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ULTRAVIOLET-INDUCED DNA EXCISION REPAIR IN HUMAN B AND T LYMPHOCYTES. III. REPAIR IN LYMPHOCYTES FROM CHRONIC LYMPHOCYTIC LEUKAEMIA

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SUMMARY

There have been conflicting reports about the capacity of lymphocytes from individuals with chronic lymphocytic leukaemia (CLL) to undertake u.v.-induced DNA repair. We have examined repair in CLL cells and in control and age-matched purified B and T lymphocytes by a technique independent of incorporation of radioactive precursor, i.e. by the recovery of normal sedimentation behaviour of nucleoid bodies obtained from these cells by lysis in high salt and non-ionic detergent. Recovery of normal sedimentation is associated with restoration of DNA supercoiling. CLL cells were found to be as sensitive to u.v. and to repair at similar rates as age-matched B controls. They are considerably more sensitive than young B cells and repair less efficiently. Reasons for the reported discrepancies in CLL repair are discussed.

INTRODUCTION

Chronic lymphocytic leukaemia (CLL) is predominantly a disease of the elderly, characterized at the cellular level by an accumulation of largely non-dividing and inert lymphocytes. The presence of IgM immunoglobulins on the surface of lymphocytes from patients with CLL suggests that these cells are of B origin (Seligman, Preud-Homme & Brouet, 1973), and that those in the peripheral circulation are arrested in a pre-*S* phase state (Lopez-Sandoval, Moayeri & Sokal, 1974).

The capacity of CLL cells to repair ultraviolet-induced damage has been the subject of a number of conflicting reports. For example, it has been argued on the basis of incorporation of labelled thymidine into DNA following u.v. that the rate of excision repair in CLL lymphocytes is considerably higher than in control unfractionated cells (Huang, Kremer, Laszlo & Setlow, 1972). Other studies, however, have either failed to find or confirm this phenomenon (Evans & Norman, 1968; Frey-Wettstein, Longmire & Craddock, 1969; Ringborg & Lambert, 1977). It has also been reported that the rates of dimer excision and rejoining of X-ray induced strand breakage in phytohaemagglutinin (PHA)-stimulated CLL cells are far higher than in stimulated control unfractionated lymphocytes (Huang *et al.* 1972), though there is considerable uncertainty about the capacity of CLL cells to respond to PHA or other more favourable mitogenic stimulation (Smith, Cowling & Barker, 1972; Monahan, Fritz & Abell, 1975). It has also been reported that the survival of non-proliferating CLL lymphocytes

following u.v. irradiation is considerably greater than normal unfractionated and unstimulated cells (Huang, 1975).

Since the large majority of CLL cells are non-proliferating it is not feasible to use conventional physical techniques to determine DNA breakage and repair because these require prior labelling of the DNA with a radioactive precursor (e.g. Ahnström & Edvardsson, 1974; Fornace, Kohn & Kahn, 1976; Collins, 1977). As with our previous studies on repair in resting B and T lymphocytes (Yew & Johnson, 1978, 1979) we have followed the loss and recovery of DNA superhelicity in nucleoid bodies obtained from CLL lymphocytes by lysis in high salt and non-ionic detergent. Single-strand nicks introduced by ultraviolet light-induced repair release supercoiling constraints and result in slower sedimentation of nucleoids in sucrose gradients presumably because of their more relaxed structure. By inference repair restores supercoiling and the sedimentation behaviour returns to control values. This technique has proved to be very sensitive in detecting ultraviolet-induced repair in human lymphocytes (Cook & Brazell, 1976; Cook, Brazell, Pawsey & Giannelli, 1978; Yew & Johnson, 1978, 1979).

In view of the conflicting findings in CLL repair we have examined the repair of u.v.-induced DNA damage in CLL lymphocytes by a method independent of the incorporation of labelled thymidine, i.e. by nucleoid sedimentation behaviour, and have compared it with the repair capacity of purified populations of age-matched human B and T cells. We have also compared the u.v. survival characteristics of CLL lymphocytes with normal unstimulated B and T cells.

MATERIALS AND METHODS

Human peripheral blood was collected from the Regional Blood Transfusion Centre 1 day before each experiment and from healthy volunteers aged over 60 years. Lymphocytes were purified by centrifugation on Lymphoprep (Nyegaard & Co.) (Boyüm, 1968). B and T cells were separately purified by rosetting with sheep red blood cells and binding with rabbit anti-human-gammaglobulin serum (Barker, Worman & Smith, 1975) details of which have been described previously (Yew & Johnson, 1978).

