

crossroads between DNA replication and recombination? The breast cancer susceptibility gene, BRCA2: at the

Ashok R. Venkitaraman

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THE ROYAL
 The breast cancer susceptibility gene, *BRCA2***: at the crossroads between DNA replication**
at the crossroads between DNA replication **incer susceptibility gen
proads between DNA re
and recombination?**

Ashok R. Venkitaraman

CRC Department of Oncology, University of Cambridge, and The WellcomeTrust Centre for the Study of Molecular Mechanisms in Disease,The Cambridge Institute for Medical Research, CRC Department of Oncology, University of Cambridge, and
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Wellcome Trust—MRC Building, Hills Road, Cambridge CB2 2XY, UK
The identification and cloning of the familial breast cancer susceptibility gene, *BRCA2*, has excited much
interest in its biological functions. Here, evidenc The identification and cloning of the familial breast cancer susceptibility gene, *BRCA2*, has excited much interest in its biological functions. Here, evidence is reviewed that the protein encoded by *BRCA2* has an essent The identification and cloning of the familial breast cancer susceptibility gene, *BRCA2*, has excited much interest in its biological functions. Here, evidence is reviewed that the protein encoded by *BRCA2* has an essent interest in its biological functions. Here, evidence is reviewed that the protein encoded by *BRCA2* has an essential role in DNA repair through its association with mRad51, a mammalian homologue of bacterial and yeast pro essential role in DNA repair through its association with mRad51, a mammalian homologue of bacterial participation in recombinational processes essential for DNA replication.

Keywords: BRCA2; DNA replication; homologous recombination; cancer

**1.BREAST CANCER SUSCEPTIBILITY GENES AST CANCER SUSCEPTIBILITY GENE
AND CANCER PREDISPOSITION**

INNET CANCER PREDISPOSITION
Inherited mutations in the *BRCA2* gene predispose humans **EXPREDISPOSITION**
therited mutations in the *BRCA2* gene predispose humans
of familial, early-onset breast cancer (Wooster *et al.* 1994,
995: Taytigian *et al.* 1996). The gene was first identified by nherited mutations in the *BRCA2* gene predispose humans

2 familial, early-onset breast cancer (Wooster *et al.* 1994,

995; Tavtigian *et al.* 1996). The gene was first identified by

positional cloning approach through % 5 familial, early-onset breast cancer (Wooster *et al.* 1994, 995; Tavtigian *et al.* 1996). The gene was first identified by positional cloning approach through the analysis of milies exhibiting an increased susceptibi 995; Tavtigian *et al.* 1996). The gene was first identified by positional cloning approach through the analysis of unilies exhibiting an increased susceptibility. Moreover, positional cloning approach through the analysis of
imilies exhibiting an increased susceptibility. Moreover,
bunder mutations in the *BRCA2* gene associated with
preased cancer susceptibility have been identified in increased susceptibility. Moreover, under mutations in the $BRCA2$ gene associated with acreased cancer susceptibility have been identified in averal geographically or ethnically restricted buman bunder mutations in the *BRCA2* gene associated with
icreased cancer susceptibility have been identified in
everal geographically or ethnically restricted human
opulations (for example Gudmundsson *et al.* 1996; porter as the example of example, Gudmundsson *et al.* 1996;
populations (for example, Gudmundsson *et al.* 1996; veral geographically or ethnically restricted human
opulations (for example, Gudmundsson *et al.* 1996;
phannesdottir *et al.* 1996;Neuhausen *et al.* 1996;Thorlacius
 $\frac{1}{d}$ 1996) In contrast mutations in *BBCA2* do not opulations (for example, Gudmundsson *et al.* 1996;

blannesdottir *et al.* 1996; Neuhausen *et al.* 1996; Thorlacius
 et al. 1996). In contrast, mutations in *BRCA2* do not appear

a be a feature of sporadic breast canc bhannesdottir *et al.* 1996; Neuhausen *et al.* 1996; Thorlacius
 \cdot *al.* 1996). In contrast, mutations in *BRCA2* do not appear
 \cdot be a feature of sporadic breast cancer (reviewed in
 \cdot alman & Stratton 1998) $\begin{bmatrix} 2 \end{bmatrix}$ is a feature of sporadic lahman & Stratton 1998).
Rahman & Stratton 1998). be a feature of sporadic breast cancer (reviewed in
thman & Stratton 1998).
BRCA2 is not simply a breast cancer susceptibility gene.
ne spectrum of cancer predisposition associated with

BRCA2 mutations has not fully been characterized. It is lready clear, for example, that *BRCA2* mutation carriers The spectrum of cancer predisposition associated with
RCA2 mutations has not fully been characterized. It is
lready clear, for example, that *BRCA2* mutation carriers
ready susceptible to familial ovarian cancer (Wooste *RCA2* mutations has not fully been characterized. It is
lready clear, for example, that *BRCA2* mutation carriers
re also susceptible to familial ovarian cancer (Wooster *et*
 $l = 1996$). Cancers of the prostate *also* clear, for example, that *BRCA2* mutation carriers
 a re also susceptible to familial ovarian cancer (Wooster *et*
 d. 1994; Tavtigian *et al.* 1996). Cancers of the prostate,
 ancreas and male breast may also pre also susceptible to familial ovarian cancer (Wooster *et l.* 1994; Tavtigian *et al.* 1996). Cancers of the prostate,
ancreas and male breast may also be associated with
 $\frac{RCA2$ mutations (Thorlacius *et al.* 1996) *I.* 1994; Tavtigian *et al.* 1996). Cancers of the prostate,
ancreas and male breast may also be associated with
 $\frac{RCA2}{R}$ mutations (Thorlacius *et al.* 1996). The occurrence) ancreas and male breast may also be associated with
 $\sum_{i=1}^{RCA2}$ mutations (Thorlacius *et al.* 1996). The occurrence

of thymic lymphomas in currently available mouse
 $\sum_{i=1}^{RCA2}$ deficiency (Connor *et al.* 1997 \sum_{c}^{RCA2} mutations (Thorlacius *et al.* 1996). The occurrence f thymic lymphomas in currently available mouse in details for *BRCA2* deficiency (Connor *et al.* 1997; riedman *et al.* 1998), to be discussed elsewhere f thymic lymphomas in currently available mouse podels for *BRCA2* deficiency (Connor *et al.* 1997; riedman *et al.* 1998), to be discussed elsewhere in this aper, deserves mention. Although there does not appear a be an excess risk of lymphoma in human *BRCA2* mutariedman *et al.* 1998), to be discussed elsewhere in this aper, deserves mention. Although there does not appear
b e an excess risk of lymphoma in human *BRCA2* muta-
on carriers the incidence of *BRCA2* mutations in aper, deserves mention. Although there does not appear

b e an excess risk of lymphoma in human *BRCA2* muta-

on carriers, the incidence of *BRCA2* mutations in

approaching the product of any product of the evaluated be an excess risk of lymphoma in human $BRCA2$ muon
on carriers, the incidence of $BRCA2$ mutations
objective cases of lymphoma remains to be evaluated.
Despite the wide scientific and public interest engor carriers, the incidence of *BRCA2* mutations in oradic cases of lymphoma remains to be evaluated.
Despite the wide scientific and public interest engen-
red by the cloning of *BRCA2* little information has

by poradic cases of lymphoma remains to be evaluated.

Despite the wide scientific and public interest engenered by the cloning of *BRCA2*, little information has

een gleaned merely by analysis of the gene's sequence. It Despite the wide scientific and public interest engenered by the cloning of *BRCA2*, little information has een gleaned merely by analysis of the gene's sequence. It ered by the cloning of *BRCA2*, little information has
een gleaned merely by analysis of the gene's sequence. It
ncodes a large protein of 3418 amino acids in humans,
hich bears no significant resemblance to molecules of ncodes a large protein of 3418 amino acids in humans,

The spectrum of cancer susceptibility gene. The spectrum of cancer predisposition associated with a spectrum of cancer predisposition associated with repeats, are not associated with a similar phenotype. known function. The only remarkable feature is the
presence of a cluster of eight repeated sequences the soknown function. The only remarkable feature is the presence of a cluster of eight repeated sequences, the so-
called BBC repeats (Bork *et al.* 1996) located within known function. The only remarkable feature is the presence of a cluster of eight repeated sequences, the so-
called BRC repeats (Bork *et al.* 1996), located within
BRC42 exon 11 (figure 1). The sequence of the BRC presence of a cluster of eight repeated sequences, the so-
called BRC repeats (Bork *et al.* 1996), located within
BRCA2 exon 11 (figure 1). The sequence of the BRC called BRC repeats (Bork *et al.* 1996), located within *BRCA2* exon 11 (figure 1). The sequence of the BRC repeats is highly conserved between several species of mammals although the intervening sequences are not *BRCA2* exon 11 (figure 1). The sequence of the BRC repeats is highly conserved between several species of mammals, although the intervening sequences are not (Bignell *et al.* 1997) Viewed in the light of the generally repeats is highly conserved between several species of mammals, although the intervening sequences are not (Bignell *et al.* 1997). Viewed in the light of the generally limited $\langle \alpha, 60\% \rangle$ homology between murine and h mammals, although the intervening sequences are not (Bignell *et al.* 1997). Viewed in the light of the generally limited $\langle ca. 60\% \rangle$ homology between murine and human (Bignell *et al.* 1997). Viewed in the light of the generally limited (*ca.* 60%) homology between murine and human BRCA2 proteins (Sharan & Bradley 1997), this suggests that the BRC repeats may have a conserved and essen limited (*ca.* 60%) homology between murine and human
BRCA2 proteins (Sharan & Bradley 1997), this suggests
that the BRC repeats may have a conserved and essential
role in the function of BRCA2. It may be significant that BRCA2 proteins (Sharan & Bradley 1997), this suggests
that the BRC repeats may have a conserved and essential
role in the function of BRCA2. It may be significant that
the *BRCA2* mutations associated with familial ovaria that the BRC repeats may have a conserved and essential role in the function of BRCA2. It may be significant that the *BRCA2* mutations associated with familial ovarian role in the function of BRCA2. It may be significant that
the *BRCA2* mutations associated with familial ovarian
cancer tend to cluster within the BRC repeat region
encoded by example (Gayther et al. 1997). It must be the *BRCA2* mutations associated with familial ovarian
cancer tend to cluster within the BRC repeat region
encoded by exon 11 (Gayther *et al.* 1997). It must be
noted however that these are truncating mutations cancer tend to cluster within the BRC repeat region encoded by exon 11 (Gayther *et al.* 1997). It must be noted, however, that these are truncating mutations, making it difficult to explain why truncations positioned encoded by exon 11 (Gayther *et al.* 1997). It must be noted, however, that these are truncating mutations, making it difficult to explain why truncations positioned more $5'$ in the gene, which also result in the loss of noted, however, that these are truncating mutations,
making it difficult to explain why truncations positioned
more 5['] in the gene, which also result in the loss of BRC
repeats are not associated with a similar phenotype making it difficult to explain why truncations position
more 5' in the gene, which also result in the loss of B
repeats, are not associated with a similar phenotype.
Positional cloning has also identified another bre

