Human 75-kDa DNA-pairing Protein Is Identical to the Pro-oncoprotein TLS/FUS and Is Able to Promote D-loop Formation*

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Homologous recombination plays a fundamental role in DNA double-strand break repair. Previously, we detected two mammalian nuclear proteins of 100 and 75 kDa (POMP100 and POMP75, respectively) that are able to promote homologous DNA pairing, a key step in homologous recombination. Here we describe the identification of human (h) POMP75 as the pro-oncoprotein TLS/FUS. hPOMP75/TLS binds both single- and double-stranded DNAs and mediates annealing of complementary DNA strands. More important, it promotes the uptake of a single-stranded oligonucleotide into a homologous superhelical DNA to form a D-loop. The formation of a D-loop is an essential step in DNA double-strand break repair through recombination. DNA annealing and D-loop formation catalyzed by hPOMP75/TLS require Mg2+ and are ATP-independent. Interestingly, the oncogenic fusion form TLS-CHOP is not able to promote DNA pairing. These data suggest a possible role for hPOMP75/TLS in maintenance of genomic integrity.

Faithful repair of DNA double-strand breaks (DSBs) is of vital importance for maintenance of genomic integrity of cells. DSBs are generated by chemical damaging agents and ionizing radiation and are specifically induced during meiosis. Unrepaired or aberrantly repaired DSBs can lead to chromosomal rearrangements, eventually resulting in the formation of tumors or cell death. In mammalian cells, two major pathways for DSB repair are non-homologous end joining and homologous recombination.

In Escherichia coli, RecA protein plays a crucial role in DSB repair by promoting homologous pairing and strand exchange between homologous DNAs (1, 2). Discovery of homologues of RecA in every eukaryote examined has underscored conservation of similar repair mechanisms throughout evolution (3, 4). The homologue of recA in Saccharomyces cerevisiae, the RAD51 gene, is a member of the RAD52 epistasis group required for genetic recombination and DSB repair (5). High expression of the mammalian RAD51 protein in meiotic and lymphoid tissues (6) and its localization in synaptonemal complexes early in meiosis (7–9), relocalization after treatment with DNA-damaging agents (7), and induction after stimulation of B-cells for class switch recombination (10) suggest a role for mammalian RAD51 in DNA recombination and repair. The finding that human and yeast Rad51 proteins promote ATP-dependent homologous pairing and strand exchange further support their central role in recombination and DSB repair (11–13).

Although these studies indicate that the basic mechanism and key players of DSB repair are evolutionarily conserved, the process in higher eukaryotes is much more complex than in E. coli and involves a number of additional factors. In this context, evidence is accumulating for a possible role for the tumor suppressor proteins p53, BRCA1, and BRCA2 in DNA recombination and repair (4, 14, 15). This includes interaction of p53, BRCA1, and BRCA2 with RAD51; colocalization of BRCA1, BRCA2, and RAD51 on the axial elements of the synaptonemal complexes during meiosis; similarities in expression of BRCA1, BRCA2, and RAD51; and early embryonic lethality of BRCA1, BRCA2, or RAD51 nullizygous mice, which is partially suppressed by homozygous p53 germ-line mutation.

We have developed an in vitro assay to measure homologous DNA-pairing activities in cellular extracts (16, 17). Using this approach, we have detected two mammalian nuclear proteins of 100 and 75 kDa (POMP100 and POMP75, respectively) that are able to promote ATP-independent homologous DNA pairing that does not require an associated exonuclease activity (17).

In this work, we describe the purification of hPOMP75 from HeLa nuclei and its identification as the human pro-oncoprotein TLS (also known as FUS). TLS (translocated in liposarcoma) is a member of the TET family of genes that includes EWS, a gene commonly involved in other sarcomas and TAF1168 that encodes a component of the basal transcriptional machinery (18–20). Although the oncogenic forms of TLS have been the subject of intense investigation, much less is known about the function of its normal cellular form. We demonstrate that purified hPOMP75/TLS binds ssDNA and dsDNA and promotes ATP-independent annealing of complementary ssDNAs and D-loop formation in superhelical dsDNA. The oncogenic fusion form TLS-CHOP is not able to promote DNA pairing. These data suggest a possible role for hPOMP75/TLS in maintenance of genomic integrity.

