Nucleic Acid Research: SURVEY AND SUMMARY article

Overexpressed of RAD51 suppresses recombination defects: a possible mechanism to reverse genomic instability **

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ABSTRACT

RAD51, a key protein in the homologous recombinational DNA repair (HRR) pathway, is the major strand-transferase required for mitotic recombination. An important early step in HRR is the formation of single-stranded DNA (ss-DNA) coated by RPA (a ss-DNA binding protein). Displacement of RPA by RAD51 is highly regulated and facilitated by a number of different proteins known as the 'recombination mediators'. To assist these recombination mediators, a second group of proteins also is required and we are defining these proteins here as 'recombination co-mediators'. Defects in either recombination mediators or co-mediators, including *BRCA1* and *BRCA2*, lead to impaired HRR that can genetically be complemented for (*i.e.* suppressed) by overexpression of RAD51. Defects in HRR have long been known to contribute to genomic instability leading to tumor development. Since genomic instability also slows cell growth, precancerous cells presumably require genomic restabilization to gain a growth advantage. RAD51 is overexpressed in many tumors, and therefore, we hypothesize that the complementing ability of elevated levels of RAD51 in tumors with initial HRR defects limits genomic instability during carcinogenic progression. Of particular interest, this model may also help explain the high frequency of *TP53* mutations in human cancers, since wild-type p53 represses RAD51.

INTRODUCTION

Homologous recombinational DNA repair plays an important role in cancer

The central protein involved in the homologous recombinational DNA repair (HRR) pathway is RAD51, a strand transfer protein. Although no mutations in the RAD51 open reading frame have been found in cancers, defects in other HRR genes have been shown to play an important role in carcinogenesis, and particularly in breast cancer. Inherited heteroallelic mutations in *BRCA1* and *BRCA2* each result in a breast cancer predisposition syndrome, and both of these genes are involved in HRR (1). In addition, eight more breast cancer predisposition syndromes have been identified, and all of these also involve defects in HRR-related genes (2). There have been several excellent and comprehensive reviews in recent years that describe the connections between HRR and cancer (particularly breast cancer) (1,3), the role of *TP53* mutations in recombination (4,5), and the observation that RAD51 is overexpressed in many tumors (6). What seems to be missing from these and other reviews is an overall hypothesis explaining the relationship between these three different components of carcinogenesis. Here, we review what we feel is the missing link that helps tie these components together. This missing link is the observation that overexpression of RAD51 partially complements (*i.e.* suppresses) a number of different HRR defects (*i.e.* mutations in recombination mediator and co-mediator genes, including *BRCA1* and *BRCA2*). This topic, which has not been reviewed before, is the central focus of this article.

RAD51 expression is upregulated in many cancers

For many years it has been observed that the levels of the RAD51 protein are greatly elevated (~2-7 fold) in many cancer cell lines and in primary tumors (reviewed by (6)). The wild-type p53 protein plays an important role both in suppressing the transcriptional expression of *RAD51* and in down-regulating RAD51 protein activity (4,5,7,8). The advantage for cancer cells of overexpressing RAD51 has yet to be adequately explained, but it has been suggested that the high levels of RAD51 are involved in tumor progression by destabilizing the genome (9). Another explanation is that elevated RAD51 confers a DNA replication advantage during the more rapid cell divisions that follow the activation of oncogenes and inactivation of tumor suppressors. Each of these explanations, at least in their basic form, suffers from the fact that, in general, overexpression of RAD51 is deleterious and slows cell growth *in vitro*, and therefore would also be likely to hinder the growth of cancer cells *in vivo*. Based on published reports about the ability of overexpressed RAD51 to suppress defects in HRR genes, two new alternative hypotheses are presented at the end of this article that may explain why *RAD51* is upregulated in many human cancers.

RECOMBINATION MEDIATORS AND CO-MEDIATORS

The HRR pathway is composed of a highly orchestrated network of proteins, many of which presumably still remain to be discovered. HRR frequently is initiated by a double-strand break, either due to endogenous lesions at the replication fork, or induced by different DNA damaging agents, including cisplatin, mitomycin C (MMC), camptothecin (CPT) and ionizing radiation. First, endonucleolytic activity produces a long 3´ single-

stranded DNA (ss-DNA) overhang that instantaneously is coated with RPA, the heterotrimeric ss-DNA binding protein. Displacement of RPA by RAD51 is critical and highly regulated, and initiates the strand transfer process (Fig. 1). The proteins directly involved in the displacement of RPA are named 'recombination mediators' (Table 1) (10,11) (here sometimes referred to as just 'mediators'). It is significant that mutations in these mediators result in high levels of genomic instability, as has been demonstrated for cells with deletions of *RAD51D* in both Chinese hamster ovary cells (CHO) and in murine embryonic fibroblast cells (MEFs) (12,13). In addition, this CHO *Rad51d* deletion has very high levels of mutagenesis.

