DNA damage, which is left unrepaird by excision repair pathways, often blocks replication, leading to lesions such as breaks and gaps on the sister chromatids. These lesions may be processed by either homologous recombination (HR) repair or translesion DNA synthesis (TLS). Vertebrate Polk belongs to the DNA polymerase Y family, as do most TLS polymerases. However, the role for Polk in vertebrate cells is unclear because of the lack of reverse genetic studies. Here, we generated cells deficient in Polk (polk cells) from the chicken B lymphocyte line DT40. Although purified Polk is unable to bypass ultraviolet (UV) damage, polk cells exhibited increased UV sensitivity, and the phenotype was suppressed by expression of human and chicken Polk, suggesting that Polk is involved in TLS of UV photoproduct. Defects in both Polk and Rad18, which regulates TLS in yeast, in DT40 showed an additive effect on UV sensitivity. Interestingly, the level of sister chromatid exchange, which reflects HR-mediated repair, was elevated in normally cycling polk cells. This implies functional redundancy between HR and Polk in maintaining chromosomal DNA. In conclusion, vertebrate Polk is involved in Rad18-independent TLS of UV damage and plays a role in maintaining genomic stability.

A wide range of potential insult to the genomic DNA is contributed not only by the environment, but also by cellular activities. DNA damages, which are left unrepaird by excision repair pathways, may arrest DNA replication, leading to breaks and gaps on the sister chromatids. These lesions are processed by two major postreplication repair pathways: homologous recombination (HR) repair and translesion DNA synthesis (TLS) (1). TLS fills a daughter strand gap that encompasses a DNA damage on the template strand by employing a number of specialized DNA polymerases (Pols) (reviewed in Refs. 2–4). On the other hand, HR functions in processing both gaps and breaks by facilitating recombination between damaged sister chromatids with the other intact ones. Thus, daughter-strand gaps can be processed by both TLS and HR in postreplication repair.

Human cells contain four Y family DNA polymerases, namely Polδ (Rad30A), Polγ (Rad30B), Polc (DinB1), and Rev1 (5–7). A number of biochemical studies have demonstrated that Y family DNA polymerases can bypass specific lesions on the template strand (8–12), whereas in vivo function of these polymerases are as yet unclear except for Polδ. Polδ is mutated in a variant form of xeroderma pigmentosum (XP-V) (13, 14), which is characterized by predisposition to skin cancer and elevated UV sensitivity.

Human Polk is a homolog of Escherichia coli DinB (pol IV) and a member of DNA polymerase Y family (15, 16). Induction of mutations by overexpression of Polk in mammalian cells is in agreement with its role in TLS (16). Likewise, purified human Polk can bypass adducts of N-2-acetylaminofluorene (AAF) and benzo[α]pyrene (BaP), and templates of 8-oxoguanine, abasic site and 1,N4-ethenedeoxyadenosine. By contrast, Polk is unable to bypass UV radiation-induced photoproducts or cisplatin adducts (8, 10, 12, 17–20).

Genetic studies of Saccharomyces cerevisiae suggest that all known components of TLS belong to the epistasis group of the RAD6-RAD18 genes (21, 22), which are conserved from yeast to mammalian cells (23–27). The Rad6 protein is one of the ubiquitin-conjugating enzymes (E2s) and forms a tight complex with the Rad18 protein, which may have E3 ubiquitin ligase activity (28, 29). Although all TLS is under Rad18 control, S. cerevisiae does not have a POLK gene. On the other hand, Schizosaccharomyces pombe does have a POLK ortholog, but no data about genetic relationship between Polk and Rad18 has been obtained. Similarly, it is not known whether Polk is regulated by Rad18 in vertebrate cells.

Here we present a phenotypic analysis of Polk-deficient cells (hereafter abbreviated as polk cells) derived from the chicken B
lymphocyte line DT40 (30). Remarkably, polk cells showed elevated sensitivity to UV, although the data are not in agreement with previous biochemical studies. We also provide genetic data that Polk and Rad18 show an additive effect on UV sensitivity, suggesting that Polk is involved in Rad18-independent TLS of UV lesions.

EXPERIMENTAL PROCEDURES

Cloning of the Chicken POLK Gene—A chicken POLK (GdPOLK) partial cDNA was amplified from chicken testis cDNA by RT-PCR with the primer pair, 5′-CCATAGTGCCAGGATCCAAGTGG-3′ and 5′-CACGAACACAAATCTCCTGTC-3′, the design of which was based on the comparison of the amino acid motif in the human and mouse POLK cDNA. An amplified 144-bp fragment was subcloned into a pCRII-TOPO vector (Invitrogen, Carlsbad, CA) and sequenced. A full-length Gd POLK cDNA was isolated by RACE reactions using the gene-specific primers, 5′-ACAACATCTAGCTGGCCACCTGTC-3′ for 5′-RACE and 5′-AATCTCAGAGCTGAGAAGAAAGGCC-3′ for 3′-RACE. The sequences of five independently isolated cDNA clones were determined. The chicken POLK cDNA sequence has been deposited in the GenBank database under the accession number AF118271.