Positional cloning has also identified another breast repeats, are not associated with a similar phenotype.
Positional cloning has also identified another breast
cancer susceptibility gene, *BRCA1*, which in humans
encodes a protein of 1863 amino acids (Miki et al. 1994). Positional cloning has also identified another breast
cancer susceptibility gene, *BRCA1*, which in humans
encodes a protein of 1863 amino acids (Miki *et al.* 1994). It
is important to emphasize that despite the similarit cancer susceptibility gene, *BRCAI*, which in humans
encodes a protein of 1863 amino acids (Miki *et al.* 1994). It
is important to emphasize that despite the similarity in
their acronyms the molecules themselves are high encodes a protein of 1863 amino acids (Miki *et al.* 1994). It is important to emphasize that despite the similarity in their acronyms, the molecules themselves are highly is important to emphasize that despite the similarity in
their acronyms, the molecules themselves are highly
distinct in sequence (figure 1). There is much circumstan-
tial evidence, however to suggest some commonality in their acronyms, the molecules themselves are highly
distinct in sequence (figure 1). There is much circumstan-
tial evidence, however, to suggest some commonality in
their functions. Mutations in either gene confer a marke distinct in sequence (figure 1). There is much circumstantial evidence, however, to suggest some commonality in their functions. Mutations in either gene confer a marked increase in breast cancer risk in humans. Targeted t tial evidence, however, to suggest some commonality in their functions. Mutations in either gene confer a marked increase in breast cancer risk in humans. Targeted truncations in the murine homologues of *BRCA1* (Gowen *et al.* 1996; Hakem *et al.* 1996; Liu *et al.* 1996; Ludwig *et al.* 1997) or *BRCA2* (Ludwig *et al.* 1997; Sharan *et al.* 1997; Suzuki *et al.* 1997) result in either early embryonic lethality at day or *BRCA2* (Ludwig *et al.* 1997; Sharan *et al.* 1997; Suzuki *et al.* 1997) result in either early embryonic lethality at day 7–9 or, if positioned more carboxyl-terminally in *BRCA2* (Connor *et al.* 1997: Friedman *et* d. 1997) result in either early embryonic lethality at day
7–9 or, if positioned more carboxyl-terminally in *BRCA2*
(Connor *et al.* 1997; Friedman *et al.* 1998), severe embryonal
growth retardation, perinatal lethality 7–9 or, if positioned more carboxyl-terminally in *BRCA2* (Connor *et al.* 1997; Friedman *et al.* 1998), severe embryonal growth retardation, perinatal lethality and the development of the division tumours in surviving a (Connor *et al.* 1997; Friedman *et al.* 1998), severe embryonal growth retardation, perinatal lethality and the development of thymic tumours in surviving adults. Both genes encode nuclear proteins that are highly expres ment of thymic tumours in surviving adults. Both genes

igure 1. Shows a schematic representation of the human igure 1. Shows a schematic representation of the human
RCA1 and BRCA2 proteins. Known structural features are
arked but are not drawn to scale. The RING and BRCT igure 1. Shows a schematic representation of the human
 RCA1 and BRCA2 proteins. Known structural features are
 $\text{ranked, but are not drawn to scale.}$ The RING and BRCT
 RCA1 are putative protein-protein interaction RCA1 and BRCA2 proteins. Known structural features are
arked, but are not drawn to scale. The RING and BRCT
pomains in BRCA1 are putative protein-protein interaction
actifs. The Rad51 binding sites in both proteins, and th arked, but are not drawn to scale. The RING and BRCT

pomains in BRCA1 are putative protein-protein interaction

potifs. The Rad51 binding sites in both proteins, and the

proteinal motifs found in BRCA2, are discussed in structural motifs found in BRCA2, are discussed in \S 1 and 3.

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The S phase of the cell cycle (Rajan *et al.* 1996; Bertwistle *et*

1 1997: In *et al.* 1997). Finally, there is evidence that **a** let S phase of the cell cycle (Rajan *et al.* 1996; Bertwistle *et l.* 1997; Jin *et al.* 1997). Finally, there is evidence that RCA1 and BRCA2 proteins co-localize to subpuclear The S phase of the cell cycle (Rajan *et al.* 1996; Bertwistle *et l.* 1997; Jin *et al.* 1997). Finally, there is evidence that RCA1 and BRCA2 proteins co-localize to subnuclear ructures in mitotic and meiotic cells an *l.* 1997; Jin *et al.* 1997). Finally, there is evidence that RCA1 and BRCA2 proteins co-localize to subnuclear ructures in mitotic and meiotic cells, and may even bysically associate at low stoichiometry (Chen *et al.* RCA1 and BRCA2 proteins co-localize to subnuclear ructures in mitotic and meiotic cells, and may even hysically associate at low stoichiometry (Chen *et al.* 1998*c*). hysically associate at low stoichiometry (Chen *et al.* \bigcirc 998*c*).

For both *BRCA1* and *BRCA2*, inheritance of a single

 $\begin{bmatrix} 5998c. \\ \text{For both } BRCA1 \text{ and } BRCA2, \text{ inheritance of a single} \\ \text{effective allele is sufficient to confer cancer predisposition, but tumours isolated from mutation carriers almost.} \end{bmatrix}$ For both *BRCA1* and *BRCA2*, inheritance of a single efective allele is sufficient to confer cancer predispotion, but tumours isolated from mutation carriers almost lwave exhibit a loss of heterozymosity (Collins *et al.* efective allele is sufficient to confer cancer predispotion, but tumours isolated from mutation carriers almost lways exhibit a loss of heterozygosity (Collins *et al.* 1995; independence *et al.* 1995; By contrast, there tion, but tumours isolated from mutation carriers almost
lways exhibit a loss of heterozygosity (Collins *et al.* 1995;
indmundsson *et al.* 1995). By contrast, there are no
enorts of tumour predisposition in mice heterozy lways exhibit a loss of heterozygosity (Collins *et al.* 1995;

ludmundsson *et al.* 1995). By contrast, there are no

eports of tumour predisposition in mice heterozygous for

argeted mutations in *RRCA1* or *RRCA2*. No Fudmundsson *et al.* 1995). By contrast, there are no eports of tumour predisposition in mice heterozygous for argeted mutations in *BRCA1* or *BRCA2*. No satisfactory xplanation is yet available for this species-specific eports of tumour predisposition in mice heterozygous for
argeted mutations in *BRCA1* or *BRCA2*. No satisfactory
xplanation is yet available for this species-specific differ-
nee in the phenotype of *BRCA2* heterozygotes argeted mutations in *BRCA1* or *BRCA2*. No saturally species-specified in the phenotype of *BRCA2* heterozygotes. **2.BRCA2 AND DNA REPAIR 2.BRCA2 AND DNA REPAIR**

There is little in the nucleotide sequence of *BRCA2* that is suggestive of its biological function. The first insights ave therefore emerged from studies of mice harbouring argeted mutations in the murine homologue of the ave therefore emerged from studies of mice harbouring
argeted mutations in the murine homologue of the
BRCA2 gene (hereafter termed *Brca2* in accordance with
the accepted nomenclature). An essential role in embryargeted mutations in the murine homologue of the $RCA2$ gene (hereafter termed $Brca2$ in accordance with the accepted nomenclature). An essential role in embry-
and cellular proliferation and as a consequence in $RCA2$ gene (hereafter termed *Brca*2 in accordance with
he accepted nomenclature). An essential role in embry-
hal cellular proliferation and as a consequence, in
trauterine viability has been inferred from the marked also be accepted nomenclature). An essential role in embry-
and cellular proliferation and as a consequence, in
trauterine viability, has been inferred from the marked
rowth retardation and early embryonal lethality nal cellular proliferation and as a consequence, in *al.* 1998; Sonoda *et al.* 1998).

