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Mini review

# RAD51, genomic stability, and tumorigenesis

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**Abstract**

Genomic instability is characteristic of malignant cells, and a strong correlation exists between abnormal karyotype and tumorigenicity. Increased expression of the homologous recombination and DNA repair protein Rad51 has been reported in immortalized cell lines and multiple primary tumor cell types which could alter recombination pathways to contribute to the chromosomal rearrangements found in these cells. In addition, Rad51 participates in a complex network of interactions that includes DNA damage sensors, tumor suppressors, and cell cycle and apoptotic regulators, and mutation of many of these proteins have also been associated with tumor initiation or progression. Insights into the connection between disregulated Rad51 and malignant phenotype indicate that Rad51 is a potential target for new anti-cancer regimens including those that use siRNA technology.


*Keywords:* Rad51; DNA repair; Recombination; Genomic stability; Tumorigenesis

## 1. Introduction

The faithful repair of DNA damage such as chromosomal double-strand breaks (DSBs) is necessary for the maintenance of genome integrity. DSBs and can result from exposure to DNA damaging agents including irradiation, alkylating agents, and topoisomerase II inhibitors, as well as during normal metabolic pathways including DNA replication and antigen receptor rearrangement in developing lymphoid cells. Illegitimate repair of DSBs is expected to result in chromosomal instability and rearrangements including translocations, deletions, duplications, and inversions, that are characteristic of immortalized and malignant cells [1,2]. In support of this, altered function of proteins involved in sensing DNA damage, DSB repair, and homologous recombination (HR) promotes or stabilizes rearrangements events that lead to malignancy [3–6].

Central to DSB repair by HR is Rad51. Rad51 promotes strand invasion and homologous pairing between two DNA duplexes [7–9]. The observation that multiple tumor cell types contain elevated amounts of Rad51 suggests a role in either the initiation or in the progression of tumorigenesis. As a consequence, extensive effort has been devoted to

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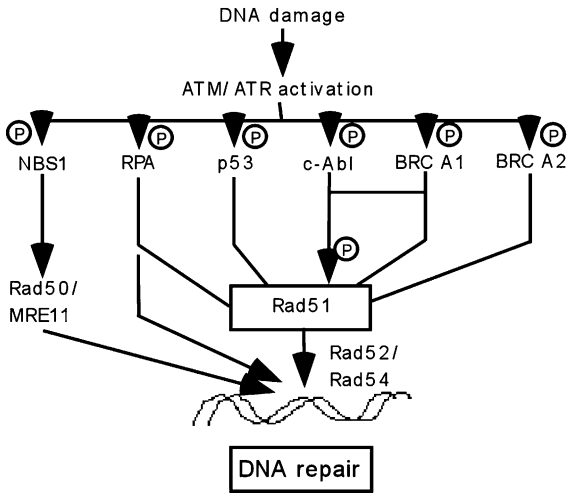


Fig. 1. Network of cellular signaling to Rad51 in response to DNA DSBs. Direct interactions and phosphorylation events lead to activation of Rad51 and formation of nucleo-protein filaments on DNA to stimulate HR.

determining the significance of this initial observation. It is now clear that in addition to its direct role in the HR biochemical reaction, Rad51 participates in an complex network of damage-sensing and cell cycle checkpoint signaling pathways (Fig. 1). This cellular cross-talk ensures that appropriate cell cycle checkpoints are initiated to allow for initial pairing and interaction with an appropriate repair template, and the final resolution of repaired products prior to cell division. However, determining the significance of altered Rad51 that results from any spectrum of mutations in malignant cells is complicated by these interactions. Regardless of the direct role of cellular Rad51 protein levels to the etiology of tumorigenesis, multiple assays have demonstrated that disregulated Rad51 leads to resistance to irradiation or cytotoxic agents, impaired protein interactions, altered fidelity of HR-mediated DSB repair, and gross chromosomal aberrations.

## 2. Mechanisms of DSB repair and genome rearrangements

The potentially tumorigenic consequence of illegitimate DNA repair events is inherently linked to the mechanism used for repair. At least two distinct processes contribute to repair of DSBs–non-homologous end-joining (NHEJ) and HR (for detailed discussion of DSB repair mechanisms see [1,10,11]). In somatic cells, HR-mediated DSB repair is best demonstrated by gene conversion that uses a homologous DNA duplex template to prime DNA synthesis across the damaged region [12–14]. The homologous template preferentially is on a sister chromatid [15], but may be on a homolog [16,17], or non-allelic repeat sequence on a heterologous chromosome [14,18]. As a consequence, chromosome rearrangements resulting from recombination between repetitive elements are associated with several genetic diseases and tumorigenesis [19,20].

### *2.1. Homologous recombination: the RAD52 epistasis group*

The RAD52 epistasis group members RAD50, RAD51, RAD52, RAD54, RAD54B, MRE11, and NBS1 participate in HR-mediated DSB repair in mitotic cells [11]. In addition, five human Rad51 paralogs encoded by XRCC2, XRCC3, RAD51B, RAD51C, and RAD51D genes were identified on the basis of sequence identity [10]. Although, two independent complexes of Rad51C-XRCC3 and Rad51B-C-D-XRCC2 have been isolated, their precise roles have yet to be defined [21–23]. It has been proposed that these are accessory proteins that assist in the loading of Rad51 onto single-stranded DNA. The RAD52 group proteins are expressed in multiple tissue types, but with higher levels seen in the testis and proliferating cells. The protein–protein interactions among various members of the epistasis group suggest two different complexes involved in DSB-induced recombination, the first involved in presynaptic functions including processing of the DSB ends, and the second involved in synaptic functions for invasion, creation of repair intermediates, and resolution. This second complex has been termed a recombinosome but has not yet been isolated.

### *2.2. Homologous recombination: central role of Rad51*

Rad51, the homolog of the *E. coli* RecA protein, is central to HR-mediated DSB repair. Rad51 forms nucleo-protein filaments on single-stranded DNA