CLL lymphocytes from untreated patients were kindly provided within 48 h of collection by Professor D. A. G. Galton and Dr D. Catovsky from the Medical Research Council Leukaemia Unit, Royal Postgraduate Medical School, Hammersmith Hospital, London. All CLL patients in this study were aged between 60 and 73 years. These lymphocytes were immediately rebanded by centrifugation on Lymphoprep and used for experiments on the same day.

One millilitre of either B, T or CLL cells (10^6 per ml) in ice-cold phosphate-buffered saline in a Petri dish were irradiated with ultraviolet light using a Philips germicidal tube emitting predominantly at 254 nm and measured by an International Light IL500 radiometer, recently calibrated to within 3% accuracy by the National Physical Laboratory, Teddington. A dose rate of 0·1 J m^{-2} s^{-1} was administered. After irradiation the cells were rapidly transferred to growth medium (Eagle's Minimal Essential Medium supplemented with 20% dialysed foetal calf serum) (Gibco-Bio: Cult Laboratories), and incubated for 1 h in a CO_2 incubator in the dark. The preparation and sedimentation of nucleoids was carried out essentially as described by Cook & Brazell (1976). 1×10^5 cells in a 50-μl sample were layered on 150 μl of a lysis mixture (2 M NaCl, 0·01 M EDTA, 0·5% Triton X-100, pH 8·0) above an isokinetic sucrose gradient (McCarthy, Stafford & Brown, 1968) (15–25% sucrose 4·8 ml, containing 2 M NaCl EDTA, pH 8·0). The gradients were centrifuged at 30000 rev/min in a Beckman SW 50 L rotor, at 20 °C for 20 min, or 30 min, so as to obtain a nucleoid band midway along the gradient. After centrifugation, the gradients were displaced using a gradient fractionator (Instrumentation

Specialities Co. Ltd.) and monitored for absorbance at 254 nm. The sedimentation behaviour of the nucleoids is expressed as a ratio of the distance travelled in the gradient relative to that of the nucleoids from unirradiated cells co-spun in one of the three tubes of the rotor. The zero time ratio was determined for cells after irradiation but without incubation. The deviation of corresponding points in various experiments was approximately 10%. Since nucleoids from unirradiated CLL lymphocytes sediment at different rates (see below), the ratio of nucleoid sedimentation for irradiated versus unirradiated is normalized for each CLL patient. One determination was made for each CLL patient.

For survival studies cells at a concentration of 2×10^6 per ml were irradiated in cold phosphate-buffered saline at a dose rate of 0·1 J m^{-2} s^{-1} for various times. After irradiation they were concentrated by centrifugation and transferred into growth medium supplemented with 20% dialysed serum at a final concentration of 10^6 cells per ml in tightly stoppered tubes, and incubated for 60 h at 37 °C in the dark. Tubes were shaken at intervals of 20 h. After incubation, four 0·1-ml samples were taken and each mixed with 0·4 ml 0·1% Trypan blue in phosphate-buffered saline. At least 200 cells were scored using a haemocytometer; cells were adjudged viable if they excluded the dye, and an average of the 4 determinations calculated.

RESULTS AND DISCUSSION

Nucleoid sedimentation

When repair is permitted the sedimentation behaviour of nucleoids prepared from u.v.-irradiated cells is characteristically biphasic (Fig. 1). An initial decrease in the relative sedimentation rate against an unirradiated control is followed by an increase so that normal sedimentation is approached. By inference incision activity predominates at early times removing superhelicity and causing a reduction in nucleoid sedimentation speed. Thereafter the balance between incision and ligation activities shifts progressively towards ligation which restores DNA superhelicity and thus increases the sedimentation speed. As judged by the return to normal nucleoid sedimentation behaviour, human B and T lymphocytes are capable of complete repair provided that the u.v. dose does not exceed 0·5 J m^{-2}. At higher u.v. doses nucleoid sedimentation takes longer to approach control unirradiated values. At all u.v. doses tested, however, B cells recovered faster than T (Yew & Johnson, 1978, 1979).

