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Physical Interaction between Human RAD52 and RPA Is Required for Homologous Recombination in Mammalian Cells*

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The yeast RAD52 protein is essential for DNA double-strand break repair, and meiotic and mitotic recombination. RPA is a protein complex of three subunits (70, 34, and 11 kDa) that has been shown to be involved in DNA replication, nucleotide excision repair, and homologous recombination. Here, we demonstrate a physical interaction between human RAD52 and RPA in vivo and in vitro. In addition, the domain (amino acids 221–280) in RAD52 protein that mediates the interaction with the 34-kDa subunit of RPA was also determined. Overexpression of mutant RAD52 proteins lacking the interaction domain (amino acids 221–240, 241–260, and 261–280) failed to induce homologous recombination in monkey cells. We have previously shown that overexpression of human RAD52 induced homologous recombination in these cells. These results suggest that direct physical interactions between RAD52 and RPA are essential for homologous recombination in mammalian cells.

Genetic information is maintained by DNA repair and propagated to offsprings through recombination. The fidelity of these processes are crucial for the maintenance of genetic integrity of living organisms. The proteins of the RAD52 epistasis group are involved in both DNA repair, and meiotic and mitotic recombination (1, 2). Both genetic and molecular studies on the yeast RAD52 epistasis group clearly indicate close links between homologous recombination and double-strand DNA break repair (3). Most of the information regarding the functions of the RAD52 protein has come from genetic studies in yeast. These studies suggested that the RAD52 protein is not required for the initiation of recombination, but is essential for the intermediate stage following the formation of double strand breaks but before the appearance of stable recombinants (4). Most recently, human RAD52 protein has been shown to confer resistance to ionizing radiation and induce homologous recombination in monkey cells (5). This indicates that the RAD52-mediated homologous recombination also plays a role in double strand break repair in mammalian cells.

RPA was originally identified as a HeLa cell protein required for the replication of simian virus 40 (SV 40) origin-containing DNA (ori + DNA) in vitro (6–9). The RPA heterotrimer consists of a tight complex of 70-, 34-, and 11-kDa subunits (6). RPA functions in the initiation and elongation stages of SV40 DNA replication. In the initiation stage, it is involved in the SV40 large tumor antigen (T antigen)-dependent unwinding of ori DNA (10–12). The unwinding reaction is supported by other single strand binding proteins, such as those isolated from Escherichia coli, adenovirus, or yeast (13, 14); however, initiation of DNA synthesis specifically requires human RPA (15). RPA is also required for nucleotide excision repair through direct interaction with XPA (16–19). We have recently shown that RPA-XPA interactions can lead to inhibition of replication, which may suggest that DNA repair overrides DNA replication in vitro through a direct interaction between RPA and XPA (20). RPA has been shown to be also involved in homologous recombination (21–24).

We have recently cloned human RAD52 and established that RAD52 is involved in a homologous recombination pathway in mammalian cells (5). We also have shown a specific interaction between human RAD52 and RAD51 in vivo and in vitro (25). During the search for other proteins that might regulate the catalytic activity of RAD51 through direct interaction with RAD52, we learned that RPA interacts with RAD52 protein. In this study, we demonstrated the physical interaction between human RAD52 and RPA and addressed the importance of this intermolecular interaction in homologous recombination in monkey cells.

MATERIALS AND METHODS

Expression of RAD52, RPA Complex, and RPA Subunits—The cloning region of human RAD52 (5) was cloned into pGEXT vector (Pharmacia Biotech Inc.) to produce glutathione S-transferase (GST)-RAD52 protein. A culture of BL21 (DE3) cells (26) harboring pGEXT-RAD52 was grown to an A590 of 0.6 in L broth supplemented with ampicillin (50 μg/ml); isopropyl-β-D-thiogalactopyranoside was then added to a final concentration of 0.5 mM, and the culture was incubated for an additional 3 h at 37°C. Bacteria were harvested by centrifugation and resuspended in 50 ml of buffer A (0.1 M Tris-HCl, pH 8.0, 2 mM EDTA) containing lysozyme (300 μg/ml), and incubated for 10 min. The soluble fraction containing the GST-RAD52 was collected by centrifugation at 15,000 rpm for 15 min in a Beckman JA-20 rotor. Protease inhibitors (10 μM each of pepstatin, chymostatin, and leupeptin, and 1 mM phenylmethylsulfonyl fluoride) were added to the lysate. GST-RAD52 was purified by GST-affinity column chromatography.

The 34-kDa subunit of RPA was cloned into a pET vector under the control of T7 promoter (26) and expressed as described for GST-RAD52 fusion protein. The cDNAs coding 34-kDa subunits were cloned into the control of T7 promoter (26) and expressed as described for GST-RAD52 fusion protein. The cDNAs coding 34-kDa subunits were cloned into pET vectors and expressed as described for GST-RAD52 fusion protein. The cDNAs coding 34-kDa subunits were cloned into pET vectors and expressed as described for GST-RAD52 fusion protein.