11 trauterine viability, has been inferred from the marked Strikingly, Brca2^{Tr/Tr} cel

12 rowth retardation and early embryonal let The anterine viability, has been inferred from the marked
rowth retardation and early embryonal lethality
parent in animals homozygous for truncations in *Brca2*
ron 10 (Ludwig *et al.* 1997: Sharan *et al.* 1997: Suzuki rowth retardation and early embryonal lethality
parent in animals homozygous for truncations in *Brea2*
xon 10 (Ludwig *et al.* 1997; Sharan *et al.* 1997; Suzuki *et*
l 1997) Perhans more amenable to further study a role **pearent in animals homozygous for truncations in** *Brea2*
al. 1997). Perhaps more amenable to further study, a role
al. 1997). Perhaps more amenable to further study, a role
by *Brea2* in the cellular response to D xon 10 (Ludwig *et al.* 1997; Sharan *et al.* 1997; Suzuki *et*
Brca2 in the cellular response to DNA damage has
leen postulated from the observation that it associates $\begin{bmatrix} 1 & 1997 \end{bmatrix}$. Perhaps more amenable to further study, a role
or *Braa2* in the cellular response to DNA damage has
been postulated from the observation that it associates
with mammalian (m)Rad51 (Chen *et al.* 1 or *Brea2* in the cellular response to DNA damage has

) een postulated from the observation that it associates

) ith mammalian (m)Rad51 (Chen *et al.* 1998*b*; Mizuta *et*

/ 1997[,] Sharan *et al.* 1997; Wong *et al.* 1 een postulated from the observation that it associates
 al. 1997; Sharan *et al.* 1997; Wong *et al.* 1997), a homologue
 al. 1997; Sharan *et al.* 1997; Wong *et al.* 1997), a homologue 1 the repair of DNA double-strand breaks (DSBs) by f the bacterial protein RecA, which is known to function

1 the repair of DNA double-strand breaks (DSBs) by

enetic recombination. Consistent with this notion,

urine blastocysts homozygous for a Rra^2 exon 10 trun-1 the repair of DNA double-strand breaks (DSBs) by
enetic recombination. Consistent with this notion,
nurine blastocysts homozygous for a *Brca*² exon 10 trun-
ation exhibit X-ray sensitivity (Sharan et al. 1997) as do enetic recombination. Consistent with this notion,
urine blastocysts homozygous for a *Brea*² exon 10 trun-
ation exhibit X-ray sensitivity (Sharan *et al.* 1997), as do
broblests harbouring a truncation in the ^{3'} regi urine blastocysts homozygous for a *Broa2* exon 10 trun-
ation exhibit X-ray sensitivity (Sharan *et al.* 1997), as do
broblasts harbouring a truncation in the 3' region of
xon 11 (Connor *et al* 1997) ation exhibit X-ray sensitivit
broblasts harbouring a true
xon 11 (Connor *et al.* 1997).
Although these observation roblasts harbouring a truncation in the 3' region of
on 11 (Connor *et al.* 1997).
Although these observations hint at a role for Brca2 in
NA repair, they admit of several explanations. The

Fig. 2.1 (Sonnor *et al.* 1997).
Although these observations hint at a role for Brca2 in
NA repair, they admit of several explanations. The Although these observations hint at a role for Brca2 in

NA repair, they admit of several explanations. The

ellular response to DNA damage (reviewed in Friedberg
 $\frac{1}{a}$ (1995) involves the activation of cell-cycle ch *et al.* 1995) involves the activation of several explanations. The ellular response to DNA damage (reviewed in Friedberg : *al.* 1995) involves the activation of cell-cycle check-*Phil. Trans. R. Soc. Lond.* B (2000) *Phil. Trans. R. Soc. Lond.* B (2000)

points to prevent the replication of damaged DNA
templates the recruitment of the machinery for DNA points to prevent the replication of damaged DNA
templates, the recruitment of the machinery for DNA
repair and sometimes the induction of apontosis in the points to prevent the replication of damaged DNA
templates, the recruitment of the machinery for DNA
repair and sometimes, the induction of apoptosis in the
face of overwhelming irreparable genetic damage Thus templates, the recruitment of the machinery for DNA
repair and sometimes, the induction of apoptosis in the
face of overwhelming, irreparable genetic damage. Thus,
an increased sensitivity to X-rays is only indicative of a repair and sometimes, the induction of apoptosis in the face of overwhelming, irreparable genetic damage. Thus, an increased sensitivity to X-rays is only indicative of a potential dysfunction in any of the cellular respon face of overwhelming, irreparable genetic damage. Thus,
an increased sensitivity to X-rays is only indicative of a
potential dysfunction in any of the cellular responses to
DNA damage, and not necessarily of defective DNA an increased sensitivity to X-rays is only indicative of a
potential dysfunction in any of the cellular responses to
DNA damage, and not necessarily of defective DNA
repair here potential dysfunction in any of the cellular responses to

DNA damage, and not necessarily of defective DNA

repair *per se*.

It is therefore important that checkpoint activation and

apoptosis appear to be largely intact

repair *per se*.
It is therefore important that checkpoint activation and
apoptosis appear to be largely intact in fibroblasts and
lymphocytes isolated from mice harbouring a targeted It is therefore important that checkpoint activation and
apoptosis appear to be largely intact in fibroblasts and
lymphocytes isolated from mice harbouring a targeted
truncation at residue 1492 in *Brca*2 exon 11 (termed t apoptosis appear to be largely intact in fibroblasts and
lymphocytes isolated from mice harbouring a targeted
truncation at residue 1492 in *Brca2* exon 11 (termed the
Brca^{2Tr} allele) (Patel *et al.* 1998) Brca^{2Tr/Tr} lymphocytes isolated from mice harbouring a targeted truncation at residue 1492 in *Brca2* exon 11 (termed the *Brca2*^{Tr} allele) (Patel *et al.* 1998). Brca2^{Tr/Tr} cells exhibit truncation at residue 1492 in *Brca2* exon 11 (termed the *Brca2*^{Tr} allele) (Patel *et al.* 1998). Brca2^{Tr/Tr} cells exhibit arrest in the G1 and G2/M phases of the cell cycle following exposure to X-rays or IIV light *Brea*^{2Tr} allele) (Patel *et al.* 1998). Brea^{2Tr/Tr} cells exhibit arrest in the G1 and G2/M phases of the cell cycle following exposure to X-rays or UV light, and abrogate DNA synthesis after treatment with hydroxyure arrest in the G1 and $G2/M$ phases of the cell cycle following exposure to X-rays or UV light, and abrogate DNA synthesis after treatment with hydroxyurea. More-over even small doses of X-rays can induce the apontotic following exposure to X-rays or UV light, and abrogate DNA synthesis after treatment with hydroxyurea. Moreover, even small doses of X-rays can induce the apoptotic DNA synthesis after treatment with hydroxyurea. Moreover, even small doses of X-rays can induce the apoptotic death of Brca2^{Tr/Tr} cells just as efficiently as in wild-type cells. Thus these observations indicate that Br over, even small doses of X-rays can induce the apoptotic
death of Brca2^{Tr/Tr} cells just as efficiently as in wild-type
cells. Thus, these observations indicate that Brca2 has an
essential function in some aspect of the cells. Thus, these observations indicate that Brca2 has an essential function in some aspect of the DNA damage response that is distinct from participation in checkpoint essential function in some aspect of the DNA damage essential function in some aspect of the DNA damage
response that is distinct from participation in checkpoint
enforcement or apoptosis. Since the Brca2^{Tr} allele leaves
the exons encoding residues $1-1492$ intact, a rol response that is distinct from participation in checkpoint
enforcement or apoptosis. Since the Brca 2^{Tr} allele leaves
the exons encoding residues $1-1492$ intact, a role for these
amino-terminal domains in checkpoints o enforcement or apoptosis. Since the Brca2^{Tr} allele leaves
the exons encoding residues $1-1492$ intact, a role for these
amino-terminal domains in checkpoints or apoptosis is
not of course, excluded by these findings (Pa the exons encoding residues $1-1492$ intact, a role for these amino-terminal domains in checkpoints or apoptosis is not, of course, excluded by these findings (Patel *et al.* 1998). It is noteworthy in this context that a not, of course, excluded by these findings (Patel *et al.* 1998). It is noteworthy in this context that a *Brcal* exon 11 in-frame deletion gives rise to abnormalities in the G2/M checknoints (X₁₁ *et al.* 1999) althoug 1998). It is noteworthy in this context that a *Brcal* exon 11 in-frame deletion gives rise to abnormalities in the $G2/M$ checkpoints (Xu *et al.* 1999), although the significance of this observation to Brca? function rem in-frame deletion gives rise to abnormalities in the $G2/M$
checkpoints (Xu *et al.* 1999), although the significance of
this observation to Brca2 function remains to be ascer-
tained tained. this observation to Brca2 function remains to be ascertained.
The spectrum of genotoxin sensitivity exhibited by

tained.
The spectrum of genotoxin sensitivity exhibited by
Brca2^{Tr/Tr} cells is consistent with a defect in DNA repair
by homologous recombination (Patel *et al.* 1998). Like The spectrum of genotoxin sensitivity exhibited by $\text{Brca2}^{\text{Tr}/\text{Tr}}$ cells is consistent with a defect in DNA repair by homologous recombination (Patel *et al.* 1998). Like $\text{Brca2}^{\text{Tr}/\text{Tr}}$ cells, yeast mutants i Brca2^{Tr/Tr} cells is consistent with a defect in DNA repair
by homologous recombination (Patel *et al.* 1998). Like
 $Brca2^{Tr/T}$ cells, yeast mutants in the *RAD52* epistasis
group of genes (including *RAD51, RAD52, RAD55* by homologous recombination (Patel *et al.* 1998). Like Brca2^{Tr/Tr} cells, yeast mutants in the *RAD52* epistasis group of genes (including *RAD51, RAD52, RAD55, RAD57, RAD59, MRE11* and *Xrs2*) involved in the repair of group of genes (including *RAD51, RAD52, RAD55, RAD57, RAD59, MRE11* and *Xrs2*) involved in the repair of DSBs by homologous recombination generally exhibit cross-sensitivity to X-rays IIV light and monofunctional $RAD57$, $RAD59$, $MRE11$ and $Xrs2$) involved in the repair
of DSBs by homologous recombination generally exhibit
cross-sensitivity to X-rays, UV light and monofunctional
alkylating agents. Similar sensitivities are observed of DSBs by homologous recombination generally exhibit
cross-sensitivity to X-rays, UV light and monofunctional
alkylating agents. Similar sensitivities are observed in cross-sensitivity to X-rays, UV light and monofunctional
alkylating agents. Similar sensitivities are observed in
vertebrate cells deficient in *Rad54* (Bezzubova *et al.* 1997;
Essers *et al.* 1997) as well as in *Rad51*alkylating agents. Similar sensitivities are observed in
vertebrate cells deficient in *Rad54* (Bezzubova *et al.* 1997;
Essers *et al.* 1997), as well as in *Rad51*-related genes (Jones
et al. 1987: I im & Hasty 1996; T vertebrate cells deficient in *Rad54* (Bezzubova *et al.* 1997; Essers *et al.* 1997), as well as in *Rad51*-related genes (Jones *et al.* 1987; Lim & Hasty 1996; Tsuzuki *et al.* 1996; Liu *et al.* 1998; Sonoda *et al. al.* 1997), as well as in *et al.* 1987; Lim & Hasty 199
al. 1998; Sonoda *et al.* 1998).
Strikingly Brea^{2Tr/Tr} cells al. 1987; Lim & Hasty 1996; Tsuzuki *et al.* 1996; Liu *et*
1998; Sonoda *et al.* 1998).
Strikingly, Brca2^{Tr/Tr} cells spontaneously accumulate
merous chromosomal aberrations (Patel *et al.* 1998)