In the present study the lymphocytes from each CLL patient showed diminished capacity to restore DNA tertiary structure over the range of u.v. tested (0·5, 2 and 10 J m^{-2}) and particularly at the higher doses, and over a similar time scale compared with both normal B and T cells from younger individuals (aged 18–40) (Fig. 1). This suggests that the repair capacity in CLL lymphocytes is more readily saturated with photochemical damage. It should be noted, however, that the competence of normal T lymphocytes to undertake u.v.-induced incision repair, as judged by the rate of incorporation of [^{3}H]thymidine into acid-insoluble radioactivity, falls with increasing age (Lambert, Ringborg & Swanbeck, 1977), and we therefore examined the recovery of superhelicity in normal B and T cells from individuals aged over 60 years (Fig. 1). Compared with B and T lymphocytes from younger persons the restoration of DNA superhelicity was retarded particularly after 2 and 10 J m^{-2} and to a degree similar to that observed in the CLL cells. This suggests that the diminished u.v.-induced repair capability of CLL cells is an age-related rather than a leukaemic-related phenomenon. Thus for both B and T lymphocytes there is clear evidence that DNA repair

capacity diminishes with age. For fibroblasts, however, the situation is less clear (Painter, Clarkson & Young, 1973; Clarkson & Painter, 1974; Hart & Setlow, 1976).

Unirradiated CLL nucleoids may be readily distinguished from their normal counterparts by their more rapid initial sedimentation (Table 1). T and B nucleoids from unirradiated young and old control lymphocytes show very similar initial sedimentation rates. CLL nucleoids, however, show considerable heterogeneity in this respect, which might reflect different stages of the disease in the 6 patients or the involvement of different populations of cells in the disease. Unfortunately, for unknown reasons, different cellular components cannot be separated from an initially mixed population by nucleoid sedimentation (e.g. B from T lymphocytes, Yew & Johnson, 1978; G_1 from S from G_2 cells, Warren & Cook, 1978). There is, however, a good correlation between the initial sedimentation rate of nucleoids and the position occupied by the cell in the cycle at the time of preparation (Warren & Cook, 1978). Nucleoids prepared from mitotic cells sediment more slowly than from G_1, and G_1

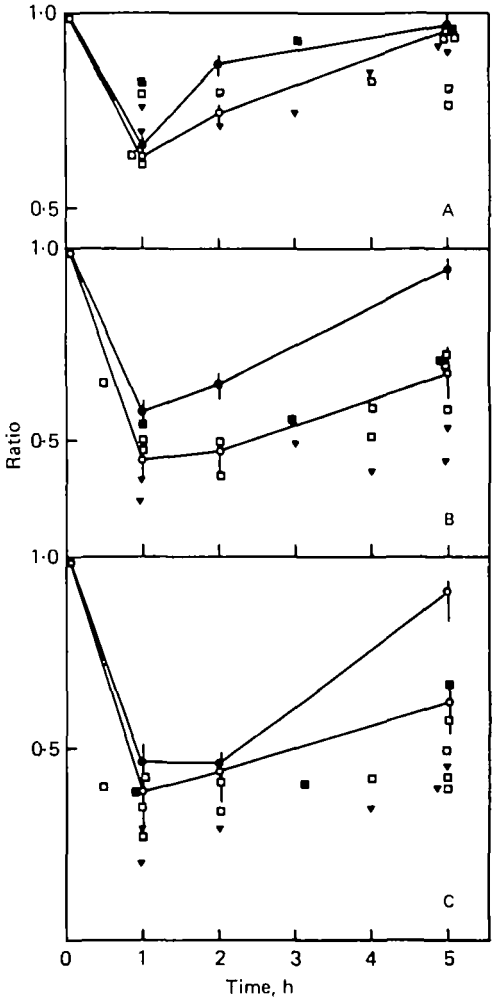

Fig. 1. For legend see facing page.

nucleoids sediment more slowly than those from *S*-phase. The reason for such consistent cyclical changes in sedimentation behaviour is not yet clear, but we also find that nucleoids from PHA-stimulated T lymphocytes (16 h after stimulation and therefore not yet in *S*-phase) sediment faster under similar centrifugation conditions than nucleoids from unstimulated cella (Table 1). The sedimentation behaviour of CLL nucleoids suggests that these cells occupy a different position in pre-*S* phase than control B cells and also that the precise position in G_1 may vary from one patient to another. Support for this conclusion comes from work by Hittelman & Rao (1978) who have used the morphology of prematurely condensed chromosomes (PCC) to construct an index of cell cycle position. They have examined PCC from bone marrow cells of patients with a variety of leukaemias including CLL. Compared with bone marrow cells of patients with solid tumour (i.e. no bone marrow involvement) the PCC of leukaemic origin were generally elongated and characteristic of PCC from a later position in G_1 phase (Schor, Johnson & Waldren, 1975; Rao, Wilson & Puck, 1977).