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1 The abbreviations used are: GST, glutathione S-transferase; aa, amino acid(s); PAGE, polyacrylamide gel electrophoresis; PCR, polymerase chain reaction.
That interacts with the 34-kDa subunit of RPA—To further map the RAD52/RPA-p34 interacting domain, six mutants containing a part of RAD52 protein (aa 1-165, 1-280, 280-418, 166-220, and 221-280) were made by ligating the PCR products to the pGEX7 vector that was restriction-digested with BamHI and XhoI. Mutant constructs were first transformed into an E. coli strain, XL2-blue (Stratagene) and subsequently screened for clones with a proper RAD52 reading frame. Then BL21(DE3) was transformed with deletion construct plasmids and subsequently screened for clones with a proper RAD52 reading frame. The mutant constructs produced truncated RAD52 proteins with the GST protein at the N terminus of the protein. Mutant proteins were purified by GST-affinity chromatography.

Interaction between RAD52 and RPA Complex in Insect Cells—To test the interaction between RAD52 and RPA complex in vivo, total cell extracts were prepared from insect cells that were simultaneously infected with four independent recombinant viruses of RAD52, RPA70, RPA34, and RPA11 subunits (25, 27). Total cell extracts were subjected to immunoprecipitation using an anti-RAD52 antisera (25), and then the immunoprecipitates were analyzed by SDS-PAGE and subsequent immunoblotting with the monoclonal antibody specific to 70-, 34-, and 11-kDa subunits of RAD52 (27).

Affinity Precipitation of RPA Complex or Subunits of RPA with GST-RAD52—In order to coprecipitate RAD52 and individual subunits or RPA complex expressed in insect cells, Sf9 cells were infected with the recombinant baculovirus constructs of 70-, 34-, and 11-kDa subunits individually or together. The proteins were metabolically labeled with [35S]methionine, and the total extracts were prepared as described previously (27). The metabolically labeled total cell extracts were mixed with the E. coli lysate containing the GST-RAD52 protein in the presence of GST-agarose beads. The proteins were prepared as described above and analyzed by PAGE and fluorography.

Determination of GST-RAD52 Region That Interacts with 34-kDa Subunit of RPA—Purified wild type or mutant RAD52 protein were mixed with the total E. coli extracts of 34-kDa subunits of RPA for 1 h at 4°C with gentle rocking. Then GST-agarose beads were added to the tube and further incubated for 2 h to overnight at 4°C with a rocking. The reaction was washed five times with the wash buffer (150 mM NaCl, 50 mM Tris-HCl, pH 7.5, 0.5 mM EDTA, 0.1% Triton X-100). Fifty μl of 2× SDS sample buffer was added to the tube, and the sample was heated at 100°C for 5 min and analyzed by SDS-PAGE.

Functional Significance of RAD52-RPA-p34 Interaction Domain in Vivo—In order to test the role of RAD52-RPA-p34 interacting domain in homologous recombination in mammalian cells, three mammalian constructs that had deletions in the interaction domain (aa 220-280) were derived from the pBKCMV-RAD52 construct that expresses RAD52 with the c-Myc epitope attached (5). These constructs had deletions in aa 220-240, 241-260, and 261-280, respectively. The internal deletions were introduced using ExSite mutagenesis kit (Stratagene, CA). The mutagenic primers were: P1(221–240), 5'-CTG CAG CTT CCG CTG GTG CGT GGC-3'; P2(221–240), 5'-TCC CCA AGC AGC TAC TCA TCC GGC GCC-3'; P3(241–260), 5'-GCT GTA GTC GTG CGC CGG TAT-3'; P4(241–260), 5'-AGG GAC AAG CAG CTC-3'; P5(261–280), 5'-CCG GAG CTT CCG GTC GTG GCC-3'; P6(261–280), 5'-ACG CGG TTA GTC GAG AGT GAG-3'. FSH2 cells were transfected with the individual mutant constructs (pBKCMVRAD52(d221–240), RAD52(d241–260), and RAD52(d261–280)) and selected for resistance to G418. FSH2 cells were seeded at a density of 10⁶ cells/100-mm dish and grown for 1 day before transfection. Cells were transfected with 10 μg of pBKCMV-RAD52 mutants by using the calcium phosphate method. After 2 weeks in selection medium containing G418 (600 μg/ml), individual colonies were picked and expanded for future use. Expanded individual colonies were subjected to PCR to test the integrity of RAD52 construct. Those PCR-positive clones were further analyzed with indirect immunofluorescence microscopy and Western blot analysis to confirm the expression and integrity of mutant RAD52 protein using anti-c-Myc antibody. Homologous recombination rate in FSH2 cells was determined as described previously (5, 28).