The bacterial mixture of the bacterial protein RecA, which is known to function
 $\begin{array}{ll}\n\bullet & \bullet & \bullet \\
\bullet & \bullet & \bullet \\
\bullet & \bullet & \bullet\n\end{array}$ (figure 2) reflect defective chromatid
 $\begin{array}{ll}\n\bullet & \bullet & \bullet \\
\bullet & \bullet & \bullet \\
\bullet & \bullet & \bullet\n\end{array}$ (Sharan *et al* al. 1998; Sonoda *et al.* 1998).

Strikingly, Brca2^{Tr/Tr} cells spontaneously accumulate

numerous chromosomal aberrations (Patel *et al.* 1998)

during passage in culture (figure 2). The aberrations numerous chromosomal aberrations (Patel *et al.* 1998) during passage in culture (figure 2). The aberrations numerous chromosomal aberrations (Patel *et al.* 1998)
during passage in culture (figure 2). The aberrations
include chromatid and chromosome breaks, and the
formation of structures termed tri-radial and quadriduring passage in culture (figure 2). The aberrations
include chromatid and chromosome breaks, and the
formation of structures termed tri-radial and quadri-
radial chromosomes previously noted in the human include chromatid and chromosome breaks, and the
formation of structures termed tri-radial and quadri-
radial chromosomes previously noted in the human
genetic disease Bloom syndrome (German 1993) These formation of structures termed tri-radial and quadri-
radial chromosomes previously noted in the human
genetic disease Bloom syndrome (German 1993). These radial chromosomes previously noted in the human
genetic disease Bloom syndrome (German 1993). These
latter abnormalities (figure 2) reflect defective chromatid
exchange during homologous recombination in mitotic genetic disease Bloom syndrome (German 1993). These
latter abnormalities (figure 2) reflect defective chromatid
exchange during homologous recombination in mitotic
cells, with tri-radials (Y-shaned chromosome structures latter abnormalities (figure 2) reflect defective chromatid
exchange during homologous recombination in mitotic
cells, with tri-radials (Y-shaped chromosome structures
with three arms) indicative of incomplete separation exchange during homologous recombination in mitotic cells, with tri-radials (Y-shaped chromosome structures
with three arms) indicative of incomplete separation
following isochromatid exchange and quadri-radials
(star-shaped structures with four arms) arising from a with three arms) indicative of incomplete separation
following isochromatid exchange and quadri-radials
(star-shaped structures with four arms) arising from a
flaved exchange between chromosomes. More recently following isochromatid exchange and quadri-radials (star-shaped structures with four arms) arising from a flawed exchange between chromosomes. More recently, similar abnormalities have been described in *Brcal* exon-(star-shaped structures with four arms) arising from a flawed exchange between chromosomes. More recently, similar abnormalities have been described in *Brca1* exon-
11-deficient murine cells (Xu *et al.* 1999). These obse similar abnormalities have been described in *Brca1* exon-
11-deficient murine cells (Xu *et al.* 1999). These observa-
tions demonstrate that Brca1 deficiency or Brca2
deficiency in mouse models may give rise to a phenot 11-deficient murine cells (Xu *et al.* 1999). These observations demonstrate that Brcal deficiency or Brca2 deficiency in mouse models may give rise to a phenotype reminiscent of other human diseases (table 1) in which tions demonstrate that Brcal deficiency or Brca2
deficiency in mouse models may give rise to a phenotype
reminiscent of other human diseases (table 1) in which chromosomal instability is associated with cancer

Figure 2. Chromosomal abnormalities that spontaneously
regime 2. Chromosomal abnormalities that spontaneously Example 12. Chromosomal abnormalities that spontaneously
cumulate in cultures of murine fibroblasts homozygous
lyn a targeted truncation in the *Brea*? gene. Note the bigh Figure 2. Chromosomal abnormalities that spontaneously
ccumulate in cultures of murine fibroblasts homozygous
for a targeted truncation in the *Brca2* gene. Note the high
sequency of the aberrations and the occurrence of ccumulate in cultures of murine fibroblasts homozy

for a targeted truncation in the *Brea*2 gene. Note the

frequency of the aberrations, and the occurrence of
 α) chromatid (ctb) and chromosome breaks (b) tri-(a) chromatid (ctb) and chromosome breaks, (*b*) tri-radial (ctb) and chromosome breaks, (*b*) tri-radial (ctb) and chromosome breaks, (*b*) tri-radial (ctb) and (*c*) quadri-radial (qr) chromosomes **R** enroduced

a) chromatid (ctb) and chromosome breaks, (b) tri-radial (r) , and (c) quadri-radial (qr) chromosomes. Reproduced om Patel *et al.* 1998, with the permission of Cell Press. (r) , and (c) quadri-radial (qr) chromosomes. Reproduced

from Patel et al. 1998, with the permission of Cell Press.
predisposition. More specifically, they suggest that some
exturns of this phenotype may arise from a defect in the features of this phenotype may arise from a defect in the bility to correctly execute or regulate DNA repair by redisposition. More specifically, they suggest that some atures of this phenotype may arise from a defect in the bility to correctly execute or regulate DNA repair by omologous recombination atures of this phenotype may arise from a defect in the bility to correctly execute or regulate DNA repair by omologous recombination.

3.DNA REPAIR BY HOMOLOGOUS RECOMBINATION

DNA REPAIR BY HOMOLOGOUS RECOMBINATION
The mechanism for homologous recombination is most
rarly understood in *Escherichia coli*. The bacterial RecA The mechanism for homologous recombination is most
learly understood in *Escherichia coli*. The bacterial RecA
rotein plays a central role in the process (reviewed in
least $\log 8$ Cox 1997) It recognizes and aligns homolo learly understood in *Escherichia coli*. The bacterial RecA
rotein plays a central role in the process (reviewed in
loca & Cox 1997). It recognizes and aligns homologous
erions in the two DNA molecules that are to undergo rotein plays a central role in the process (reviewed in
loca & Cox 1997). It recognizes and aligns homologous
egions in the two DNA molecules that are to undergo
ecombination, and mediates the strand exchange reacloca & Cox 1997). It recognizes and aligns homologous egions in the two DNA molecules that are to undergo ecombination, and mediates the strand exchange reacthe two DNA molecules that are to undergo
the exchange reachination, and mediates the strand exchange reaching
on, which generates a crossover between them. A
umber of additional proteins are pecessary to initiate ecombination, and mediates the strand exchange reac-
on, which generates a crossover between them. A
umber of additional proteins are necessary to initiate,
equilate and complete the reactions catalyzed by RecA on, which generates a crossover between them. A umber of additional proteins are necessary to initiate, egulate and complete the reactions catalysed by RecA. The RecRCD protein complex which includes DNA heliumber of additional proteins are necessary to initiate,
egulate and complete the reactions catalysed by RecA.
The RecBCD protein complex, which includes DNA heli-
ase ATPase exo- and endonuclease activities, acts at egulate and complete the reactions catalysed by RecA.

The RecBCD protein complex, which includes DNA heliase, ATPase, exo- and endonuclease activities, acts at

SRs to generate a stretch of single-strand DNA that The RecBCD protein complex, which includes DNA heliase, ATPase, exo- and endonuclease activities, acts at SBs to generate a stretch of single-strand DNA that ase, ATPase, exo- and endonuclease activities, acts at SSBs to generate a stretch of single-strand DNA that express as a substrate for homologous strand pairing by lecA. The single-strand DNA substrate is coated by Figures as a substrate for homologous strand pairing by
lecA. The single-strand DNA substrate is coated by
lecA polymers to form a nucleoprotein filament. Fila-
ent assembly is regulated by the RecFOR proteins and ecA. The single-strand DNA substrate is coated by

lecA polymers to form a nucleoprotein filament. Fila-

ent assembly is regulated by the RecFOR proteins and

reginale-strand binding protein SSR Finally the RuyAtent assembly is regulated by the RecFOR proteins and
ae single-strand binding protein SSB. Finally, the RuvA-The results and the recombination intermediates
act to resolve the recombination intermediates
are a recombination intermediates
are the action of RecA through effects on branch The single-strand binding protein SSB. Finally, the RuvA-

Proteins act to resolve the recombination intermediates

primed by the action of RecA through effects on branch

principle and on Holliday interior resolution by e For proteins act to resolve the recombination intermediates
of the action of RecA through effects on branch
igration, and on Holliday junction resolution by endo-
releasing cleavage Formed by the action

igration, and on Ho

ucleolytic cleavage.

Homologous recom expration, and on Holliday junction resolution by endo-
cleolytic cleavage.
Homologous recombination in *E. coli* has classically
en studied as a mechanism for the generation of diver-

b ucleolytic cleavage.

