>8</td>
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</tr>
<tr>
<td>HSC 92</td>
<td>F</td>
<td>12</td>
<td>Normal</td>
</tr>
<tr>
<td>HSC 93</td>
<td>F</td>
<td>9</td>
<td>Normal</td>
</tr>
<tr>
<td>HSC 99</td>
<td>F</td>
<td>19</td>
<td>FA</td>
</tr>
<tr>
<td>HSC 230</td>
<td>M</td>
<td>3</td>
<td>FA</td>
</tr>
<tr>
<td>HSC 231</td>
<td>F</td>
<td>26</td>
<td>FA heterozygote</td>
</tr>
<tr>
<td>GM2250</td>
<td>F</td>
<td>10</td>
<td>XP Group A</td>
</tr>
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</table>

* J. Mapleson, P. Sargent, R. Ishida, and M. Buchwald, unpublished results.
The above results extended the number of cross-linking agents to which FA cells are sensitive, solidifying the evidence that FA cells are specifically affected by such agents. It was next of interest to examine drugs where the mode of action is more complex. Nitrosourea analogs such as BCNU, CCNU, and MeCCNU have been reported to cause DNA cross-links in vivo and in vitro (12, 25). We therefore tested the effect of these drugs on FA and control cells. Chart 2 illustrates a typical result obtained with BCNU and Table 3 summarizes the data for all 3 compounds. The first and most important conclusion from these results is that these drugs are also more toxic to FA cells than to normal cells. However, there are some significant differences from the results obtained earlier. Whereas normal cells give a relatively uniform response with the 6 drugs mentioned above, they can be separated into 2 groups when nitrosourea is used. Depending on the nitrosourea compound used, there is a difference in EC50 of a factor of 3 to 7 between the more sensitive (HSC 92 and 93) and the other, more resistant, control lines (p < 0.02, d.f. = 7). In the case of FA cells, HSC 72 and 230 are most sensitive to all 3 drugs while HSC 99 cells are somewhat more resistant. The sensitivity of HSC 62 is nearly the same as that of HSC 92 and 93, the most sensitive control lines. Since HSC 99 seems to be less sensitive than would have been expected from the studies with the 6 cross-linking agents illustrated in Chart 1, the heterogeneity among control lines in terms of sensitivity to nitrosourea may also be present in FA lines.

**Sensitivity to Monofunctional Alkylating Agents.** Nitrosourea compounds cause monoadducts in addition to DNA interstrand cross-links (12, 25, 47). Heterogeneity with respect to the capacity to repair monoadducts caused by nitrosourea (11) or MNNG (9) and to growth after treatment with MNNG (9) has been observed in a group of human tumor lines. We therefore examined the effect of monofunctional alkylating agents using our assay system to establish if the heterogeneity that we had observed with nitrosoureas was also evident with these drugs. A typical experiment with MNNG is illustrated in Chart 3 and the complete data for that compound and EMS and MMS are presented in Table 4. HSC 92 and 93 are again more sensitive (40 times for MNNG) than all other control lines including those from FA heterozygotes, and from patients with AT and XP (p < 0.02; d.f. = 6). Heterogeneity is also evident for the FA lines.

The above results extended the number of cross-linking agents to which FA cells are sensitive, solidifying the evidence that FA cells are specifically affected by such agents. It was next of interest to examine drugs where the mode of action is more complex. Nitrosourea analogs such as BCNU, CCNU, and MeCCNU have been reported to cause DNA cross-links in vivo and in vitro (12, 25). We therefore tested the effect of these drugs on FA and control cells. Chart 2 illustrates a typical result obtained with BCNU and Table 3 summarizes the data for all 3 compounds. The first and most important conclusion from these results is that these drugs are also more toxic to FA cells than to normal cells. However, there are some significant differences from the results obtained earlier. Whereas normal cells give a relatively uniform response with the 6 drugs mentioned above, they can be separated into 2 groups when nitrosourea is used. Depending on the nitrosourea compound used, there is a difference in EC50 of a factor of 3 to 7 between the more sensitive (HSC 92 and 93) and the other, more resistant, control lines (p < 0.02, d.f. = 7). In the case of FA cells, HSC 72 and 230 are most sensitive to all 3 drugs while HSC 99 cells are somewhat more resistant. The sensitivity of HSC 62 is nearly the same as that of HSC 92 and 93, the most sensitive control lines. Since HSC 99 seems to be less sensitive than would have been expected from the studies with the 6 cross-linking agents illustrated in Chart 1, the heterogeneity among control lines in terms of sensitivity to nitrosourea may also be present in FA lines.
the release of bases, and disruption of the deoxyribose moiety (27, 31). The mechanism of DNA strand breakage by bleomycin previously observed, we next tested their sensitivity to UV and results showed that FA cells had a broader sensitivity than growth of 4 FA, 5 normal, 3 AT, and one XP lines in the presence of bleomycin and 4NQO. We therefore tested the sensitivity to UV and bleomycin (45, 46). 4NQO binds to DNA and has a mechanism of action similar to UV (26, 43). XP cells are sensitive to UV (8, 44). We therefore tested the sensitivity of FA cells. It is probable, therefore, that the defect(s) in FA is at the level of repair of the damage in DNA.