There are also a number of proteins that function to assist these mediators or localize them to the site of the DNA break. These proteins have not previously been given a general name, but we propose to call them 'recombination co-mediators'. Many of the mediators and co-mediators are known tumor suppressor proteins, mutant versions of which frequently can be suppressed by overexpression of RAD51, as outlined below. This makes considerable biological sense, since these proteins function to assist RAD51. However, in their absence, RAD51 overexpression appears to be able to partially compensate. It is still unknown whether defects in other HRR proteins (*i.e.* non-mediators such as MRE11 and RAD54) can also be suppressed by RAD51 overexpression. Also, only some of the mediators/co-mediators have been tested for suppression by RAD51 overexpression, and there are additional proteins that may also be mediators/co-mediators since they interact with BRCA1 or BRCA2 (*i.e.* BARD1, BCCIPα&β, BRIP1/FANCJ/BACH1, and SHFM1/DSS1). With the use of the RNAi technique, it should be relatively easy to test these other potential human mediators/co-

mediators for complementation by RAD51 overexpression, and ideally these experiments should be done in human cell lines that initially express low levels of endogenous RAD51.

FUNCTIONAL SUPPRESSION BY RAD51 OVEREXPRESSION

Functional suppression in model organisms

Overexpression of RAD51 has been shown to partially suppress defects in recombination mediators and co-mediators in yeast, avian, rodent and human cells, although suppression of the HRR defect by exogenous RAD51 is generally not as complete as the complementation by a wild-type copy of the HRR gene that is mutated. In addition, in these experiments many different end-points were assessed, and for each end-point, the relative degree of complementation by exogenous RAD51 differs, for unknown reasons.

Yeast. In *Saccharomyces cerevisiae*, two different groups observed that cells with deletion mutations in *RAD55* and *RAD57*, the two yeast RAD51 paralogs, are partially suppressed by overexpression of RAD51 (14,15). In addition, overexpression of RAD52 resulted in partial suppression of both X-ray sensitivity and gene conversion defects, and simultaneous overexpression of both RAD51 and RAD52 gave near complete suppression for both phenotypes (14). Furthermore, although most mutations in *RAD52* are not suppressed by RAD51 overexpression, there is one allele of *RAD52* that is suppressed (16). Since *S. cerevisiae* lacks both *BRCA1* and *BRCA2* genes, it is not possible to test defects in these genes for complementation by RAD51 overexpression.

Chicken DT40 cells. The chicken DT40 cell line (p53 deficient) has been extensively used to characterize DNA repair defects. Each of the five RAD51 paralog genes has been separately knocked out in DT40 cells, and each knockout is partially complemented by overexpression of human RAD51 (17,18). The complementation of *RAD51B*$^{-/-}$ was the most extensively studied, and very interestingly, the authors observed significant complementation for MMC, cisplatin and X-ray sensitivity, and for genomic instability, but not for homologous integration events (17). This result argues that in DT40 cells and under conditions where a RAD51 paralog is lost, overexpression of human RAD51 largely, but not fully, ameliorates the HRR-deficiency. In addition, RAD51 overexpression partially complemented a *BRCA1* deletion, and overexpression of human RAD51 in *BRCA1*$^{\Delta/\Delta}$ DT40 cells almost completely rescued defects in cell proliferation (*i.e.* slow growth) and in DNA damage survival, and also partially rescued the defect in gene targeting frequency (19). These investigators also showed that human tumors with *BRCA1* mutations frequently exhibit elevated *RAD51* transcripts, as well as elevated transcripts of *RAD51AP1* and *RAD54*, encoding two late acting HRR proteins (19). This is indirect evidence that these *BRCA1*-deficient tumors had undergone selection for overexpression of *RAD51*, *RAD51AP1* and *RAD54*, and the authors suggested a somewhat similar hypothesis to the one presented here, although confined to *BRCA1*-deficiency only (19).

Functional suppression in mammalian cells

In the first direct studies in mammalian cells, two recent independent publications report that *BRCA2* defects are suppressed by RAD51 overexpression. In one study, the

BRCA2 mutant Capan-1 human pancreatic carcinoma cell line (with mutant p53) was shown to be partially complemented by overexpression of RAD51, assaying for cell survival after exposure to X-rays or cisplatin (20). In addition, complementation was better, and nearly complete, when a mutant form of RAD51 that is resistant to caspase-3 cleavage was expressed. In the same study, similar results on complementation by overexpression of wild-type Rad51 were also observed for *Brca2* mutant mouse embryonic fibroblasts (MEFs). In the second study, mouse hybridoma cell lines depleted for *Brca2*, using stable expression of siRNA, were studied for the effect of overexpression of the mouse Rad51, Rad52 and Rad54 proteins (21). In mouse hybridoma cells with low levels of Brca2, the reduced frequency of targeted integration and DNA damage-induced Rad51 foci formation was partially complemented for by overexpression of Rad51, but not by overexpression of either Rad52 or Rad54.

We have found only one relevant report that demonstrated a lack of complementation by human RAD51, and these experiments were carried out in *Xrcc3*-deficient CHO cells (22). In this study, complementation by RAD51 was assessed using an integrated recombinational reporter plasmid. It is possible that, if these *Xrcc3*-deficient CHO cells had been tested for the cellular sensitivity to MMC or cisplatin, a different result with respect to RAD51 complementation would have been observed, as discussed above for the DT40 *RAD51B*$^{-/-}$ cell line (17). It is worth noting that RAD51 is one of the most highly conserved proteins known. Consequently, the fact that the heterologous human RAD51 protein was expressed in *Xrcc3*-deficient CHO cells is unlikely to have biased the results reported by Pierce and collaborators (22). There is a *Brca2* mutant hamster V79 cell line (with mutant *Tp53*) (23), which would provide a

unique tool to study whether or not wild-type human RAD51 can complement *Brca2*-deficiency in a hamster background.