Construction of Targeting and Expression Vectors—A 14-kb fragment containing part of the chicken genetic Polk locus was isolated from a DT40 genomic DNA library by hybridization with the 144-bp PCR-amplified fragment. The positions of the exons and introns were determined by base sequencing. Chicken Polk disruption constructs containing drug resistance genes, POLK-HIS and POLK-BSR, were made by replacing 2-kb genomic sequences containing exons encoding amino acids 96–209 with histidinol-D and blasticidin-S selection marker cassettes. Since DT40 cells have a single Polk gene, the genotype of Polk-deleted cells is described as Polk-/-Polk-BSR was used for generating rad18 polk (RAD18-/-POLK-) cells from rad18 (RAD18-/-) cells containing the Histidinol-D and Hygromycin-resistance genes (27). To construct an HA-tagged GdPOLK expression vector (designated as pcDB3), we amplified Gd POLK cDNAs including the sequence encoding human hemaggulutinin at the 3′ end by high-fidelity PCR with the following positions of modification for cell proliferation. To analyze UV-induced chromatid aberrations, 1 × 10^6 asynchronous populations of cells were suspended in 0.5 ml of phosphate-buffered saline containing 1% fetal calf serum, introduced onto 6-well cluster plates and irradiated with UV (wavelength, 254 nm), followed by addition of 1 ml of complete medium. For exposure of cells to cisplatin (CDDP, Aldrich, Milwaukee, WI) and mimosine blocks as described previously (34).

Analyses of Chromosome Aberrations and Sister Chromatid Exchange Events—Measurement of chromosome aberrations and sister chromatid exchanges (SCEs) was carried out as previously described (35, 36). Cell synchronization was performed at 1 × 10^6 cells/ml in a 1:1 mixture of serum-free medium and S-9 mix liver extract (Orienta Co, Tokyo, Japan) for 1 h at 39.5 °C. Exposure of cells to AAF (Nacalai Tesque, Kyoto, Japan) was performed at 1 × 10^6 asynchronous populations of cells, with a 1:100 dilution of AAF. Cells were treated with 0.1 μg/ml of colcemid (Invitrogen Life Technologies, Inc.) for the final 3 h of the incubation to enrich for mitotic cells. To measure SCEs induced by 4-nitroquinoline 1-oxide (4-NQO; Nacalai-Tesque, Kyoto, Japan), cells were treated with 0.2 μg/ml of 4-NQO for the last 8 h of incubation with 10 μM BrdUrd for 18 h, which corresponds to two cell cycle periods of DT40 cells. The cells were also treated with 0.1 μg/ml of colcemid for the final 2 h of the incubation to enrich for mitotic cells.

RESULTS

Isolation of Chicken POLK Gene and Generation of polk Mutants—We isolated chicken POLK cDNA, which encodes a protein of 867 amino acids with a predicted molecular mass of 97 kDa (see Supplemental Data). The chicken Polk protein shows ~60% amino acid identity to the human and mouse Polk overall. Amino acid sequence conservation is significant particularly within the four conserved motifs (37) of the DNA polymerase Y family, with 90% identity to those of human and mouse Polk, and ~60% to those of E. coli DinB (38). Additionally, residues Asp81, Asp199, and Gla200 in the polymerase motifs are perfectly conserved with strict intervals from bacterial DinB to the vertebrate Polk proteins. FISH analysis indicated that the chicken POLK gene is located on the sex chromosome Z (data not shown). DT40 cells carry the ZW sex chromosome (35) and carry only a single POLK gene.

Gene targeting constructs were generated to delete amino acids 96–209 including all the DNA polymerase motifs. Targeting events were verified by the appearance of a 3.7-kb band and the disappearance of an 8.5-kb band in Southern blot analysis of EcoRI-digested genomic DNA (Fig. 1, A and B). We isolated three POLK-disrupted cell clones (D12, D32, and D33), which proliferated with the same kinetics as did wild-type cells (Fig. 1, C and D). These mutant clones are designated polk cells. Flow cytometric analysis showed a normal cell cycle distribution of an asynchronous population of polk cells (Fig. 1D).