**Sensitivity to Bleomycin and 4NQO.** Since the previous results showed that FA cells had a broader sensitivity than previously observed, we next tested their sensitivity to UV and X-ray mimetic agents. Bleomycin causes DNA strand breaks, the release of bases, and disruption of the deoxyribose moiety (27, 31). The mechanism of DNA strand breakage by bleomycin is similar to that caused by X-irradiation, and AT cells have been found to be more sensitive than normal cells to both X-irradiation and bleomycin (45, 46). 4NQO binds to DNA and has a mechanism of action similar to UV (26, 43). XP cells are sensitive to 4NQO and UV (8, 44). We therefore tested the growth of 4 FA, 5 normal, 3 AT, and one XP lines in the presence of bleomycin and 4NQO.

As illustrated in Chart 4A, AT cells are, as expected, more sensitive to bleomycin than controls or FA cells. However, there is no difference between FA and control lines (p > 0.05, d.f. = 2), the sensitivity of HSC 99 is similar to that of the rest of the controls. As was observed with the nitrosourea compounds, the EC50 of HSC 62 is comparable to those of HSC 92 and 93.

**DISCUSSION**

Among the DNA-cross-linking agents we have examined, MMC has been the drug most commonly used in studies of FA cells. MMC has been found to be more toxic to FA cells than to normal cells, causing an increased number of chromosome breaks in fibroblasts and lymphocytes as well as decreased survival in fibroblasts and lymphoblasts (16, 23, 28, 35, 36, 49). Nitrogen mustard and DEB have also been shown to induce a high frequency of chromosome breaks in FA cells (2, 3) as well as to cause DNA cross-links (29, 33). We have extended these observations by demonstrating that MMC as well as the latter 2 drugs are more toxic to FA lymphoblasts than to controls cells. We have also shown that cis-platinum, melphanal, and cyclophosphamid are more effective in inhibiting the growth of FA cells. These 3 drugs are known to cause DNA cross-linking in vivo and in vitro (5, 21, 33) but have only been occasionally (e.g., Ref. 4), if at all, used to study FA cells. Therefore, DNA-cross-linking drugs can be used to separate control and FA lines into 2 groups, one resistant (control) and one sensitive (FA) to the cytotoxic action of these drugs.

In our earlier studies using MMC (49), we had found what seemed to be 2 classes of FA cells, one more sensitive than the other. Our present results indicate that this is also true for the other cross-linking agents. HSC 72, 99, and 230 were always very sensitive whereas HSC 62 had an intermediate sensitivity relative to controls. The difference between HSC 62 and the other 3 FA lines may represent allelic variation or separate genetic groups. Complementation experiments between these lymphoblast lines are in progress and may help answer this question.

Without exception, the pattern of sensitivity of FA cells is similar for all of these compounds, even though the drugs have a variety of interactions with the cells. For example, MMC requires activation by a NADPH-generating system (22) before it will cross-link DNA while melphanal does not (32), yet FA cells have similar sensitivities to the 2 drugs. Similarly, the various cross-linking agents are transported by either carrier-dependent or -independent systems (7), suggesting that defects in such systems are an unlikely cause of the increased sensitivity of FA cells. It is probable, therefore, that the defect(s) in FA is at the level of repair of the damage in DNA.

Nitrosourea analogs such as BCNU, CCNU, and MeCCNU have been shown to produce interstrand cross-links (12, 25, 35, 36, 49). The other control cell lines examined were HSC 3, 14, 15, 49, 50, 55, and 89 for BCNU and CCNU and HSC 3, 15, and 49 for MeCCNU.

### Table 3

<table>
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<tr>
<th>Compound</th>
<th>EC50 (µM)</th>
<th>Other control cell lines</th>
</tr>
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<tbody>
<tr>
<td>BCNU</td>
<td>3.0 ± 0.2 (8.8)</td>
<td>13 ± 4 (38)</td>
</tr>
<tr>
<td>CCNU</td>
<td>1.0 ± 0.6 (6.3)</td>
<td>5 ± 2 (35)</td>
</tr>
<tr>
<td>MeCCNU</td>
<td>2.8 ± 0.1 (12)</td>
<td>15 ± 4 (65)</td>
</tr>
</tbody>
</table>

*The differences between the values of the 4 FA Lines and that of all controls was significant to p < 0.005 (d.f. = 11) (BCNU and CCNU) and to p < 0.02 (d.f. = 7) (MeCCNU).*

*The other control cell lines examined were HSC 3, 14, 15, 49, 50, 55, and 89 for BCNU and CCNU and HSC 3, 15, and 49 for MeCCNU.*