RESULTS

Interaction of RAD52 with RPA Complex in Vivo—RPA is a stable complex of three polypeptides of 70, 34, and 11 kDa. To examine whether RAD52 could associate with the RPA complex in vivo, whole cell extracts were prepared from the insect cells that had been transfected simultaneously with four recombinant viruses (RAD52, RPA70, RPA34, and RPA11), and immunoprecipitated with an anti-RAD52 antisera. The immunoprecipitants were analyzed by immunoblotting with anti-p11, -p34, and -p70 antibodies. As shown in Fig. 1, all three subunits were present in the immunoprecipitate that was produced with anti-RAD52 antisera (lane 2), but not by preimmune serum (lane 1).

Interaction of RAD52 with RPA Complex in Vitro—To further confirm the association of RAD52 with RPA complex, in vitro binding assays were performed. We produced a GST-RAD52 fusion protein. The GST or GST-RAD52 was immobilized onto glutathione-agarose beads. Sf9 insect cells were singly or multiply infected with the baculovirus recombinant constructs of p11, p34, and p70 subunits. The total cell extracts were prepared from insect cells that had been metabolically labeled with [35S]methionine and incubated with either GST or GST-RAD52 beads. After washing the beads, the GST or GST-RAD52 bound proteins were analyzed by SDS-PAGE. As shown in Fig. 2, RPA complex bound to GST-RAD52 but not to GST.

Interaction of RAD52 with 70- and 34-kDa Subunits of RPA in Vitro—In order to determine which subunits of RPA interact with RAD52, extracts were prepared from insect cells that had been independently infected with the recombinant baculoviruses containing each subunit of RPA and mixed with either GST or GST-RAD52 beads. As shown in Fig. 2, the p70 and p34 subunits interacted with GST-RAD52, but the p11 subunit did not exhibit binding. The p34 subunit appeared to have high activity in GST and GST-RAD52 than the p70 subunit of RPA.

Because both p70 subunit of RPA and RAD52 are DNA-binding proteins, it is possible that their interaction could be mediated by DNA in the lysates, rather than direct protein-protein interaction. We can eliminate this possibility since: 1) mutant RPA p70 proteins (p70d293–373 and p70d374–458) lacking DNA binding activity can also interact with RAD52 (29), and 2) pretreatment of p70 lysate with DNase I had no effect on RPA p70–RAD52 interaction (data not shown).

Mapping of the RAD52 Region That Interacts with 34-kDa Subunit of RPA in Vitro—In order to map the RAD52 region that mediates the intermolecular interactions with p34 subunit of RPA, we made several deletion mutant proteins of GST-RAD52. These GST-RAD52 mutant proteins were then expressed in E. coli, purified, and mixed with the bacterial lysate containing the p34 subunit of RPA. Then, the RAD52-p34 complexes were precipitated with GST-agarose beads as described earlier. Proteins were analyzed by SDS-PAGE and subsequent immunoblotting experiments with anti-RP34 antibody to confirm the interaction between p34 and RAD52 mutants. As shown in Fig. 3, the region between the amino acids 221 and 280 of RAD52 is sufficient for the intermolecular association between RAD52 and p34 subunit of RPA.

**Fig. 1. Interaction of RAD52 with RPA complex in vivo.** SF-9 insect cells were infected with four different recombinant viruses for RAD52 and p11, p34, and p70 subunits of RPA, and total cell extracts were prepared as described under "Materials and Methods." Lane 1, total cell extracts immunoprecipitated with preimmune serum; lane 2, immunoprecipitated with anti-RAD52 antibody. Immunoprecipitates were then immunoblotted with antibodies specific to subunits of RPA. M, molecular weight marker.
RAD52 Deletion Mutants in RPA-p34 Interaction Domain Failed to Induce Homologous Recombination in Monkey Cells—
Since the region (aa 221–280) appeared to be required for the intermolecular interaction between RAD52 and 34-kDa sub-
unit of RPA in vitro, functional significance of this region was
tested in vivo. We have shown previously the enhanced homologous recombination by overexpression of human RAD52 in
monkey cells (5). In order to test the importance of the RAD52/ RPA-p34 interacting domain in vivo, we built three mutant
constructs that had deletions in the interacting domain (aa 221–280) of RAD52 and tested their ability to induce homolo-
gous recombination in monkey cells. All three deletion con-
structs (d221–240, d241–260, and d261–280) were able to ex-
press intact mutant proteins in FSH2 cells, demonstrated by
indirect immunofluorescence microscopy and Western analysis
on total cell extracts using anti-c-Myc antibody (data not
shown).