EFFECTS OF ECTOPIC OVEREXPRESSION OF RAD51

Since the effects of RAD51 overexpression in many different cellular systems have recently been extensively reviewed (6), the results of only some studies will be discussed here. In chicken DT40 cells with wild-type HRR, overexpression of human RAD51 resulted in increased cellular sensitivity to cisplatin, and this enhanced sensitivity of wild-type DT40 cells was equal to the cellular sensitivity of *BRCA1*$^{\Delta/\Delta}$ DT40 cells that did not express ectopic RAD51 (19). On the other hand, when RAD51 was overexpressed in the *BRCA1*$^{\Delta/\Delta}$ DT40 cells, near complete complementation was observed for cell survival after both cisplatin and X-rays. These experiments suggest that overexpression of RAD51 in cells with normal HRR can be deleterious, while overexpression in cells with an HRR defect can be beneficial (Fig. 2). (Note: the authors did not see X-ray sensitization of wild-type DT40 cells following RAD51 overexpression, but this test is not very sensitive, since non-homologous end-joining is the major repair pathway for X-ray damage.)

In wild-type (*i.e.* HRR-proficient) mammalian cells the effects of ectopic RAD51 overexpression are somewhat contradictory, but this may relate to the end-points assessed, the levels of RAD51 overexpression achieved, and the p53 status of the cell lines utilized. In CHO cells, overexpression of hamster RAD51 resulted in increased HRR, while a second study reported that overexpression of human RAD51 in CHO cells reduced homologous recombination at a double-strand break (24,25). In mouse ES

cells, RAD51 overexpression led to aneuploidy and chromosomal rearrangements (9). In the human fibrosarcoma HT1080 cell line, ectopic overexpression of human RAD51 was very deleterious to cells, resulting in a slow growth phenotype and increased levels of apoptosis (26).

UPREGULATION OF RAD51 IN TUMORS AND CANCER-DERIVED CELL LINES

Many different cancer-derived cell lines, as well as many tumors have been shown to have higher than normal levels of RAD51, as recently reviewed (6). The exact cause of this overexpression is not known, but there are important clues. For example, wild-type p53 has been reported to suppress the transcriptional regulation of *RAD51*, and *TP53* deletions and some *TP53* point mutations have been shown to upregulate the expression of RAD51 (7). There are also a number of additional factors that appear to play a role in *RAD51* regulation, most prominently the transcriptional activator protein 2 (AP2) (27). In addition to its role in transcriptional repression of *RAD51*, the wild-type p53 protein directly interacts with the RAD51 protein, inhibiting its activity (8).

TP53 MUTATIONS ARE UNDER REPRESENTED IN MISMATCH-REPAIR INITATED CANCERS

Approximately 50% of all cancers have mutations in *TP53*. In particular, cancers initiated by general genomic instability frequently have mutations in *TP53*. Alternatively, cancers initiated by mutations in genes of the mismatch repair (MMR) pathway and the subsequent microsatellite instability (MSI) are less frequently associated with mutations in *TP53* (28,29). This disparate occurrence of *TP53* mutations has never been

satisfactorily explained. The hypothesis presented here, that one of the main functions of mutant p53 is to upregulate RAD51, takes this disparity into account and provides an explanation for it, as discussed below. It is important to note that *TP53* mutations are very heterogeneous (4,30), and only a few mutant versions, other than the *TP53* homozygous deletion, have been tested for their effects on upregulating *RAD51* expression.

MODEL 1: UPREGULATION OF RAD51 SUPPRESSES HRR DEFECTS TO RESTABILIZE THE GENOME

We proposed that carcinogenesis is frequently initiated by defects in HRR genes (particularly in genes encoding recombination mediators or co-mediators) that result in genomic instability (Fig. 3A and 4A). There are likely to be many ways for a normal cell to develop an HRR defect, since HRR is a complex DNA repair pathway with many genes involved and presumably some yet to be discovered. In addition, there is evidence for haploinsufficiency for some HRR defects, and epigenetic silencing events also may account for compromised HRR ability. Interestingly, there is also evidence that point mutations in known HRR genes are not common in either breast or colorectal cancers (31). In their study, most of the transcripts from 11 cancers of each type were sequenced and only a small number of mutations in a few HRR-related genes were identified in cancers of the breast (*i.e. BCCIP*, *BRCA1*, *BRCA2*, *MRE11*, *FANCA* and *FANCM*) and of the colon (*FANCG*). Of these only mutations in *BRCA1* and *BRCA2* are known to be suppressible by RAD51 overexpression.

Genomic instability presumably facilitates both the activation of oncogenes and the inactivation of tumor suppressor genes (with the exception of *TP53*, which in the current model occurs as a later event). However, genomic instability initiated by defects in HRR is also deleterious due to the inhibitory effects on cell growth. Therefore, there is pressure to suppress genomic instability initiated by HRR deficiencies, and *TP53* mutations and/or mutations in other genes are selected for largely because they lead to the upregulation of RAD51, which then at least partially suppresses the initial HRR defect. It also seems likely that due to synergistic effects, some cancers may select for the overexpression of both RAD51 and HRR proteins that function later than the recombination mediators/co-mediators. (Note: there is evidence that RAD51AP1 functions late in HRR after the mediators (32,33), and RAD51AP1 has been shown to be upregulated in a number of cancers (19,34,35).) With regards to genomic rearrangements, there is evidence from cell lines derived from breast cancers, that genomic stability appears to be partially restored during tumor development (36), consistent with the proposed model.