Increased Sensitivity of polk Cells to UV in Early S Phase—To analyze the DNA repair capacity of polk cells, we examined viability of cells after various genotoxic treatments using colony survival assays. All three polk clones consistently showed a ~1.8-fold increase in UV sensitivity as judged by the evaluation of the doses that reduce survival to 1% (Fig. 2A). The polk clones showed no significant increase in sensitivities...
**Fig. 1.** Generation of polk cells and their growth properties. A, schematic representation of restriction map of the chicken POLK locus, the gene disruption construct, and the configuration of the targeted locus. Solid boxes indicate the positions of exons that were disrupted and open boxes show exons. RI indicates relevant EcoRI sites. B, Southern blot analysis of EcoRI-digested genomic DNA from wild-type (Wt) and POLK-disrupted (polk; D12, D32, and D33) clones. Genomic DNA digested with EcoRI was hybridized with the probe DNA shown in A. Note that DT40 cells have only a single POLK gene in a sex chromosome. C, normal growth kinetics of polk cells. The growth rate of three independently isolated polk clones is essentially the same as that of wild-type cells, which divide every 8 h. Each value represents the mean of relative cell numbers from three independent experiments. D, normal cell cycle kinetics of polk cells. Representative cell-cycle distribution of the indicated cell cultures as measured by BrdUrd incorporation and DNA content in flow cytometric analysis. Cells were pulse-labeled with BrdUrd for 10 min and subsequently stained with FITC-anti-BrdU to detect BrdU incorporation (vertical axis, log scale) and propidium iodide to detect total DNA content (horizontal axis, linear scale). The upper gate identifies cells incorporating BrdUrd (~S phase), the lower-left gate identifies G1 cells, and the lower-right gate displays G2/M cells. Numbers show the percentage of cells falling in each gate.

**Fig. 2.** Elevated UV sensitivity of polk cells. The indicated genotypes of cells were exposed to UV, γ-rays (IR) (B), cisplatin (CDDP) (C), MMS (D), AAF (E), and BaP (F). Disruption of both POLK and XPA genes have a synergistic effect on UV sensitivity (G), while disruption of both POLK and RAD18 genes have an additive effect on UV sensitivity (H). The doses and concentrations (conc.) of genotoxic agents are displayed on the x-axis on a linear scale, while the fractions of surviving colonies are displayed on the y-axis on a logarithmic scale. Error bars show the S.E. for at least three independent experiments. Plating efficiencies of wild-type and mutant cells were ~100% in the IR, UV, and CDDP assays and were reduced to ~50% in the MMS, AAF, or BaP assays because of a 1-h incubation in serum-free medium.
to IR, cisplatin, or MMS in comparison to wild-type cells (Fig. 2, B–D). Moreover, we were unable to detect significant increases in sensitivities of polk cells to AAF or BaP (Fig. 2, E and F).

To confirm that the elevated UV sensitivity is caused by defective Polk, the polk cells were reconstituted with the chicken or human Polk cDNA. We found that the reconstitution did restore the tolerance to UV to that of wild-type cells (Fig. 2A). We next examined UV sensitivity of polk cells at each cell cycle phase, comparing with that of wild-type cells. To this end, the cells were synchronized at the G1/S boundary using sequential nocodazole and mimosine blocks (34). After the release from the G1/S block, cells were exposed to UV at a number of time points including early S phase (1.5 h after the release), late S phase (4.5 h after the release), and the G2/M phase (6 h after the release) (Fig. 3A). Wild-type cells showed increased resistance to UV as DNA replication progressed, reflecting lower frequencies of replication blockage caused by UV-induced damage at late S phase compared with early S phase. In contrast, only at early S phase, the UV sensitivity of polk cells was significantly greater than that of wild-type cells. The early S phase-specific increase in UV sensitivity of polk cells is in agreement with defective TLS in the mutant cells.

UV-induced damage is expected to block DNA replication, leading to gaps and double-strand breaks (DSBs) in sister chromatids. To evaluate UV-induced DSBs, we measured cytologically detectable chromosomal aberrations following UV irradiation in asynchronous populations of polk cells (Fig. 4). The cell cycle progression following UV irradiation is comparable between wild-type and polk cells (data not shown). Cells irradiated at late S to G2 phase are expected to enter the M phase within 3 h following UV irradiation, whereas cells irradiated at G1 to early S phase may need 3–6 h to enter the M phase (39). We found no increase in the level of spontaneous chromosomal aberrations in polk cells when compared with wild-type cells (Fig. 4), as expected from the normal growth property of polk cells (Fig. 1, C and D). The levels of UV-induced chromosomal aberrations in polk cells were up to 3-fold higher than those of wild-type cells in each 3-h period following UV irradiation (Fig. 4), indicating that the mutants are not able to deal with replication block as efficiently as are wild-type cells. It should be noted that in DT40 cells, UV irradiation induces both chromosome-type breaks, where a pair of sister chromatids are broken at the same site, and chromatid-type breaks, where only one sister chromatid is broken, although it is known that UV causes only chromatid-type breaks in other vertebrate cells (40). Thus, we may have to take into account DT40-specific mechanisms for the induction of chromosome-type breaks, such as efficient interactions between damaged chromatids and other intact ones through HR.

