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RNA-templated DNA double-strand break repair: Role of RAD52

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Statement of the Problem: Homologous recombination (HR) is a high-fidelity process that uses homologous DNA sequences as a template to repair damaged DNA. However, we recently demonstrated that transcript RNA can also serve as template for DSB repair via HR in yeast. Currently, little is known about the enzymatic machinery that executes RNA-templated DSB repair. Our results from budding yeast implicated Rad52 in this RNA-directed DSB repair mechanism. However, the exact mechanism of how RAD52 contributes to RNA-dependent DSB repair remains to be elucidated.

Methodology & Theoretical Orientation: Using biochemical and genetic approaches in yeast we investigate this mechanism.

Findings: We found that RAD52 carries inverse strand exchange activity between homologous dsDNA and ssRNA, which could account for the role of RAD52 in RNA-dependent DNA repair identified in our genetic experiments. This activity is distinct from canonical "forward" DNA strand exchange which is carried by the major recombinase RAD51 between ssDNA and homologous dsDNA. We demonstrate that both human and yeast RAD52 efficiently promotes inverse strand exchange between dsDNA and homologous ssRNA or ssDNA. We show that in eukaryotes, inverse RNA strand exchange is a distinctive activity of RAD52; neither the major recombinase RAD51, nor the yeast RAD59 carries this activity. Our genetic experiments in yeast support the biological significance of inverse RNA strand exchange.

Conclusion & Significance: It was demonstrated that RAD52 inactivation causes synthetic lethality in combination with mutations in BRCA1 and BRCA2 proteins, defects of which are associated with various types of cancer. These data indicated an essential back-up function of RAD52, which may complement the BRCA-dependency in humans. We suggest that the novel RAD52 inverse strand exchange activities contribute to this back-up function. Thus, our findings may help to identify new therapeutic targets for cancer.

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