We also propose that cancers initiated by MMR defects do not select for *TP53* mutations. Such mutations would upregulate RAD51, which would be deleterious in HRR-proficient cells. Besides, in such cancers there is no need to upregulate RAD51 for suppression purposes, and the precancerous cells achieve the additional benefits of *TP53* inactivation, such as downregulation of both apoptosis and checkpoint functions, by selecting for mutations in other genes that do not affect RAD51 expression

The model presented here, if correct, has profound implications for how cancers might be treated more effectively in the future. Our proposed hypothesis argues that

many more cancers may arise from HRR defects than has previously been suggested. If so, downregulation of RAD51 to normal levels (*i.e*. no longer suppressing the original HRR defect) may sensitize these tumor cells to genotoxic agents that kill HRR defective cells. Imatinib (Gleevec) has been reported to suppress the overexpression of RAD51, while not strongly affecting the levels of RAD51 in non-cancerous cells (37). Imatinib sensitizes tumors to radiation and to chemotherapy (38), and the model presented here provides a new perspective on such cancer treatment, that is based on the pro-oncogenic activity of RAD51 overexpression. Recently, PARP inhibitors have been used to target tumors with HRR defects such as *BRCA1* and *BRCA2* (39). Since PARP inhibitors preferentially target HRR-defective tumor cells, we propose that a combination therapy using both imatinib-type compounds and PARP inhibitors may be highly potent in the treatment of RAD51 overexpressing cancers.

MODEL II: RAD51 UPREGULATION LEADS TO GENOMIC INSTABILITY FIRST, FOLLOWED BY SELECTION FOR INACTIVATION OF AN HRR GENE TO RESTABILIZE THE GENOME

Overexpression of RAD51, like mutations in HRR, can destabilize the genome (9), as previously discussed. An alternative to Model I is that in some cancers the upregulation of RAD51 is an early event (Fig. 3B and 4B). Subsequently, as carcinogenesis proceeds, there is selection for an HRR defect to specifically counteract the effects of RAD51 overexpression. The consequence of each of these two proposed cancer developmental processes (*i.e.* Model I and Model II) is the same (*i.e.* cells with both an HRR defect and higher than normal levels of RAD51 protein), but the order of events is

reversed. The alternative Model II helps to explain why in some *BRCA*+/- carriers, inactivation of the second *BRCA* allele is a late event (40). This model suggests that in cancers arising by this order of events, the *BRCA* heterozygosity has little to do with the early events of carcinogenesis, but is required to rescue highly unstable cancer cells from the RAD51 upregulation. It is important to note that, although both models are mutually exclusive to explain the origin of a single tumor, each hypothesis may correctly explain the origin of some cancers. For both spontaneous and inherited predisposition-related cancers, some may have evolved with an HRR defect first, while other may have evolved first with a *TP53* mutation that upregulates RAD51.

FUTURE RESEARCH FOR EXAMINING RAD51 OVEREXPRESSION AND SUPPRESSION

There are a number of questions that should be experimentally addressed to further examine RAD51 overexpression and complementation. 1) Which HRR genes/defects are suppressed by RAD51 overexpression, and are all of these suppressible HRR defects in either recombination mediator or co-mediator genes? 2) Are elevated levels of RAD51AP1 and/or RAD54 synergistic to RAD51 overexpression in this suppression? 3) In addition to *TP53* and *AP2*, what other genes are involved in regulating the expression of *RAD51*? 4) Do most tumors that overexpress RAD51 have suppressed HRR defects and also *TP53* mutations? 5) If epigenetic silencing is involved in inactivating HRR functions, can these silencing events be reversed by drugs, and if so, is this reversal lethal or semi-lethal to cancer cells with high levels of RAD51 protein, even in the absence of genotoxic agents?

CONCLUDING REMARKS

In summary, overexpression of RAD51 in a number of different organisms has been shown to partially suppress defects in recombination mediator and co-mediator functions. In addition, *RAD51* is frequently upregulated in cancer cell lines and in primary tumors, although *RAD51* overexpression in the absence of any underlying HRR defect is frequently detrimental to growth of cells, at least in tissue culture.

Largely based on the published findings reviewed here, two closely related models are proposed that may help explain the role of *RAD51* upregulation in cancers. It is worth remembering that cancer is an extremely complex set of diseases, and that cancer cells develop many different mechanisms to achieve the same phenotype of independent and uncontrolled growth (41). The models presented here strive to explain certain aspects of oncogenic progression, and if these models prove correct, they will point the way to how some cancers arise and to novel roles for DNA repair functions in carcinogenesis.

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Figure legends

Figure 1. The mediator step of recombination: displacement of RPA by RAD51. A critical step in homologous recombinational repair is the displacement of RPA, the trimeric ss-DNA binding protein, by the RAD51 strand transfer protein This step is highly regulated by cells to ensure that potentially deleterious events are avoided. Many different proteins are involved in assisting RAD51 to displace RPA at this stage, and the proteins that are directly involved are known as the 'recombination mediators' (Table 1). There are also additional proteins that function to assist the mediators or assist in their localization to DNA damage, and in this review the proteins assisting the mediators are defined as 'recombination co-mediators'. Abbreviations: DSB - double-strand break; M/R/N – MRE11-RAD50-NBS1 complex.