Homologous recombination in E *coli* has classically

een studied as a mechanism for the generation of diveren studied as a mechanism for the generation of diverty during conjugation, a process for which the RecA
athway is essential. There is much evidence, however,
at the pathway also plays an important role in DNA ty during conjugation, a process for which the RecA
athway is essential. There is much evidence, however,
nat the pathway also plays an important role in DNA
enair and may in particular be an effective response to athway is essential. There is much evidence, however,
at the pathway also plays an important role in DNA
epair, and may in particular be an effective response to
 $2N_A$ strand gaps or DSBs (Meselson & Radding 1975; at the pathway also plays an important role in DNA

epair, and may in particular be an effective response to

DNA strand gaps or DSBs (Meselson & Radding 1975;

Vest et al. 1981: Szostak et al. 1983) This is certainly tru epair, and may in particular be an effective response to
DNA strand gaps or DSBs (Meselson & Radding 1975;
Vest *et al.* 1981; Szostak *et al.* 1983). This is certainly true
vest where homologous recombination is the major INA strand gaps or DSBs (Meselson & Radding 1975;
Vest *et al.* 1981; Szostak *et al.* 1983). This is certainly true
1 yeast, where homologous recombination is the major
1 years, where homologous recombination is the majo Vest *et al.* 1981; Szostak *et al.* 1983). This is certainly true a yeast, where homologous recombination is the major athway for the repair of DSBs. It has been asserted that, a contrast, mammalian cells repair DSBs pri in yeast, where homologous recombination is the major non-homology-dependent mechanisms such as non-

Table 1. *Genetic diseases where aberrations in chromosome structure are associated with cancer predisposition* structure are associated with cancer predisposition

Charly understood in *Escherichia coli*. The bacterial RecA
learly understood in *Escherichia coli*. The bacterial RecA
deficient avian cells, defective in NHEJ or recombination homologous end joining (NHEJ) (reviewed in Friedberg et dl 1995; Jackson & Jeggo 1995). The evidence to *et al.* 1995; Jackson & Jeggo 1995). The evidence to the sympart this assertion is largely indiced coming from homologous end joining (NHEJ) (reviewed in Friedberg *et al.* 1995; Jackson & Jeggo 1995). The evidence to support this assertion is largely indirect, coming from studies in which integration as opposed to homologous *et al.* 1995; Jackson & Jeggo 1995). The evidence to support this assertion is largely indirect, coming from studies in which integration, as opposed to homologous recombination of transfected DNA predominates in support this assertion is largely indirect, coming from
studies in which integration, as opposed to homologous
recombination, of transfected DNA predominates in
mammalian.cells. More recent work, however, challenges studies in which integration, as opposed to homologous
recombination, of transfected DNA predominates in
mammalian cells. More recent work, however, challenges
the notion that homologous recombination is a minor or recombination, of transfected DNA predominates in
mammalian cells. More recent work, however, challenges
the notion that homologous recombination is a minor or
unimportant pathway for DSB repair in mammalian mammalian cells. More recent work, however, challenges
the notion that homologous recombination is a minor or
unimportant pathway for DSB repair in mammalian the notion that homologous recombination is a minor or
unimportant pathway for DSB repair in mammalian
cells. DSBs experimentally induced into mammalian
chromosomes by the activity of rare-cutting endonuunimportant pathway for DSB repair in mammalian
cells. DSBs experimentally induced into mammalian
chromosomes by the activity of rare-cutting endonu-
cleases enhance homologous recombination by two to cells. DSBs experimentally induced into mammalian
chromosomes by the activity of rare-cutting endonu-
cleases enhance homologous recombination by two to
three orders of magnitude (Rouet et al. 1994). As many as chromosomes by the activity of rare-cutting endonu-
cleases enhance homologous recombination by two to
three orders of magnitude (Rouet *et al.* 1994). As many as
30–50% of DSBs introduced in this way at direct repeat cleases enhance homologous recombination by two to three orders of magnitude (Rouet *et al.* 1994). As many as $30-50\%$ of DSBs introduced in this way at direct repeat sequences are resolved by homology-directed repair three orders of magnitude (Rouet *et al.* 1994). As many as 30–50% of DSBs introduced in this way at direct repeat sequences are resolved by homology-directed repair mechanisms (Liang *et al.* 1998). Indeed, although rodent cells deficient in the major NHFI pathway dependent on sequences are resolved by homology-directed repair
mechanisms (Liang *et al.* 1998). Indeed, although rodent
cells deficient in the major NHEJ pathway dependent on
the *xrc4*–7 genes are bigbly sensitive to ionizing radia mechanisms (Liang *et al.* 1998). Indeed, although rodent cells deficient in the major NHEJ pathway dependent on the *xrcc4*⁻⁷ genes are highly sensitive to ionizing radiation during Gl they are relatively resistant late cells deficient in the major NHEJ pathway dependent on
the $xrc4-7$ genes are highly sensitive to ionizing radiation
during G1, they are relatively resistant late in the S phase
or in $G²$ when homologous recombinati the *xrce*4–7 genes are highly sensitive to ionizing radiation
during G1, they are relatively resistant late in the S phase
or in G2, when homologous recombination can occur
between replicated DNA strands (Stamato *et al.* during Gl, they are relatively resistant late in the S phase
or in G2, when homologous recombination can occur
between replicated DNA strands (Stamato *et al.* 1988;
Whitmore *et al.* 1989; Cheong *et al.* 1994). A similar or in G2, when homologous recombination can occur
between replicated DNA strands (Stamato *et al.* 1988;
Whitmore *et al.* 1989; Cheong *et al.* 1994). A similar
phenotype is apparent in Ku70-deficient or RAD54between replicated DNA strands (Stamato et al. 1988; deficient avian cells, defective in NHEJ or recombination phenotype is apparent in Ku70-deficient or RAD54-
deficient avian cells, defective in NHEJ or recombination
mechanisms, respectively (Takata *et al.* 1998). Collectively,
these observations suggest that homologous recombin deficient avian cells, defective in NHEJ or recombination
mechanisms, respectively (Takata *et al.* 1998). Collectively,
these observations suggest that homologous recombina-
tion may be of particular importance for DNA re mechanisms, respectively (Takata *et al.* 1998). Collectively, these observations suggest that homologous recombination may be of particular importance for DNA repair during DNA replication in mammalian cells these observations suggest that homologous recombination may be of particular importance for DNA repair during DNA replication in mammalian cells. It should be emphasized that, quite apart from its should be emphasized that, quite apart from its intential role in DNA replication and/or repair in mitotic

during DNA replication in mammalian cells.
It should be emphasized that, quite apart from its
potential role in DNA replication and/or repair in mitotic
cells homologous recombination initiated at DSBs is It should be emphasized that, quite apart from its
potential role in DNA replication and/or repair in mitotic
cells, homologous recombination initiated at DSBs is
essential for the normal completion of meiosis (Haber potential role in DNA replication and/or repair in mitotic
cells, homologous recombination initiated at DSBs is
essential for the normal completion of meiosis (Haber cells, homologous recombination initiated at DSBs is
essential for the normal completion of meiosis (Haber
1997; Keeney *et al.* 1997). It is therefore provocative that
RRCA2 (as well as RRCA1 and mRad51) co-localize to essential for the normal completion of meiosis (Haber 1997; Keeney *et al.* 1997). It is therefore provocative that BRCA2 (as well as BRCA1 and mRad51) co-localize to the synaptonemal complexes formed at meiotic chromo-1997; Keeney *et al.* 1997). It is therefore provocative that BRCA2 (as well as BRCA1 and mRad51) co-localize to the synaptonemal complexes formed at meiotic chromo-somes (Chen *et al.* 1998*c*). Indeed the reproductive BRCA2 (as well as BRCA1 and mRad51) co-localize to
the synaptonemal complexes formed at meiotic chromo-
somes (Chen *et al.* 1998*c*). Indeed, the reproductive
sterility and germ cell abnormalities observed in Rra^2 . the synaptonemal complexes formed at meiotic chromosomes (Chen *et al.* 1998*c*). Indeed, the reproductive sterility and germ cell abnormalities observed in *Brca2*- deficient mice (Connor *et al.* 1997; Friedman *et al.* sterility and germ cell abnormalities observed in *Broa2*-deficient mice (Connor *et al.* 1997; Friedman *et al.* 1998) are consistent with defective meiosis, although this has yet to be firmly established deficient mice (Connor *et*
are consistent with defecti
to be firmly established.
In eukaryotes, Radāl : Exercise is the defective meiosis, although this has yet
the firmly established.
In eukaryotes, Rad51 plays a central role in homolo-
us recombination analogous to that of RecA, RAD51