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§ The abbreviations used are: DSBs, DNA double-strand breaks; POM, pairing on membrane; h, human; r, recombinant; ssDNA, single-stranded DNA; dsDNA, double-stranded DNA; PAGE, polyacrylamide gel electrophoresis; BiTnTris, 2-[bis(2-hydroxyethyl)aminol]-2-(hydroxymethyl)-propane-1,3-diol; HNEs, HeLa nuclear extracts; ATPyS, adenosine 5′-O-(thiotriphosphate).
**RESULTS**

**Isolation and Identification of hPOMP75 as the Human Pro-ontcoprotein TLS**—We previously described a 75-kDa protein as one of the major DNA-pairing proteins detected by the POM assay in different mammalian cell lines (17). Using the POM blot as a functional assay, we purified hPOMP75 from HeLa nuclear extracts (HNEs) to near homogeneity (Fig. 1B) and used it in the studies described below. In all purification steps, the hPOMP75 activity coincided with the presence a 75-kDa protein (Fig. 1C). No nuclease activity with ssDNA or dsDNA was detected in the purified fraction (data not shown). Moreover, the purified protein did not contain any hRAD51 protein as revealed by immunoblot analysis of the preparation with anti-RAD51 antibodies purchased from Calbiochem (data not shown).

hPOMP75 (Fraction VI) was resolved by SDS-PAGE and subjected to internal sequence analysis. Four peptide sequences were obtained (Fig. 2A) and found to be identical to that of the human pro-ontcoprotein TLS (18, 19).

Furthermore, we immunoprecipitated TLS from HNEs with an excess of monoclonal antibody 4H11 to TLS (23). This resulted in significant depletion of the hPOMP75 activity from the extract and recovery of such activity in the immune complex (Fig. 2B). The hPOMP100 activity was unaffected by these steps, reflecting the specificity of the immunodepletion procedure. hPOMP75 purified from HeLa nuclei and bacterially expressed recombinant TLS exhibited similar electrophoretic mobility and DNA-pairing activity and were recognized by the anti-TLS monoclonal antibody (Fig. 2C). These results establish the identity of TLS to a component of the hPOMP75 activity.

**DNA-binding Properties of hPOMP75**—TLS was shown to contain an RNA-binding domain of the RRM type and to bind RNA in vitro and in vivo (18, 23, 24). We reported previously
that the human 75-kDa DNA-pairing activity bound to ssDNA- and dsDNA-cellulose (17). Using an electrophoretic mobility shift assay, we investigated further the DNA-binding properties of hPOMp75/TLS. Upon incubation of increasing amounts of hPOMp75/TLS with the 32P-labeled 49-mer oligonucleotide, protein-DNA complexes that exhibited retarded mobility were observed (Fig. 3A). In contrast to RecA protein or its human homologues (RAD51 and DMC1), the addition of ATP had no effect on the binding (data not shown).

To compare hPOMp75/TLS affinity for ssDNA and dsDNA, its binding to the labeled 49-mer oligonucleotide was carried out in the presence of increasing amounts of unlabeled competitor dX174 replicative form I ssDNA or dsDNA. dX174 ssDNA competed more efficiently with the labeled oligonucleotide for hPOMp75/TLS binding than did dX174 dsDNA. Indeed, a 12-fold molar excess of ssDNA completely abolished binding, whereas a 24-fold molar excess of duplex competitor was needed to achieve a similar effect (Fig. 3B, compare lanes 3–6 with lanes 7–10). Similar results were obtained with M13mp19 ssDNA and dsDNA (data not shown). Thus, hPOMp75/TLS binds both ssDNA and dsDNA, with a 2-fold higher affinity for ssDNA.