*Mean ± S.D. from 2 to 3 experiments.*

*Numbers in parentheses, ratios of the average EC50 to that of HSC 72.*

While HSC 72 and 230 are very sensitive to the alkylating drugs [3 to 10 times more sensitive than HSC 92 and 93 (p < 0.05, d.f. = 2)], the sensitivity of HSC 99 is similar to that of the rest of the controls. As was observed with the nitrosourea compounds, the EC50 of HSC 62 is comparable to those of HSC 92 and 93.
Table 5

<table>
<thead>
<tr>
<th>Compound</th>
<th>MMC ( \times 10^3 )</th>
<th>BCNU</th>
<th>MNNG</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSC 92 (normal)</td>
<td>3.0 ± 1.9 (0.9)</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>HSC 99 (FA)</td>
<td>38 ± 5.0 (11.0)</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>HSC 62 (FA), 72 (FA), and 230 (FA)</td>
<td>24 ± 4.1 ± 0.01 (1.1)</td>
<td>S</td>
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</tr>
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</table>

Sensitivity of lymphoblasts to DNA-damaging drugs

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>MMC</th>
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<th>MNNG</th>
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<tr>
<td>Most controls</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>HSC 92 (normal) and 93 (normal)</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>HSC 99 (FA)</td>
<td>S</td>
<td>S</td>
<td>R</td>
</tr>
<tr>
<td>HSC 62 (FA), 72 (FA), and 230 (FA)</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>

 MMC, BCNU, and MNNG are taken as prototypes of the drugs in Tables 2, 3, and 4, respectively.

The strains are considered resistant (R) if their \( EC_{50} \) for a particular drug is similar to that of most of the control strains (for example, HSC 3). They are considered sensitive (S) if their \( EC_{50} \) is significantly different (\( p < 0.05 \)) from that of those control lines.

Compounds such as MNNG are known to cause monofunctional alkylating damage to bases (39). We have found no correlation between the presence of the FA gene and the sensitivity of lymphoblast lines to this and the other alkylating agents. However, among both controls (HSC 92 and 93) and FA lines (HSC 72 and 230), there are lines that are significantly more sensitive than others to the toxicity of these drugs. The classification of lines as sensitive or resistant is summarized in Table 5. Since nitrosoureas are also known to cause alkylating damage (25, 47), it is probable, on the basis of the results with MNNG, that the sensitivity of HSC 92 and 93 to nitrosourea is the result of their inability to repair alkylations rather than cross-links.

We have found previously (49) that fibroblasts derived from FA patients and controls have a similar sensitivity to monofunctional alkylating agents but have now found that some FA lymphoblast lines are sensitive to these drugs. Similar observations have been reported by others studying human SV40-transformed and tumor lines. A phenotype called mer\(^-\) (9) [or
mex- (40) has been described as an increased sensitivity to the toxic action of MNNG (9, 40) and nitrosourea (11) and as decreased capacity to remove O6-alkylguanine adducts in DNA of cells exposed to these compounds (9, 11, 40). Normal (untransformed) strains are mer*, and some, but not all, SV40-transformed lines derived from these mer* strains are mer-.

On the basis of patterns of sensitivity summarized in Table 5, we suggest that lines HSC 92, 93, 72, and 230 are mer- while HSC 99 and the rest of the controls are mer*.

While writing this paper, 2 reports have been published in which lymphoblast lines from patients with XP and AT were examined for sensitivity to alkylating agents (38, 40). Both mer* and mer- phenotypes were found among the XP and AT lines. There was no difference in sensitivity to MNNG or in the capacity to remove O6-methylguanine between mer- lines from patients or controls. In contrast, the mer- phenotype seems to interact with the FA repair defect since both HSC 72 and 230 are severalfold more sensitive to MNNG than HSC 92 and 93.

The origin of the increased sensitivity to MNNG (most probably the mer- phenotype) is not known. It may be due to a major polymorphism in the human population that can only be observed in transformed lines. This question could be answered by comparing the mer phenotype of SV40-transformed and lymphoblast lines derived from the same donor. Lack of concordance in the mer phenotype would argue against the existence of such a polymorphism. Alternatively, the mer- phenotype may be a consequence of the transformation event(s) that result in the establishment of the cell line. The mechanism(s) by which this event could occur is not understood at this time.

Lymphoblasts are permanent cell lines that grow in suspension. Those derived from patients with FA do not show the growth defect manifested by FA fibroblasts (10, 49). In spite of this growth difference, the basic FA phenotype is still expressed, since FA lymphoblasts are uniformly sensitive to all DNA-cross-linking agents tested. These features of FA lymphoblasts should make them extremely useful in studies aimed at the elucidation of the basic defect in the disease.

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FA Lymphoblasts
Susceptibility of Fanconi's Anemia Lymphoblasts to DNA-cross-linking and Alkylating Agents

Ryoji Ishida and Manuel Buchwald


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