Homologous recombination in *E. coli* has classically was its meiosis-specific homologue; Dmcl (Bishop *et al.* een studied as a mechanism for the generation of diver-
ty during conjugation, a process for which the RecA In to be firmly established.
In eukaryotes, Rad51 plays a central role in homologous recombination analogous to that of RecA. RAD51 In eukaryotes, Rad51 plays a central role in homologous recombination analogous to that of RecA. RAD51 was first identified in yeast (Shinohara *et al.* 1992*b*), as was its meiosis-specific homologue: Dmcl (Bishop *et al.* gous recombination analogous to that of RecA. RAD51
was first identified in yeast (Shinohara *et al.* 1992*b*), as
was its meiosis-specific homologue; Dmc1 (Bishop *et al.*
1992). Mammalian homologues of both proteins exis Interestingly, however, at least five further mRad51-like 1992). Mammalian homologues of both proteins exist.
Interestingly, however, at least five further mRad51-like
molecules are also present in vertebrate cells, including
the products encoded by the *xrc*² and *xrc*² gen Interestingly, however, at least five further mRad51-like
molecules are also present in vertebrate cells, including
the products encoded by the *xrcc2* and *xrcc3* genes isolated
by complementation of X-ray-sensitive CHO c molecules are also present in vertebrate cells, including
the products encoded by the *xrcc2* and *xrcc3* genes isolated
by complementation of X-ray-sensitive CHO cell mutants
(Cartwright *et al.* 1998: I in *et al.* 1998 the products encoded by the *xrcc2* and *xrcc3* genes isolated
by complementation of X-ray-sensitive CHO cell mutants
(Cartwright *et al.* 1998; Liu *et al.* 1998), as well as *Rad51B*,
Rad51C and *Rad51D* (Albala *et al* (Cartwright *et al.* 1998; Liu *et al.* 1998), as well as *Rad51B*, *Rad51C* and *Rad51D* (Albala *et al.* 1997; Dosanjh *et al.* 1998; Pittman *et al.* 1998). The reason for the multiplicity of mRad51-like molecules in ve Rad51C and Rad51D (Albala et al. 1997; Dosanjh et al. 1998; Pittman et al. 1998). The reason for the multiplicity of mRad51-like molecules in vertebrates is uncertain. Yet there appears to be little redundancy for those fu 1998; Pittman *et al.* 1998). The reason for the multiplicity of mRad51-like molecules in vertebrates is uncertain. Yet there appears to be little redundancy for those functions of mRad51 that are essential for cell division and viability,

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avian cells (Lim & Hasty 1996; Tsuzuki *et al.* 1996; Sonoda ince its targeted disruption is lethal both to murine and
vian cells (Lim & Hasty 1996; Tsuzuki *et al.* 1996; Sonoda
al. 1998). In contrast, mutations in yeast *RAD51*
ngender defective homologous recombination and vian cells (Lim & Hasty 1996; Tsuzuki *et al.* 1996; Sonoda

: *al.* 1998). In contrast, mutations in yeast *RAD51*

ngender defective homologous recombination and

reiosis but do not cause lethality (Shinohara *et al.* 1 ngender defective homologous recombination and
reiosis, but do not cause lethality (Shinohara *et al.* 1992*a*). gender defective homologous recombination and
eiosis, but do not cause lethality (Shinohara *et al.* 1992*a*).
Despite this important phenotypic difference, the avail-
le biochemical evidence suggests a great similarity reiosis, but do not cause lethality (Shinohara *et al.* 1992*a*).
Despite this important phenotypic difference, the avail-
ble biochemical evidence suggests a great similarity
retween the function of yeast and mammalian R Despite this important phenotypic difference, the avail-
ble biochemical evidence suggests a great similarity
etween the function of yeast and mammalian Rad51
alolecules in homologous recombination. Both proteins ble biochemical evidence suggests a great similarity
etween the function of yeast and mammalian Rad51
nolecules in homologous recombination. Both proteins Exercise the function of yeast and mammalian Rad51
and in a more in homologous recombination. Both proteins
or helical filaments on DNA in a manner similar to
acterial RecA (Ogawa et al. 1993: Sung & Robberson bacterial RecA (Ogawa *et al.* 1993; Sung & Robberson
acterial RecA (Ogawa *et al.* 1993; Sung & Robberson
acterial RecA (Ogawa *et al.* 1993; Sung & Robberson
ag5) In concert with Rad52 (Sung 1997; Benson *et al.* 1995). In concert with Rad52 (Sung 1997; Benson *et al.* 1998; New *et al.* 1998; New *et al.* 1998; Shinohara *et al.* 1998), they mediate ampleons pairing between N_A strands (Sung 1994: 995). In concert with Rad52 (Sung 1997; Benson *et al.* 1998; New *et al.* 1998; Shinohara *et al.* 1998), they mediate mologous pairing between DNA strands (Sung 1994; $\lim_{n \to \infty}$ & Robberson 1995; Baumann *et al.* 1997 **Superior** 1998; New *et al.* 1998; Shinohara *et al.* 1998), they mediate

Sumplogous pairing between DNA strands (Sung 1994;

lung & Robberson 1995; Baumann *et al.* 1997) to

Sumple a strand exchange reaction. The sing • omologous pairing between DNA strands (Sung 1994;

I ung & Robberson 1995; Baumann *et al.* 1997) to

• romote a strand exchange reaction. The single-strand

• NA binding protein RPA considerably enhances this l ung & Robberson 1995; Baumann *et al.* 1997) to
fromote a strand exchange reaction. The single-strand
DNA binding protein, RPA, considerably enhances this
denotion which is associated with (Sung 1994: Baumann Fromote a strand exchange reaction. The single-strand

(NA binding protein, RPA, considerably enhances this

(Sung 1994; Baumann

(Sung 1994; Baumann

(California et al. 1997) but may not depend on **Example 1998** is associated with (Sung 1994; Baumann b: *al.* 1997; Gupta *et al.* 1997), but may not depend on Sung & Stratton 1996), a DNA-dependent ATPase The Section, which is associated with (Sung 1994; Baumann

2: *al.* 1997; Gupta *et al.* 1997), but may not depend on

Sung & Stratton 1996), a DNA-dependent ATPase

civity intrinsic to yeast and mammalian Rad51 2: *al.* 1997; Gupta *et al.* 1997), but may not dependent β civity intrinsic to yeast and mammalian Rad51.
Differences between RecA and eukaryotic Rad

ung & Stratton 1996), a DNA-dependent ATPase
tivity intrinsic to yeast and mammalian Rad51.
Differences between RecA and eukaryotic Rad51 are
so considerable The strand exchange reaction promoted Differences between RecA and eukaryotic Rad51 are
lso considerable. The strand exchange reaction promoted
y the eukaryotic enzymes is far weaker than that
rediated by RecA (Sung 1994; Baumann et al. 1997) lso considerable. The strand exchange reaction promoted
y the eukaryotic enzymes is far weaker than that
rediated by RecA (Sung 1994; Baumann *et al.* 1997).
Acreover their ATPase activity is some 100-fold less than y the eukaryotic enzymes is far weaker than that
rediated by RecA (Sung 1994; Baumann *et al.* 1997).
Toreover, their ATPase activity is some 100-fold less than
hat of RecA (Gunta *et al.* 1997). These biochemical rediated by RecA (Sung 1994; Baumann *et al.* 1997).
Joreover, their ATPase activity is some 100-fold less than
hat of RecA (Gupta *et al.* 1997). These biochemical Iorreover, their ATPase activity is some 100-fold less than
hat of RecA (Gupta *et al.* 1997). These biochemical
reasurements in *in vitro* experimental systems hint at the
gessity for additional eukaryotic proteins to mod hat of RecA (Gupta *et al.* 1997). These biochemical reasurements in *in vitro* experimental systems hint at the ecessity for additional eukaryotic proteins to modulate be activity of Rad51 and to regulate—in a manner not reasurements in *in vitro* experimental systems hint at the ecessity for additional eukaryotic proteins to modulate
he activity of Rad51 and to regulate—in a manner not
equired in E coli—the in vivo progress and extent ecessity for additional eukaryotic proteins to modulate
he activity of Rad51 and to regulate—in a manner not
equired in *E. coli*—the *in vivo* progress and extent of the he activity of Rad51 and to regulate—in a manner not
equired in *E. coli*—the *in vivo* progress and extent of the
ecombination reaction. It is in this context that the
bysical association of mRad51 with tumour suppressor equired in *E. coli*—the *in vivo* progress and extent of the ecombination reaction. It is in this context that the hysical association of mRad51 with tumour suppressor rateins such as $n53$ (Sturzbecher *et al* 1996) BRC ecombination reaction. It is in this context that the
hysical association of mRad51 with tumour suppressor
roteins such as p53 (Sturzbecher *et al.* 1996), BRCA1
Scully *et al.* 1997), and BRCA2 (Chen *et al.* 1998*b*) hysical association of mRad51 with tumour suppressor
roteins such as p53 (Sturzbecher *et al.* 1996), BRCA1
Scully *et al.* 1997) and BRCA2 (Chen *et al.* 1998*b*; roteins such as p53 (Sturzbecher *et al.* 1996), BRCA1
Scully *et al.* 1997) and BRCA2 (Chen *et al.* 1998*b*;
Aizuta *et al.* 1997; Sharan *et al.* 1997; Wong *et al.* 1997)
ave be of considerable importance to its essent Scully *et al.* 1997) and BRCA2 (Chen *et al.* 1998*b*;
 Aizuta et al. 1997; Sharan *et al.* 1997; Wong *et al.* 1997) ay be of considerable importance to its essential role in ell division and viability. fizuta *et al.* 1997; Sharan ay be of considerable impell division and viability.
Civen the central role estahow the central role importance to its essential role in ell division and viability.
Given the central role established for mRad51 in homolo-

ell division and viability.
Given the central role established for mRad51 in homolo-
ous recombination, it is striking that several lines of
ircumstantial evidence indicate a shared function with Given the central role established for mRad51 in homolo-
ous recombination, it is striking that several lines of
ircumstantial evidence indicate a shared function with
 $\frac{\text{cm}}{2}$. The genes encoding these proteins show ircumstantial evidence indicate a shared function with rea2. The genes encoding these proteins show a similar Frequency in the set of rea2. The genes encoding these proteins show a similar spression pattern in mammalian cells, with low levels spressed in many tissues and with particularly high levels and in the thymus and testes. Expression is restricte spression pattern in mammalian cells, with low levels
spressed in many tissues and with particularly high levels
and in the thymus and testes. Expression is restricted, as
a stricted, as xpressed in many tissues and with particularly high levels
bund in the thymus and testes. Expression is restricted, as
a the case of *BRCA1*, primarily to the S phase of the cell ycle. As mentioned earlier, mRad51 and Brca2 are The case of *BRCAI*, primarily to the S phase of the cell
ycle. As mentioned earlier, mRad51 and Brca2 are
hysically associated at relatively high stoichiometry. Co-
evaluation can be demonstrated to nuclear foci in mitot ycle. As mentioned earlier, mRad51 and Brca2 are
hysically associated at relatively high stoichiometry. Co-
calization can be demonstrated to nuclear foci in mitotic
lells and to synaptonemal complexes in meiotic cells hysically associated at relatively high stoichiometry. Co-
calization can be demonstrated to nuclear foci in mitotic
ells, and to synaptonemal complexes in meiotic cells.
and the Brca^{9Tr/Tr} cells. Rad51-deficient verteb Finalization can be demonstrated to nuclear foci in mitotic Cells, and to synaptonemal complexes in meiotic cells.
Cinally, like Brca2^{Tr/Tr} cells, Rad51-deficient vertebrate cells bells, and to synaptonemal complexes in meiotic cells.
Simally, like $Brca2^{Tr/T}$ cells, $Rad51$ -deficient vertebrate cells
sontaneously accumulate chromosomal abnormalities and
reunable to maintain continued division in cul inally, like $\text{Brca2}^{\text{Tr}/\text{Tr}}$ cells, Rad51-deficient vertebrate continued above and a continued division in culture.