Figure 2. Effects of RAD51 overexpression in wild-type and in HRR-mutant cells. **(A)** In cells with wild-type HRR, overexpression of RAD51 frequently results in the reduced ability to repair DNA damage at the replication fork, promoting sensitivity to genotoxic agents such as cisplatin and MMC, and this increased sensitivity normally coincides with genomic instability in untreated cells, due to unrepaired spontaneous damage. **(B)** On the other hand, overexpression of RAD51 in cells with a pre-existing HRR defect (labeled 'mutant') complements the imparted cell survival in HRR mutant cell, and presumably also complements the recombination defect and genomic instability. (Note: this figure is based on published data for wild-type and *BRCA1*$^{\Delta/\Delta}$ DT40 cells overexpressing human RAD51 (19).)

Figure 3. Schemes to explain the order of events in the two proposed models. **(A)** Model I: Normal cells that develop an HRR defect (*e.g. BRCA1*$^{-/-}$) select for loss of *TP53*, which then acts to upregulate RAD51 expression (red intensity of the nucleus represents RAD51 levels). Overexpression of RAD51 can in some cases lead to partial suppression of the original HRR defect, helping to stabilize the genome. **(B)** Model II: In some cancers, *TP53* mutations are early events and these upregulate RAD51 expression, resulting in increased genomic instability. Subsequent mutations/silencing in an HRR function partially suppresses the phenotype of RAD51 overexpression, reducing genomic instability.

Figure 4. **(A)** Summary of Model I explaining cancer development initiated by HRR defects. The model suggests that many cancers with genomic instability are initiated by HRR defects, just as cancers with MSI are initiated by MMR defects. In cancers with HRR defects, selection for upregulation of RAD51 acts to suppress the original HRR defect, partially restoring genomic stability and enhancing cell proliferation. *TP53* mutations frequently result in the upregulation of RAD51, and are selected for in cancers with a pre-existing HRR defect. **(B)** Summary of Model II explaining cancer development initiated by RAD51 upregulation. In this model inactivation of *TP53* and upregulation of RAD51 occur early in spontaneous oncogenesis (left side). In some *BRCA* heterozygous cells (*BRCA1*$^{+/-}$ or *BRCA2*$^{+/-}$), these events occur prior to functional loss of HRR resulting from a mutation or silencing of the second *BRCA* allele (right side). These are identical models, with the exception of the underlined phrases.

Table 1. Human recombination mediator and co-mediator proteins*

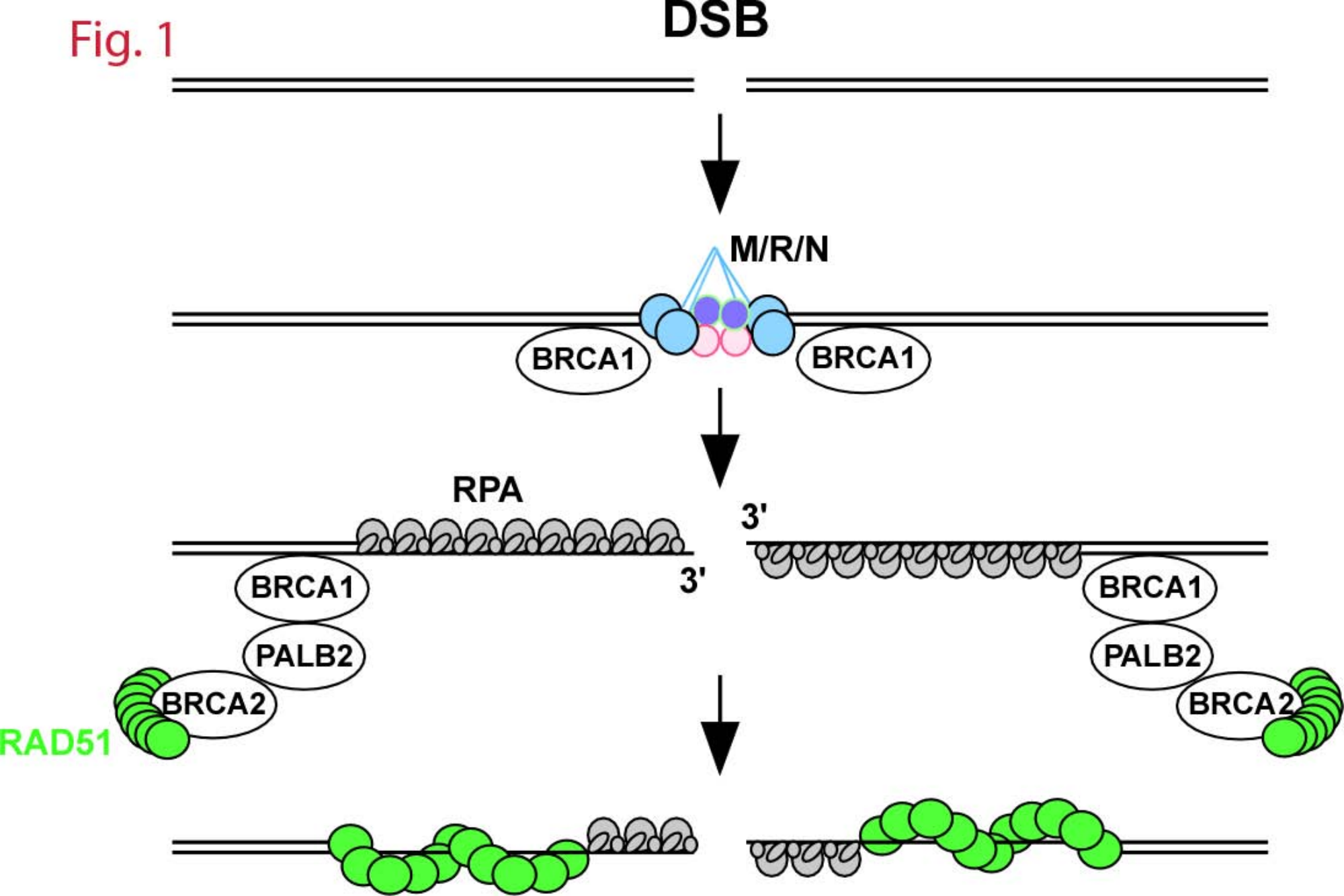
Recombination mediators:	**Involved in cancer?**	**Suppressed by RAD51 overexpression in DT40 or human cells?**
BRCA2/FANCD1	Yes	Yes
RAD51 paralogs:		
RAD51B/RAD51L1	?	Yes
RAD51C	?	Yes
RAD51D/RAD51L3	?	Yes
XRCC2	?	Yes
XRCC3	?	Yes
RAD52	?	nt**
Recombination co-mediators:		
BRCA1	Yes	Yes
CHK2	Yes	nt**
PALB2/FANCN	Yes	nt**