**hPOMp75/TLS-mediated Annealing of Complementary ssDNAs**—To examine the ability of hPOMp75/TLS to anneal complementary ssDNAs, we incubated increasing amounts of the protein with a heat-denatured 32P-labeled 422-base pair DNA fragment. The products were analyzed by gel electrophoresis followed by autoradiography. As shown in Fig. 4, hPOMp75/TLS promoted annealing of 422-nucleotide DNA strands in a concentration-dependent manner. Optimal activity was observed at one hPOMp75/TLS molecule/6–10 nucleotides of ssDNA. The reaction required Mg2+, but not ATP (Fig. 4, lanes 12 and 13; data not shown). Under optimal conditions, the efficiency of hPOMp75/TLS-promoted renaturation approached 50% within 20 min of incubation at 37 °C, and further incubation did not result in an increase of the product (Fig. 4).

**Formation of D-loops in Superhelical DNA by hPOMp75/TLS**—The incorporation of ssDNA into homologous duplex DNA, leading to the formation of a D-loop, is an essential feature of homologous recombination. The E. coli recombination proteins RecA, RecT, and RecO and the yeast (S. cerevisiae Rad51) and human (DMC1) RecA homologues are able to catalyze this reaction (25–30). Moreover, this in vitro reaction cannot have resulted from contaminating exonuclease activity since such activity should diminish D-loop formation. To study the ability of hPOMp75/TLS to promote the formation of D-loops, hPOMp75/TLS was incubated with the 32P-labeled 49-mer oligonucleotide and the homologous superhelical dsDNA. Following incubation, protein was removed by the addition of proteinase K, SDS, and EDTA, and the reaction products were analyzed by agarose gel electrophoresis. The incorporation of radioactivity into the superhelical DNA was visualized by autoradiography. As a positive control, we tested the D-loop formation mediated reaction (Fig. 5B). Two major DNA bands were observed similar to those formed in the RecA-mediated reaction (Fig. 5B, compare lanes 8–10 with lane 12). The more slowly migrating DNA species migrated similarly to relaxed dsDNA and might represent the assimilation of ssDNA into relaxed dsDNA present in the superhelical DNA preparation. In agreement with results reported previously for RecA protein (25), this reaction is less efficient. When the superhelical...
protein was substituted for hPOMp75/TLS in D-loop formation; this
and hPOMp75/TLS (40 nM) were incubated for the indicated times
reaction.
matic diagram of DNA substrates and the expected product of the
lanes 3–7
amounts of hPOMp75/TLS (2.5–5 mm Mg2+, (Fig. 5B, lanes 11 and 13–15). In contrast to the RecA-promoted reaction, the addition or omission of ATP had no effect on D-loop formation (Fig. 5C, compare lanes 6 and 7).

The RNA-binding proteins SF2/ASF and U2AF65 have previously been shown to promote annealing of complementary nucleic acid strands (32, 33). Given the evidence that these proteins and hPOMp75/TLS have at least one highly conserved RNA recognition motif of the RRM type, it raises the question whether D-loop formation is a specific feature of hPOMp75/TLS. Therefore, we tested the ability of SF2/ASF and U2AF65 to promote D-loop formation. In contrast to hPOMp75/TLS, both proteins did not mediate the formation of D-loops (data not shown).

TLS-CHOP Protein Does Not Display POM Activity—In human myxoid and round cell liposarcomas, chromosomal translocation fuses TLS to the CHOP (also known as GADD153) gene, resulting in expression of the fusion oncoprotein TLS-CHOP (18, 19). To investigate the DNA-pairing activity of TLS-CHOP, bacterially expressed TLS-CHOP was purified by nickel chelate chromatography and analyzed by SDS-PAGE and Western blotting using anti-His and anti-CHOP antibodies. Although TLS-CHOP is slightly bigger than TLS (75 versus 68 kDa), both proteins exhibited similar electrophoretic mobility under our SDS-PAGE conditions (Fig. 6, upper panel). Only TLS-CHOP, however, was recognized by the anti-CHOP monoclonal antibody, whereas both recombinant proteins reacted with antibodies to the polyhistidine tag in the N terminus of the proteins (Fig. 6, middle panels). Interestingly, when equal amounts of rTLS or rTLS-CHOP were examined by the POM assay, rTLS-CHOP was completely inactive, whereas rTLS displayed a high POM activity (Fig. 6, lower panel).