4.*BRCA2***: AT THE CROSSROADS BETWEEN DNA RA2: AT THE CROSSROADS BETWEEN DN:**
REPLICATION AND RECOMBINATION?

4.BRCA2: AT THE CROSSROADS BETWEEN DNA
REPLICATION AND RECOMBINATION?
What are the common biological functions that may
derlie the essential requirement for Rad51 and Brca? What are the common biological functions that may
nderlie the essential requirement for Rad51 and Brca2
a cell division and chromosome stability? Paradigms What are the common biological functions that may

independent of Rad51 and Brca2

in cell division and chromosome stability? Paradigms

in work on F celi suggest that they may be related to nderlie the essential requirement for Rad51 and Brca2
1 cell division and chromosome stability? Paradigms
com work on *E. coli* suggest that they may be related to
he necessity for RecA-catalysed strand exchanges to n cell division and chromosome stability? Paradigms

when replication fork progression is stalled (reviewed in West *et al*. 1981; Kuzminov 1995; Kogoma 1996, 1997; Cox when replication fork progression is stalled (reviewed in West *et al.* 1981; Kuzminov 1995; Kogoma 1996, 1997; Cox 1997). Several lesions encountered by a replication fork could lead to its collapse including strand gaps West *et al.* 1981; Kuzminov 1995; Kogoma 1996, 1997; Cox 1997). Several lesions encountered by a replication fork could lead to its collapse, including strand gaps, base adducts causing template distortion or DSBs. In the 1997). Several lesions encountered by a replication fork
could lead to its collapse, including strand gaps, base
adducts causing template distortion, or DSBs. In these
situations replication restart in F coli is depende could lead to its collapse, including strand gaps, base
adducts causing template distortion, or DSBs. In these adducts causing template distortion, or DSBs. In these situations, replication restart in E . *coli* is dependent on the use of recombinational mechanisms to bypass the lesion and enable origin-independent reinitiation o situations, replication restart in E . *coli* is dependent on the use of recombinational mechanisms to bypass the lesion and enable origin-independent reinitiation of the replica-
tion fork from recombination intermediat use of recombinational mechanisms to bypass the lesion
and enable origin-independent reinitiation of the replica-
tion fork from recombination intermediates (for example, and enable origin-independent reinitiation of the replication fork from recombination intermediates (for example, Kogoma 1996; Liu *et al.* 1999). Failure to carry out replication restart would result not only in defective tion fork from recombination intermediates (for example,
Kogoma 1996; Liu *et al.* 1999). Failure to carry out repli-
cation restart would result not only in defective DNA
synthesis and cell proliferation, but could also Kogoma 1996; Liu *et al.* 1999). Failure to carry out replication restart would result not only in defective DNA synthesis and cell proliferation, but could also provoke the occurrence of discontinuities in replicated chro cation restart would result not only in defective DNA
synthesis and cell proliferation, but could also provoke the
occurrence of discontinuities in replicated chromosomes.

ctivity intrinsic to yeast and mammalian Rad51. This mismatches caused by replication errors, or simply by
Differences between RecA and eukaryotic Rad51 are replication fork encounter with DNA-bound proteins. No
lso consid An important element in this scheme is the notion that occurrence of discontinuities in replicated chromosomes.
An important element in this scheme is the notion that
replication forks are frequently stalled during normal cell
division Conditions that precipitate stalling coul An important element in this scheme is the notion that replication forks are frequently stalled during normal cell
division. Conditions that precipitate stalling could concei-
vably arise in many different ways. These may replication forks are frequently stalled during normal cell
division. Conditions that precipitate stalling could concei-
vably arise in many different ways. These may include
hase lesions created by DNA modification (revie division. Conditions that precipitate stalling could conceivably arise in many different ways. These may include
base lesions created by DNA modification (reviewed in
Lindahl 1993–1996), through hydrolysis, oxidation and vably arise in many different ways. These may include
base lesions created by DNA modification (reviewed in
Lindahl 1993, 1996) through hydrolysis, oxidation and
other reactions. UV-induced strand alterations, base base lesions created by DNA modification (reviewed in Lindahl 1993, 1996) through hydrolysis, oxidation and other reactions, UV-induced strand alterations, base mismatches caused by replication errors or simply by Lindahl 1993, 1996) through hydrolysis, oxidation and
other reactions, UV-induced strand alterations, base
mismatches caused by replication errors, or simply by
replication fork encounter with DNA-bound proteins. No other reactions, UV-induced strand alterations, base
mismatches caused by replication errors, or simply by
replication fork encounter with DNA-bound proteins. No
direct measurement of the extent of replication stalling mismatches caused by replication errors, or simply by replication fork encounter with DNA-bound proteins. No
direct measurement of the extent of replication stalling
during normal growth is available. In *E. coli* RecBCD or
RecARecD mutants, stalling of replication forks resu direct measurement of the extent of replication stalling
during normal growth is available. In E. coli RecBCD or
RecARecD mutants, stalling of replication forks results in
the generation of DSBs (Michel et al. 1997: Seigne during normal growth is available. In *E. coli* RecBCD or RecARecD mutants, stalling of replication forks results in the generation of DSBs (Michel *et al.* 1997; Seigneur *et al.* 1998). It is provocative that in these st the generation of DSBs (Michel *et al.* 1997; Seigneur *et al.* 1998). It is provocative that in these strains, DSBs spontaneously accumulate to high levels during normal growth indicative of the considerable frequency of 1998). It is provocative that in these strains, DSBs spontaneously accumulate to high levels during normal growth indicative of the considerable frequency of replication fork stalling which must occurre during DNA rep neously accumulate to high levels during normal growth
indicative of the considerable frequency of replication fork
stalling which must occur during DNA replication.
Moreover DSR accumulation is even further elevated in indicative of the considerable frequency of replication fork
stalling which must occur during DNA replication.
Moreover, DSB accumulation is even further elevated in this background when DNA replication is impeded by Moreover, DSB accumulation is even further elevated in this background when DNA replication is impeded by disruption of replicative helicases (Michel *et al.* 1997), emphasizing the role of homologous recombination in the this background when DNA replication is impeded by disruption of replicative helicases (Michel *et al.* 1997), emphasizing the role of homologous recombination in the repair of DNA damage induced by defective replication disruption of replicative helicases (Michel *et al.* 1997), emphasizing the role of homologous recombination in the repair of DNA damage induced by defective replication.
To what extent can the paradigms developed in work phasizing the role of homologous recombination in the
pair of DNA damage induced by defective replication.
To what extent can the paradigms developed in work
bacteria be extended to eukaryotes? There is limited

repair of DNA damage induced by defective replication.
To what extent can the paradigms developed in work
on bacteria be extended to eukaryotes? There is limited
but intriguing evidence that homologous recombination To what extent can the paradigms developed in work
on bacteria be extended to eukaryotes? There is limited
but intriguing evidence that homologous recombination
is stimulated by and necessary for eukaryotic DNA on bacteria be extended to eukaryotes? There is limited
but intriguing evidence that homologous recombination
is stimulated by, and necessary for, eukaryotic DNA
replication. Recombination intermediates representing but intriguing evidence that homologous recombination
is stimulated by, and necessary for, eukaryotic DNA
replication. Recombination intermediates representing
unresolved Holliday iunctions accumulate sportaneously is stimulated by, and necessary for, eukaryotic DNA
replication. Recombination intermediates representing
unresolved Holliday junctions accumulate spontaneously
during the S phase of the cell cycle in synchronously replication. Recombination intermediates representing
unresolved Holliday junctions accumulate spontaneously
during the S phase of the cell cycle in synchronously
dividing yeast cells in the absence of exogenously induced unresolved Holliday junctions accumulate spontaneously
during the S phase of the cell cycle in synchronously
dividing yeast cells in the absence of exogenously induced
DNA damage suggesting that recombination operates to during the S phase of the cell cycle in synchronously
dividing yeast cells in the absence of exogenously induced
DNA damage, suggesting that recombination operates to
repair replication-associated lesions (Zou & Rothstein dividing yeast cells in the absence of exogenously induced
DNA damage, suggesting that recombination operates to
repair replication-associated lesions (Zou & Rothstein
1997) Indeed mutations affecting components of the DNA damage, suggesting that recombination operates to
repair replication-associated lesions (Zou & Rothstein
1997). Indeed, mutations affecting components of the
replicative machinery increase the level of recombination repair replication-associated lesions (Zou & Rothstein
1997). Indeed, mutations affecting components of the
replicative machinery increase the level of recombination
intermediates detected in this system. This may provide 1997). Indeed, mutations affecting components of the replicative machinery increase the level of recombination intermediates detected in this system. This may provide some mechanistic substance to the off-noted observation replicative machinery increase the level of recombination
intermediates detected in this system. This may provide
some mechanistic substance to the oft-noted observation
that in mammalian cells, mutations in DNA polymerase intermediates detected in this system. This may provide
some mechanistic substance to the oft-noted observation
that in mammalian cells, mutations in DNA polymerases, some mechanistic substance to the oft-noted observation
that in mammalian cells, mutations in DNA polymerases,
ligases or helicases such as the RecQ homologue altered
in Bloom syndrome, greatly stimulate genetic exchange that in mammalian cells, mutations in DNA polymerases,
ligases or helicases such as the RecQ homologue altered
in Bloom syndrome, greatly stimulate genetic exchange
hetween sister chromatics as detected by differential ligases or helicases such as the RecQ homologue altered
in Bloom syndrome, greatly stimulate genetic exchange
between sister chromatids as detected by differential
RrdII labelling of newly replicated DNA strands in Bloom syndrome, greatly stimulate genetic exchange
between sister chromatids as detected by differential
BrdU labelling of newly replicated DNA strands
(reviewed in Rothstein & Gangloff 1995). between sister chromatids as detected l
BrdU labelling of newly replicated
(reviewed in Rothstein & Gangloff 1995).
In the model proposed here in which re dU labelling of newly replicated DNA strands
viewed in Rothstein & Gangloff 1995).
In the model proposed here, in which recombinational
occesses dependent on Rad51 and Brca? are required for