Potential mediators/co-mediators:	**Main interacting protein partner:**
BARD1	BRCA1
BCCIPα&β	BRCA2
BRIP/FANCJ/BACH1	BRCA1
DSS1/ SHFM1	BRCA2

* For references and further information see the following review articles: (1,2,11,42-44)

** nt – not tested yet

Fig. 1


DSB
M/R/N
BRCA1
BRCA1
RPA
3'
3'
BRCA1
PALB2
BRCA2
BRCA1
PALB2
BRCA2
RAD51

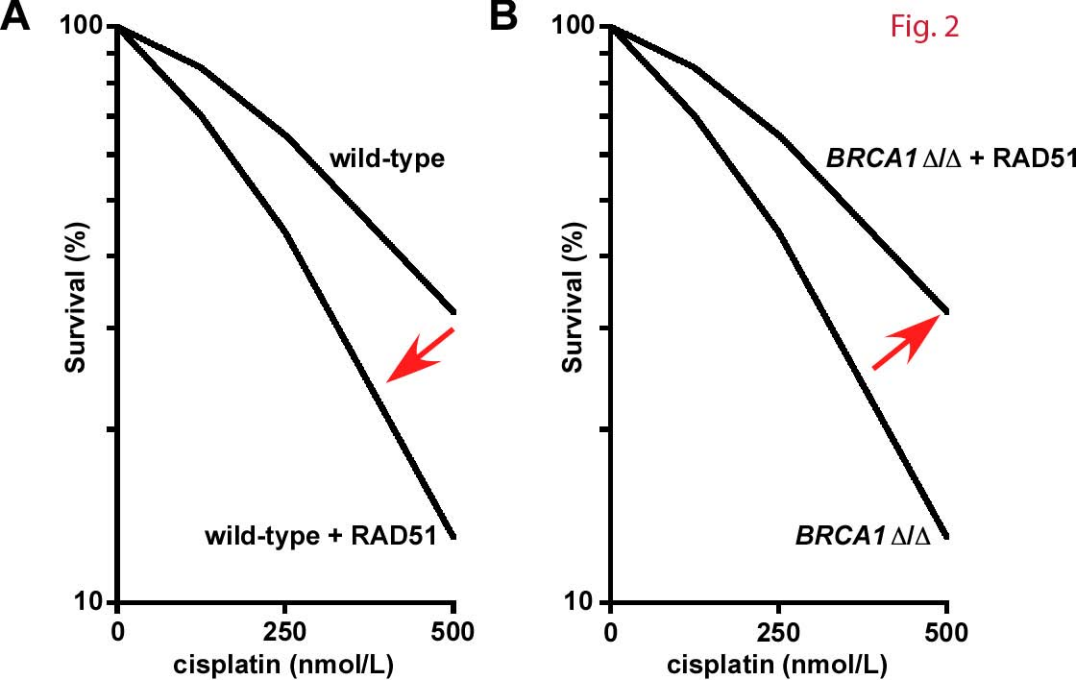
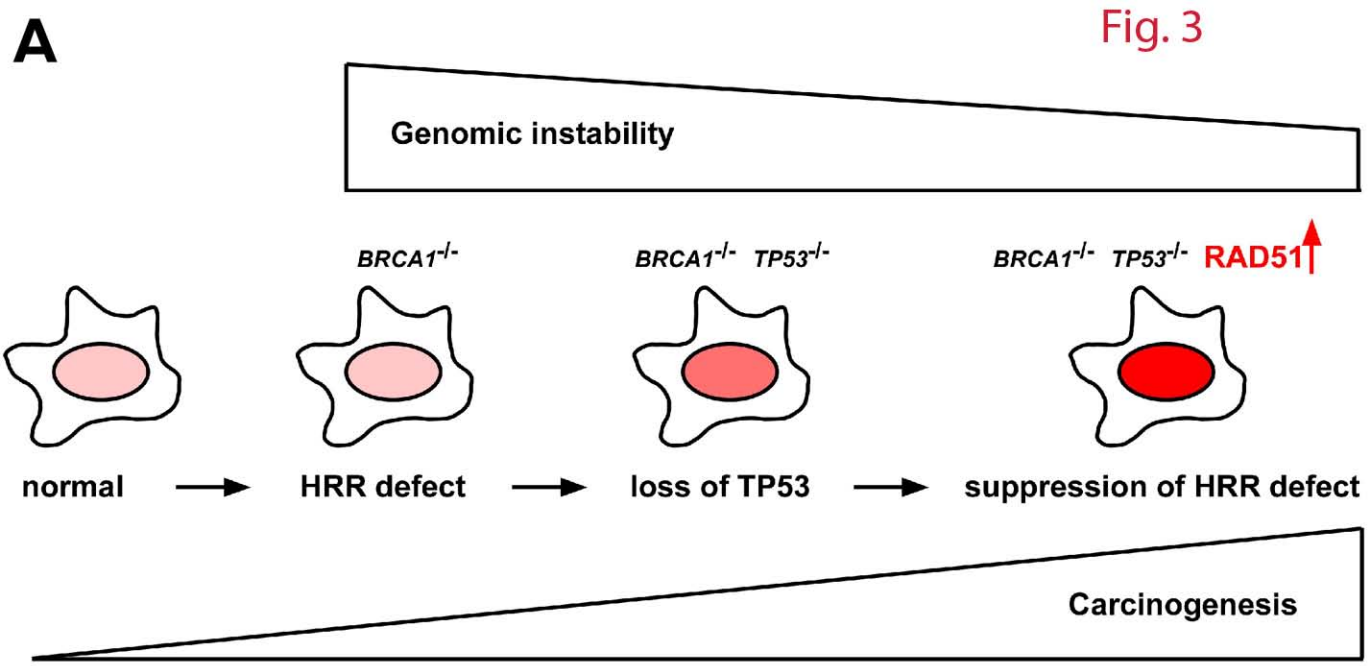