Table 1 also includes data on the concentration of ethidium bromide (EB) required to minimize superhelicity in CLL and control B and T nucleoids, and as such provides preliminary information about the degree of superhelicity in these cells. Normal B and T cells show identical sedimentation profiles in the presence of increasing amounts of EB (Yew & Johnson, 1978) indicating that their DNA has similar superhelical density. CLL nucleoids also show the standard biphasic response to EB showing that

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Fig. 1. Patterns of sedimentation of human B, T and CLL lymphocyte nucleoids after different amounts of u.v. irradiation. Nucleoids were prepared from the lymphocytes at the following times during incubation at 37 °C: 0, 0·5, 1, 2, 3, 4 and 5 h. The distance sedimented by u.v.-irradiated nucleoids in isokinetic sucrose gradients is expressed as the ratio of the distance travelled relative to reference mock-irradiated nucleoids sedimenting under the same conditions. The data in each figure result from a number of experiments. Purified B (●) and T (○) cells were obtained from pooled blood samples donated by the Regional Blood Transfusion Service, and collected from healthy individuals aged between 18 and 40. The points on these curves represent: for B cells, the mean values and range of the 4 separate experiments; for T cells, the mean values and range of 10 separate experiments.

The CLL points (□) represent single sedimentation ratio determinations for different individuals normalized against the mock-irradiated controls. It was necessary to do this on an individual basis because of the different initial sedimentation rates of the unirradiated CLL cells from different patients. Complete sets of time points were not taken for each CLL population. The sedimentation behaviour of nucleoids from purified T cells from 2 healthy individuals aged over 60 are presented separately (▼). One experiment was carried out on purified B cells pooled from 4 healthy individuals aged over 60 (■). Lymphocytes were ultraviolet or mock-irradiated, transferred into growth medium and incubated for different times at 37 °C. At each time 50-μl samples containing 1×10^5 cells were added directly to the lysis buffer which was layered on top of the sucrose gradient. The centrifugation was carried out at 30000 rev/min for 20 or 30 min. A ratio of 1 refers to unirradiated nucleoids sedimenting under standard conditions in a reference tube; the distance sedimented by the u.v.-irradiated nucleoids under the same conditions (in the same rotor at the same time) is expressed as a ratio relative to the distance sedimented by the unirradiated nucleoids. A. 0·5 J m^{-2}; B, 2 J m^{-2}; C, 10 J m^{-2}.

their DNA is supercoiled, but the amount of EB needed to minimize superhelicity is somewhat greater than for control cells. This may indicate a difference in the superhelical density of CLL DNA, although further work is needed to confirm this point.

Survival

As judged by their survival curves the u.v. sensitivity of B lymphocytes increases with age. For T cells there is little apparent change – they are always exceedingly sensitive. Though there is some variation in the survival of cells from different CLL

Table 1. *Sedimentation data for CLL patients and normal donors*

CLL patient	Age	Ratio	Concentration of ethidium bromide (μg/ml) required to minimize the nucleoid sedimentation ratio
1	62	1·38	6
2	68	1·19	4
3	60	1·28	4
4	65	1·2	n.d.
5	70	1·1	6
6	73	1·2	n.d.
Normal donors	18–40	1·0	3–4
Phytohaemagglutinin-stimulated normal lymphocytes (16 h stimulation)*	18–40	1·5	n.d.

* Difco Bacto – PHA reconstituted to 5 ml, using 1 μl/ml. n.d., not done.