**DISCUSSION**

Using an assay that measures homologous DNA pairing in cell extracts, we have purified a 75-kDa DNA-pairing protein (termed hPOMp75) from HeLa nuclei. Microsequencing and immunoblot analysis revealed its identity to the human pro-
oncoprotein TLS (18, 19). Moreover, purified bacterially expressed TLS promotes homologous DNA pairing and exhibits major functional characteristics identical to those of hPOMp75 purified from HeLa nuclei. However, TLS exists in mammalian cells in a complex with RNA and other proteins, and these are

tained with a 60-mer oligonucleotide and homologous superhelical pUC19 or M13mp19 DNAs (data not shown).

The reaction catalyzed by hPOMp75/TLS required Mg2+, and optimal activity was observed at 2.5–5 mm Mg2+ (Fig. 5B, lanes 11 and 13–15). In contrast to the RecA-promoted reaction, the addition or omission of ATP had no effect on D-loop formation (Fig. 5C, compare lanes 6 and 7).

**FIG. 4.** DNA-annealing activity of hPOMp75/TLS. The indicated amounts of hPOMp75/TLS (lanes 3–7) were incubated with 60 nM heat-denatured 32P-labeled 422-base pair DNA fragment at 37 °C for 20 min. Shown is the time course of DNA annealing promoted by 8 nM hPOMp75/TLS (lanes 8–12). A 8 nM hPOMp75/TLS was added and MgCl2 was omitted from the reaction in lane 13. The products were analyzed by PAGE as described under "Experimental Procedures." In lane 1, undenatured dsDNA was loaded; in lane 2, no protein was added.

**FIG. 5.** hPOMp75/TLS can promote D-loop formation. A, schematic diagram of DNA substrates and the expected product of the reaction. B, time course and requirements of D-loop formation. DNAs and hPOMp75/TLS (40 nM) were incubated for the indicated times (lanes 5–10). dsDNA was omitted (lane 2), and Asp700-linearized pUCSy dsDNA or heterologous M13mp19 dsDNA was added instead of pUCSy dsDNA (lanes 3 and 4, respectively). D-loop formation was conducted in the absence (lane 11) or presence (lanes 13–15) of the indicated MgCl2 concentrations. 40 nM hPOMp75/TLS was added to the reactions in lanes 2–4, 11, and 13–15. As a positive control, RecA protein was substituted for hPOMp75/TLS in D-loop formation; this reaction was performed in the presence of 10 mM MgCl2 at 37 °C for 15 min (lane 12). C, stoichiometric requirements for hPOMp75/TLS (lanes 2–6). Reactions containing the 32P-labeled 49-mer oligonucleotide, superhelical pUCSy DNA, and the indicated amounts of hPOMp75/TLS were incubated at 37 °C for 15 min. ATP was omitted from the reaction in lane 7. In lanes 1, no protein was added.
co-immunoprecipitated by antibodies to TLS (23, 34). Therefore, we cannot exclude that comigrating components of this complex such as TAFII168 might also contribute to the hPOMp75 activity in HeLa extracts.

hPOMp75/TLS binds both ssDNA and dsDNA, with a slightly higher affinity for ssDNA. In contrast to RecA protein or its human homologues (RAD51 and DMC1), ATP is not required for DNA binding of hPOMp75. Unlike RecA protein (35) and similar to hRAD51 protein (36), hPOMp75/TLS does not bind to ssDNA with high cooperativity.

One of the characteristic activities associated with homologous DNA-pairing proteins like E. coli RecA, RecT, and RecO; Ustilago maydis Rec2; and S. cerevisiae Rad52 is the ability to catalyze the annealing of two complementary DNA strands (37–41). This type of activity has also been demonstrated with hPOMp75/TLS. The hPOMp75/TLS-promoted annealing requires Mg\(^{2+}\), but unlike the RecA- or Rec2-mediated reactions, is ATP-independent. In this respect, the reaction is similar to that promoted by RecT or RecO (38, 39).