A
100
Survival (%)
wild-type
wild-type + RAD51
10
0
250
500
cisplatin (nmol/L)
B
100
Survival (%)
BRCA1 Δ/Δ + RAD51
BRCA1 Δ/Δ
10
0
250
500
cisplatin (nmol/L)

Fig. 2

Fig. 3


A
Genomic instability
BRCA1-/-
BRCA1-/- TP53-/-
BRCA1-/- TP53-/- RAD51
normal
HRR defect
loss of TP53
suppression of HRR defect
Carcinogenesis

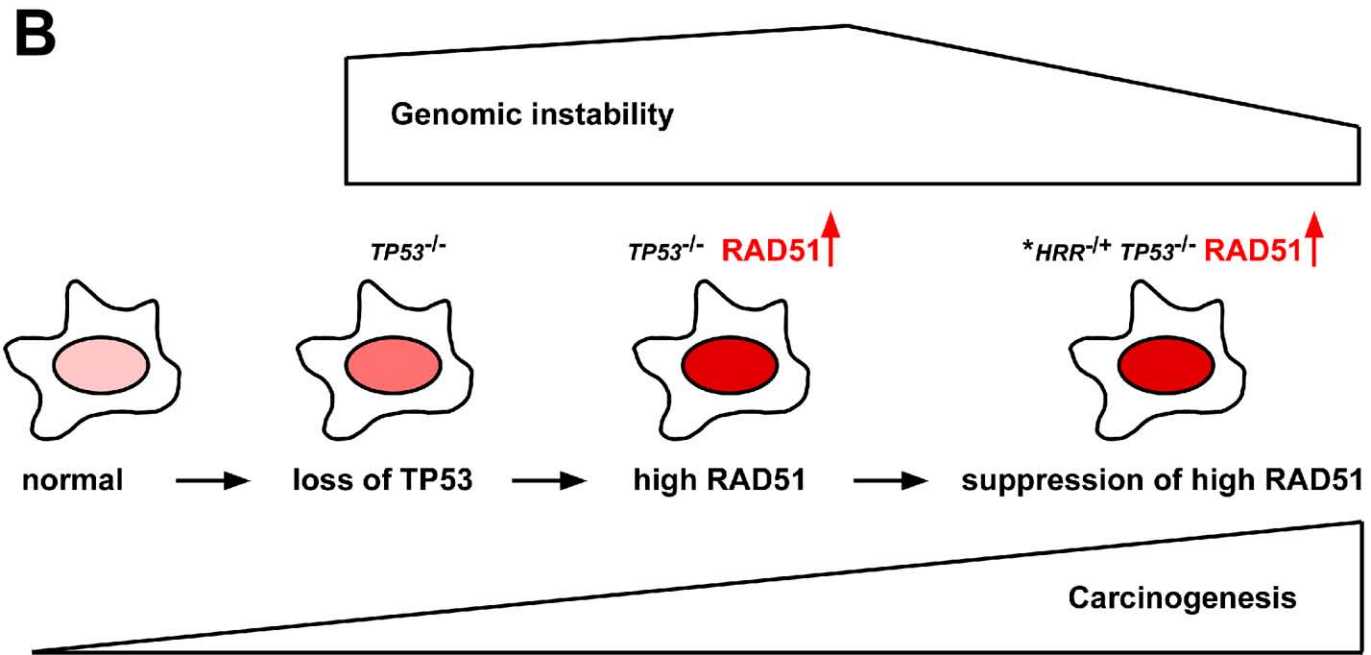
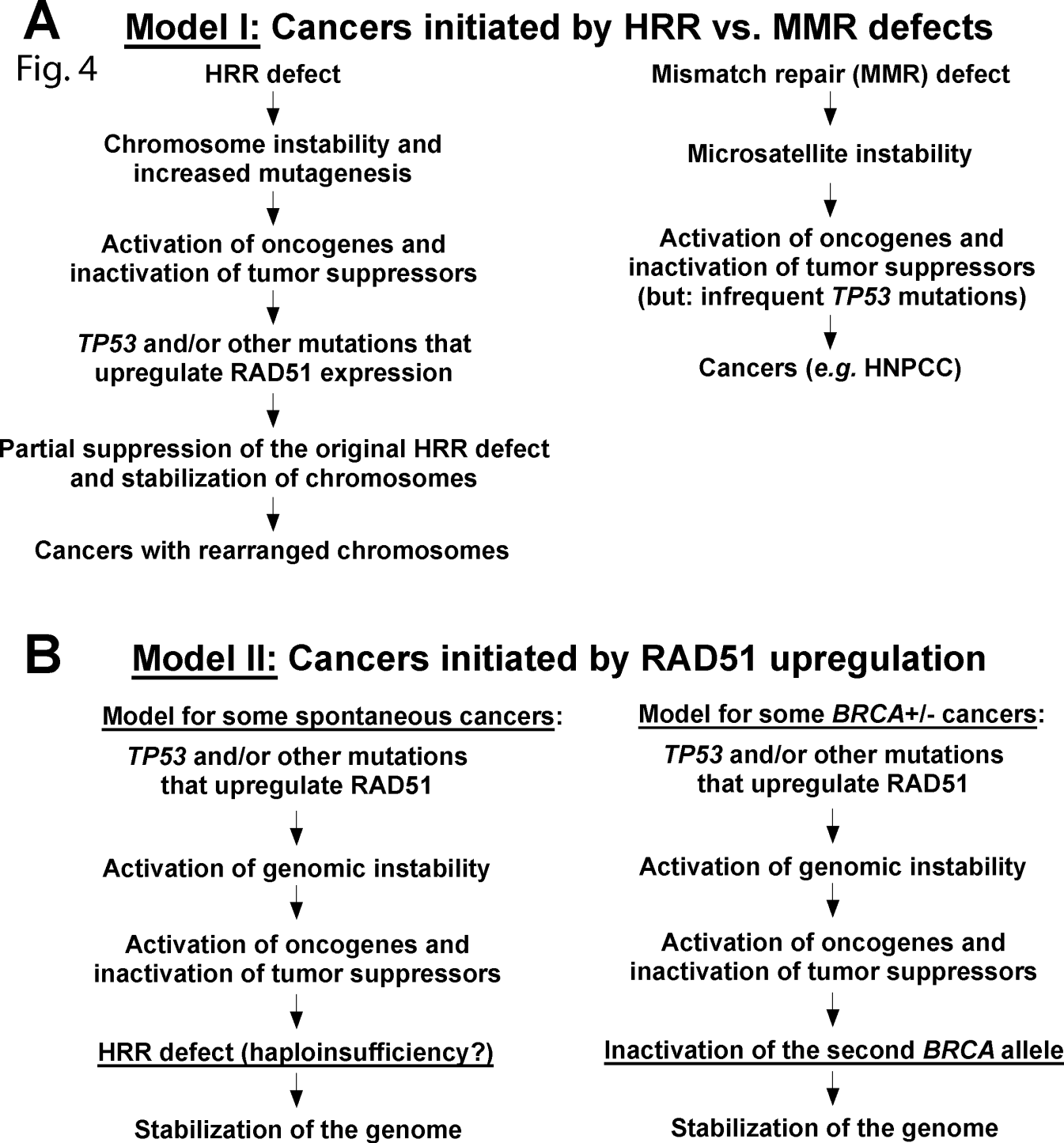

B
Genomic instability
TP53-/-
TP53-/- RAD51
*HRR-/+ TP53-/- RAD51
normal
loss of TP53
high RAD51
suppression of high RAD51
Carcinogenesis

Fig. 4


A
Model I: Cancers initiated by HRR vs. MMR defects
HRR defect
Chromosome instability and increased mutagenesis
Activation of oncogenes and inactivation of tumor suppressors
TP53 and/or other mutations that upregulate RAD51 expression
Partial suppression of the original HRR defect and stabilization of chromosomes
Cancers with rearranged chromosomes
Mismatch repair (MMR) defect
Microsatellite instability
Activation of oncogenes and inactivation of tumor suppressors (but: infrequent TP53 mutations)
Cancers (e.g. HNPCC)
B
Model II: Cancers initiated by RAD51 upregulation
Model for some spontaneous cancers:
TP53 and/or other mutations that upregulate RAD51
Activation of genomic instability
Activation of oncogenes and inactivation of tumor suppressors
HRR defect (haploinsufficiency?)
Stabilization of the genome
Model for some BRCA+/- cancers:
TP53 and/or other mutations that upregulate RAD51
Activation of genomic instability
Activation of oncogenes and inactivation of tumor suppressors
Inactivation of the second BRCA allele
Stabilization of the genome