The initial nucleoid sedimentation ratios of the unirradiated CLL lymphocytes and the control purified B or T cells were obtained by comparing the distances sedimented by the nucleoids in the sucrose gradients under the same conditions at the same time. Under standard conditions (30000 rev/min, 20 min) nucleoids of B and T cells from healthy individuals sediment to a similar distance (deviation among experiments 10%) regardless of the age of the donor. The initial sedimentation ratio for each CLL nucleoid preparation was measured once. The initial sedimentation ratio of pooled phytohaemagglutinin-stimulated normal lymphocytes from healthy young individuals 16 h after stimulation was determined by comparing the distance sedimented by their nucleoids with that of their unfractionated unstimulated counterparts (from the same pooled blood) cosedimented for reference at the same time. The range of ethidium bromide concentrations used to titrate the minimum nucleoid sedimentation ratio was 0 to 20 μg/ml and the minimum ratio was obtained by comparing the distance sedimented by nucleoids in sucrose gradients containing ethidium bromide with the distance travelled by a co-spun nucleoid from the same individual in the absence of ethidium bromide.

patients, they are similar in sensitivity to age-matched B lymphocytes, i.e. considerably more sensitive than young B cells (Fig. 2). The CLL result is compatible with their low-repair capacity demonstrated by nucleoid behaviour, but contrasts with a report by Huang (1975) which concludes the CLL cells are much less sensitive to u.v. than unfractionated normal lymphocytes, and is based on a different technique the full details of which and its controls have not been published.

Our results do not support the conclusion by Huang *et al.* (1972) that CLL lymphocytes have enhanced DNA repair capacity. We have measured repair by a technique

independent of the incorporation of radioactive precursor and one which measures the reconstitution of superhelical DNA. We find that CLL lymphocytes, like their normal counterparts, are extremely sensitive to u.v. irradiation, and have limited ability to repair damage. Presumably their long-patch repair capacity is subject to the same constraints that limit repair in normal lymphocytes, e.g. DNA precursor availability (Yew & Johnson, 1979).

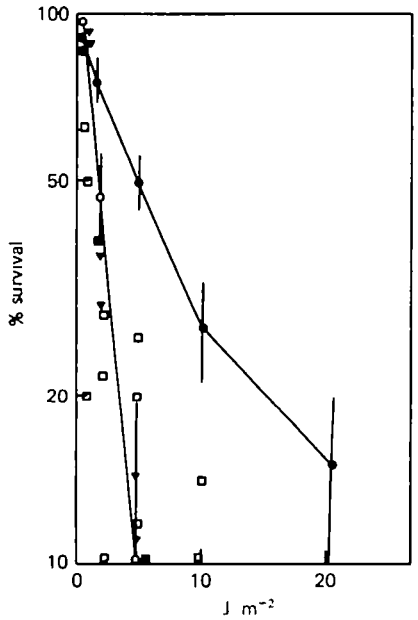

Fig. 2. Survival of unstimulated lymphocytes estimated by Trypan blue dye exclusion 60 h after ultraviolet irradiation. The curves for purified B and T cells from young healthy individuals represent the mean and range of 3 and 10 experiments respectively. CLL lymphocytes from 6 patients were tested for survival though no attempt is made to separate the individual curves; the full range of u.v. doses was not given to each CLL population. Survival of purified T cell population from 2 healthy individuals aged over 60 are presented separately. One survival experiment was carried out on purified B cells pooled from 4 healthy individuals aged over 60. ●, B lymphocytes; ○, T lymphocytes; □, CLL lymphocytes; ▼, age-matched normal T lymphocytes; ■, age-matched normal B lymphocytes.

It is possible that the high rate of incorporation of [^{3}H]thymidine into DNA reported in u.v.-irradiated CLL cells in the absence of hydroxyurea (Huang *et al.* 1972) consists largely of semi-conservative synthesis. For example, other workers have reported up to 20-fold increase in [^{3}H]thymidine uptake (presumably a measure of DNA synthesis) in unirradiated populations of CLL than in control unfractionated lymphocytes (Lopez-Sandoval *et al.* 1974). In addition, in the presence of hydroxyurea the amount of DNA synthesis in CLL lymphocytes is significantly reduced (Ringborg & Lambert, 1977). Despite the possibility that enhanced thymidine incorporation follows u.v. irradiation of CLL cells (Huang *et al.* 1972), and there is more evidence to the contrary (Evans & Norman, 1968; Frey-Wettstein *et al.* 1969; Ringborg & Lambert, 1977),

we find that the final rate of ligation of the phosphodiester bond is no faster in these cells than in either normal B or T lymphocytes.

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