**Defective Postreplication Repair Following UV Irradiation in polk Cells**—There are three major pathways for repairing DNA damage induced by UV, i.e. the NER, HR, and TLS pathways (1). It is not entirely clear which DNA polymerases are involved in the NER or HR pathways in vertebrate cells. To analyze the epistatic relationship of Polk to the NER pathway, we generated cells deficient in the XPA protein (xpa cells) as well as cells deficient in both XPA and Polk (xpa polk cells). The XPA protein is involved in an early step of NER, and its defect causes hypersensitivity to UV and skin cancer. We found that both xpa and xpa polk cells proliferated with normal kinetics (data not shown). Their UV sensitivity showed an additive effect of the mutations of XPA and Polk on UV sensitivity (Fig. 2G), suggesting that Polk does not function in the NER pathway. We also examined the involvement of Polk in the HR pathway by assessing HR capability in polk cells. Analyses of
gene-targeting efficiencies (Table I) and IR sensitivity (Fig. 2B) consistently showed that HR capability is not reduced in polk cells. Thus, defective HR does not account for increased UV sensitivity in polk cells. In summary, the increased UV sensitivity of polk cells is most likely to be explained by a defect in TLS, rather than a defect in NER or HR.

Increased Levels of SCE, an HR-Mediated Repair Process in polk Cells—We have shown that SCE, cytogenetically detectable crossover, reflects postreplication repair mediated by HR (36, 41). Interestingly, polk cells exhibited a significant increase in the level of spontaneous SCEs (Fig. 5). This observation suggests that Polk plays a role in maintaining chromosomal DNA during the cell cycle. To analyze SCE induced by genotoxic treatments, we exposed cells to 4-NQO, which is known to form DNA adducts similar to UV damage and to stimulate SCE (1). The level of induced SCE events was also higher in polk cells when compared with wild-type cells (Fig. 5). These observations support the notion that defective TLS in polk cells is compensated by HR, the other major postreplication repair pathway.

Polk-dependent TLS Can Function in the Absence of Rad18—To examine the epistatic relationship between Polk and Rad18, we generated cells deficient in both Rad18 and Polk (rad18 polk cells). We have previously shown that rad18 cells are sensitive to various DNA damaging agents including IR, UV, and CDDP (27); consistent with the phenotype of the yeast POLK specific characteristics, because both the human and chicken postulate that the elevated UV sensitivity in markedly, the mutant cells showed elevated UV sensitivity. We conclusion leads to the notion that the relative usage of POLK gene-targeting efficiencies (Table I) and IR sensitivity (Fig. 2B) consistently showed that HR capability is not reduced in polk cells. Thus, defective HR does not account for increased UV sensitivity in polk cells. In summary, the increased UV sensitivity of polk cells is most likely to be explained by a defect in TLS, rather than a defect in NER or HR.

It is interesting that defects in Rad18 and Polk showed an additive effect on UV sensitivity. The data suggest that Polk participates in Rad18-independent TLS of UV lesions and that Rad18 does not necessarily regulate all TLS polymerases in vertebrate cells. Recent genetic studies of S. cerevisiae also suggested that the existence of Rad18-independent TLS of UV lesion (48).

Polk Contributes to the Maintenance of Chromosomal DNA in Cooperation with HR Pathway—A significant increase in the level of SCE was observed in polk cells not only after 4-NQO treatment but also during the cell cycle. Likewise, the level of spontaneously arising SCE events is increased in cells from XP-V patients (49). We interpret these increased levels of SCE as more frequent usage of the HR pathway for postreplication repair. Presumably, gaps that should be filled by Polk may accumulate in polk cells and stimulate HR with the other sister chromatid, leading to an increase in SCE events. Importantly, increased levels of spontaneous SCE in polk cells imply the functional cooperation between the Polk-dependent TLS and HR pathways in the maintenance of chromosomal DNA. This conclusion leads to the notion that the relative usage of POLK in postreplication repair may determine mutation frequency in cycling cells, since Polk-dependent TLS is highly mutagenic (16). Recent studies showed that the expression of mammalian POLK is inducible by environmental mutagens, BaP and dioxin (50), and that Polk is overexpressed in human non-small cell lung cancer. Thus, these studies and our study shed light on the understanding of mutagenesis and carcinogenesis.

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