Although the ability to anneal complementary ssDNA molecules is a prerequisite of recombination proteins, it is a rather simple reaction that can occur nonenzymatically and that can be facilitated by unrelated proteins and by agents that concentrate or condense DNA (3). In this regard, D-loop formation is a much more specific reaction, representing an invasion of a single-stranded end of one molecule into intact homologous duplex DNA, an essential step in DSB repair through recombination. hPOMp75/TLS is able to catalyze the formation of D-loops in superhelical duplex DNA. The reaction promoted by hPOMp75/TLS differs in several respects from that promoted by RecA: it does not require ATP or ATP\(\gamma\)S, is much slower, and does not exhibit pseudo-reversibility. Similar characteristics have been demonstrated for the formation of D-loops by RecT and RecO proteins (27, 39). The hPOMp75/TLS-promoted D-loop formation requires Mg\(^{2+}\); however, the optimal concentration of the ion is lower than for the RecA-promoted reaction. The formation of D-loops by RecO protein and strand transfer by hRAD51 are also optimal at low Mg\(^{2+}\) concentrations, implying inability of these proteins to remove secondary structures from ssDNA (39, 36). Finally, the ability to promote D-loop formation is a specific feature of hPOMp75/TLS; two other RNA-binding proteins, SF2/ASF and U2AF\(^{65}\), which efficiently mediate RNA and DNA annealing (32, 33), are not able to promote D-loop formation.

The biochemical characterization of hPOMp75/TLS presented here suggests that the protein may play a role in homologous DNA pairing and recombination. This hypothesis is supported by recent observations made on mice with an induced mutation in Tls. Male Tls\(^{-/-}\) mice are sterile, with demonstrable defects in chromosome pairing during meiosis. Nuclear extracts from Tls\(^{-/-}\) testes lack the POM75 activity. Moreover, mutant mice and cells derived from them exhibit increased sensitivity to ionizing irradiation.\(^2\)

TLS was originally identified as contributing the N-terminal part of fusion genes with CHOP in myxoid liposarcoma or with ERG in acute myeloid leukemia (18, 19, 42). The N-terminal portion of TLS is a potent transcriptional activator essential for the oncogenic potential of TLS-CHOP and TLS-ERG fusion proteins, whereas the C terminus is required for RNA binding (18, 24, 34). The association of TLS with components of the basal transcriptional machinery (20) and transcription factors (43, 44) suggests participation of this multifunctional protein in various aspects of nucleic acid metabolism. TLS nucleic acid-binding activity may be activated by BCR/ABL, an abnormal form of the c-Abl tyrosine kinase (45). c-Abl kinase activity is normally regulated by genotoxic agents (46). The protein is expressed at high level in pachytyne spermatocytes, and male c-Abl\(^{-/-}\) mice have defects in meiosis (47). These results suggest the possibility that hPOMp75/TLS and c-Abl may participate in the same pathway activated by DSB. Of note is that c-Abl has recently been shown to interact with hRAD51 and to inhibit in vitro its recombination activity by phosphorylation (48).

Several recent reports have suggested the association of factors controlling tumorigenesis such as p53, BRCA1, and BRCA2 with DSB repair machinery (4, 14, 15), although the specificity and functionality of this association remain to be determined. In addition to the well established role of p53 in DNA repair via cell cycle control, it is suspected to participate more directly in this process (49). The pro-oncogene hPOMp75/TLS might represent another example of a tumorigenic factor with recombination enzymatic potential. Intriguingly, its oncogenic fusion form, TLS-CHOP, is not able to promote DNA pairing under the POM conditions. Given the presence of the second normal allele of TLS in liposarcomas, it is tempting to speculate that TLS-CHOP may interfere with hPOMp75/TLS function in DNA repair, leading to additional instability of liposarcoma cells. Further experimental evidence is needed to substantiate this hypothesis and to elucidate a role for this multifunctional protein in maintenance of genomic integrity.

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