As shown in Fig. 4, the FSH2 cells overexpressing the mu-
tant proteins failed to induce homologous recombination. The
lack of activation of homologous recombination in monkey cells
carrying the mutations in the p34-RAD52 interaction domain
could be due to the lack of a direct physical interaction between
these two proteins. However, we cannot rule out the possibil-
ity that the lack of physical interaction could be due to more
general defects in mutant RAD52 protein, for example im-
proper folding of the mutant proteins.

DISCUSSION
Multiprotein complexes are found to be involved in varieties of
DNA metabolism, including various types of DNA repair
(30–32) in mammalian cells. Recently, a mammalian protein
complex that repairs double strand breaks by recombination
has been identified (33). Formation of higher order complexes
through direct physical association appears to be crucial for
proper biochemical activities of these complexes. Here, we re-
port a direct physical association of human recombination pro-
tein RAD52 and RPA both
in vivo
and
in vitro.
We further
identified a RAD52 region that mediates this intermolecular
interaction. We also determined functional significance of this
domain
in vivo
using a homologous recombination assay in
monkey cells.

So far there has been only limited information on biochemi-
cal activities that are associated with the human RAD52 pro-
tein. However, yeast genetic studies provide a great deal of
insights about the potential role of RAD52 in mammalian cells.
Most recently, we demonstrated that RAD52 protein protects...
mammalian cells from ionizing radiation (5). This resistance of monkey cells to \textgamma-rays appears to be achieved by intrachromosomal recombination that is mediated by RAD52 protein. Throughout the years, it has been postulated that RAD52 might modulate the catalytic activities of RAD51 protein such as homologous pairing and strand exchange, but there is no direct biochemical evidence to support this hypothesis. Most recently, we have shown a physical interaction between human RAD51 and RAD52. In this study, we demonstrated a direct physical association between RAD52 and RPA complex both in vivo and in vitro. We speculate that the catalytic activity of RAD51 can be further fine-tuned through the formation of the ternary complex among RAD51, RAD52, and RPA. It is also tempting to speculate that RAD52 may bring different molecules together that are involved in recombination. This notion is supported by the unusual nature of structural organization of RAD52 protein. The RAD52 protein contains several distinct functional domains as shown in Fig. 5A. Remarkably, most parts of this 418-amino acid protein are used for diverse functions, including DNA binding,\(^2\) self-association,\(^3\) interaction with RPA (present study), and interaction with RAD51 (25). This clearly suggests the versatility of this protein in terms of intra/intermolecular interactions and its potential role as a nucleating factor that brings many different molecules together to the site of action. Another corroborating evidence comes from our previous observation of the dominant positive effects of RAD52 in mammalian recombination in vivo. The positive effect could have been due to the efficient nucleation of many other players such as RPA and RAD51 to the site of action through intermolecular interactions. These other players could be human homologs of yeast Rad55 and Rad57 that were proposed to constitute part of a complex, a "recombinosome" (34, 35).

The region of RAD52 that mediates the interaction with the 34-kDa subunit of RPA appears to be located between aa 221 and 280. This region is highly divergent among species and has only a limited amount of homology (\~7% identity, Fig. 5B) between yeast and human (5). This suggests that a species-specific interaction between human RPA and RAD52 is required for a productive biochemical transaction such as mammalian recombination. It has been shown previously that heterologous single strand binding proteins could not substitute for mammalian RPA in diverse aspects of DNA metabolism (13, 16, 22). The interaction between RAD51 and RAD52 also appears to be species-specific, because the overexpression of mammalian RAD51 genes failed to functionally complement yeast Rad51 null mutations (36). The interacting domain also has a very limited homology between yeast and human (Fig. 5B). Taken together, species-specific intermolecular interactions among human RPA, RAD52, and RAD51 appear to add another level of complexity to the intermolecular interactions among proteins that are involved in mammalian homologous recombination.

The primary structure of the RAD52 region that interacts with the 34-kDa subunit of RPA reveals an interesting feature of stretches of basic residues, suggesting a potential for interaction with the acidic C terminus of the 34-kDa subunit of RPA. This acidic domain on the 34-kDa subunit of RPA has been shown to interact with other proteins such as SV40 T-antigen (37) and XPA (37). This hypothesis is proven to be valid by our observation of the absence of physical interaction between RAD52 and a 34-kDa deletion mutant lacking the last 33 amino acids at the C terminus.\(^4\) All these data taken together suggest that this particular domain of the 34-kDa subunit is specifically required for diverse DNA transactions. This invokes a novel role of the 34-kDa subunit of RPA as a universal modulator of DNA replication, repair, and recombination. These transactions may be dependent on species-specific intermolecular interactions in vivo.

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