From work on *E. coli* suggest that they may be related to results in a gradual loss of replicative capacity (Sonoda *et* he necessity for RecA-catalysed strand exchanges to *al.* 1998), with progressive accumulation in t In the model proposed here, in which recombinational
processes dependent on Rad51 and Brca2 are required for normal DNA replication, the proliferative impediment processes dependent on Rad51 and Brca2 are required for
normal DNA replication, the proliferative impediment
apparent in Rad51-deficient avian cells and in Brca2^{Tr/Tr}
mouse fibroblasts is of particular interest. Rad51 d normal DNA replication, the proliferative impediment
apparent in Rad51-deficient avian cells and in Brca2^{Tr/Tr}
mouse fibroblasts is of particular interest. Rad51 deletion
results in a gradual loss of replicative canacit apparent in Rad51-deficient avian cells and in Brca $2^{\text{Tr}/\text{Tr}}$
mouse fibroblasts is of particular interest. Rad51 deletion
results in a gradual loss of replicative capacity (Sonoda *et*
 aI , 1998), with progressive ac mouse fibroblasts is of particular interest. Rad51 deletion phases of the cell cycle consistent with arrest at the check**PHILOSOPHICAL**
TRANSACTIONS

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PHILOSOPHICAL
TRANSACTIONS

oints that monitor the completeness of DNA replication. oints that monitor the completeness of DNA replication.
 $\text{irca2}^{\text{Tr}/\text{Tr}}$ fibroblasts also display a progressive impedi-

tent to their canacity to undergo cell division (Patel et al. oints that monitor the completeness of DNA replication.
 $\text{irca2}^{\text{Tr}/\text{Tr}}$ fibroblasts also display a progressive impedi-

tent to their capacity to undergo cell division (Patel *et al.* 998). When freshly isolated fro ient to their capacity to undergo cell division (Patel *et al.* 998). When freshly isolated from murine embryos, they re roughly similar in their proliferative competence to *i*ld-type or heterogygous control cells. A seve 998). When freshly isolated from murine embryos, they
re roughly similar in their proliferative competence to
ild-type or heterozygous control cells. A severe prolif-
rative defect becomes apparent and progressively re roughly similar in their proliferative competence to

vild-type or heterozygous control cells. A severe prolif-

rative defect becomes apparent, and progressively

corsens the more often the cells are passed in culture vild-type or heterozygous control cells. A severe prolif-
rative defect becomes apparent, and progressively
vorsens, the more often the cells are passed in culture,
accompanied by increasing Gl and G2/M phase arrest rative defect becomes apparent, and progressively vorsens, the more often the cells are passed in culture, companied by increasing G1 and $G2/M$ phase arrest. These phenotypes of Rad51-deficient and Brca2^{Tr/Tr} cells
These phenotypes of Rad51-deficient and Brca2^{Tr/Tr} cells
These phenotypes of Rad51-deficient and Brca2^{Tr/Tr} cells
Treminiscent of RecE pathway mutants of *E* companied by increasing G1 and $G2/M$ phase arrest.

These phenotypes of Rad51-deficient and Brca $2^{Tr/T}$ cells

re reminiscent of RecF pathway mutants of *E. coli*, which

lso exhibit an inability to sustain oppoint rounds re reminiscent of RecF pathway mutants of E . *coli*, which lso exhibit an inability to sustain ongoing rounds of re reminiscent of RecF pathway mutants of *E. coli*, which
lso exhibit an inability to sustain ongoing rounds of
 \bigcirc NA replication even in the absence of exogenously
aduced DNA damage (Courcelle *et al*, 1997) **iso** exhibit an inability to sustain ongoing
 INA replication even in the absence of example and induced DNA damage (Courcelle *et al.* 1997). NA replication even in the absence of exogenously
duced DNA damage (Courcelle *et al.* 1997).
Studies of co-localization also lend support to the idea
at mRad51 and BRCA2 participate in repair processes

Anduced DNA damage (Courcelle *et al.* 1997).

A Studies of co-localization also lend support to the idea

Anat mRad51 and BRCA2 participate in repair processes
 $\sum_{n=1}^{\infty}$ secolated with DNA replication. Nuclear foci Fundies of co-localization also lend support to the idea

at mRad51 and BRCA2 participate in repair processes

ssociated with DNA replication. Nuclear foci containing
 λ_1 Rad51 BRCA1 and BRCA2 are formed during late S and mRad51 and BRCA2 participate in repair processes
sociated with DNA replication. Nuclear foci containing
and space of the BRCA2 are formed during late S
and G2 (Chen et al. 1998c). Following exposure to hydrosociated with DNA replication. Nuclear foci containing
 λ Rad51, BRCA1 and BRCA2 are formed during late S
 λ nd G2 (Chen *et al.* 1998*c*). Following exposure to hydro-
 λ which depletes nucleotide pools required The Pharta and BRCA2 are formed during late S
and G2 (Chen *et al.* 1998*c*). Following exposure to hydro-
yurea, which depletes nucleotide pools required for
NA replication BRCA2-containing foci costain with

and G2 (Chen *et al.* 1998*c*). Following exposure to hydro-
yurea, which depletes nucleotide pools required for
DNA replication, BRCA2-containing foci costain with
CNA (Chen *et al.* 1998) suggesting localization at repl yurea, which depletes nucleotide pools required for DNA replication, BRCA2-containing foci costain with CNA (Chen *et al.* 1998), suggesting localization at repli-
ation foci. These observations are consistent with a N MA replication, BRCA2-containing foci costain with CNA (Chen *et al.* 1998), suggesting localization at repliation foci. These observations are consistent with a CNA (Chen *et al.* 1998), suggesting localization at repli-
ation foci. These observations are consistent with a
5 iodel in which the activity of BRCA2 and Rad51 is
cessary to overcome the replication fork stalling at ation foci. These observations are consistent with a
5 rodel in which the activity of BRCA2 and Rad51 is
ecessary to overcome the replication fork stalling at
xand gaps induced by hydroxyurea. It is currently strand gaps induced by hydroxyurea. It is currently
realized by hydroxyurea. It is currently
relating at rand gaps induced by hydroxyurea. It is currently
relating the scheme of BRCA2 or Rad51 interact directly with compoecessary to overcome the replication fork stalling at rand gaps induced by hydroxyurea. It is currently nclear if BRCA2 or Rad51 interact directly with comporand gaps induced by hydroxyurea. It is currently
nclear if BRCA2 or Rad51 interact directly with compo-
ents of the eukaryotic DNA replication machinery or
ith the accessory molecules involved in regulating the nclear if BRCA2 or Rad51 interact directly with compo-
ents of the eukaryotic DNA replication machinery or
ith the accessory molecules involved in regulating the
pixentic effects associated with DNA replication This is ents of the eukaryotic DNA replication machinery or
ith the accessory molecules involved in regulating the
pigenetic effects associated with DNA replication. This is
prediction of the model proposed here, and is likely to ith the accessory molecules involved in regulating the pigenetic effects associated with DNA replication. This is prediction of the model proposed here, and is likely to e a worthwhile focus for further analysis pigenetic effects associated with DNA repli
prediction of the model proposed here, a
e a worthwhile focus for further analysis.
The model proposed here for the function

prediction of the model proposed here, and is likely to
e a worthwhile focus for further analysis.
The model proposed here for the function of BRCA2-
nRad51 in eukaryotic DNA replication has important
milications for the r The model proposed here for the function of BRCA2-

1Rad51 in eukaryotic DNA replication has important

mplications for the role of BRCA2 mutations in cancer

redisposition Defects in components of the replication n_{Rad51} in eukaryotic DNA replication has important mplications for the role of BRCA2 mutations in cancer redisposition. Defects in components of the replication vachinery have clearly been associated with a mutator mplications for the role of BRCA2 mutations in cancer
redisposition. Defects in components of the replication
nachinery have clearly been associated with a mutator
henotype in eukaryotes (Chen et al. 1998a) suggesting redisposition. Defects in components of the replication iachinery have clearly been associated with a mutator henotype in eukaryotes (Chen *et al.* 1998*a*), suggesting ast BRCA2-deficient cells may also sustain elevated rachinery have clearly been associated with a mutator henotype in eukaryotes (Chen et al . 1998 a), suggesting nat BRCA2-deficient cells may also sustain elevated henotype in eukaryotes (Chen *et al.* 1998*a*), suggesting nat BRCA2-deficient cells may also sustain elevated for intation rates even without exogenously induced DNA expanse. The replication defect and chromosomal in at BRCA2-deficient cells may also sustain elevated
autation rates even without exogenously induced DNA
amage. The replication defect and chromosomal
autability observed in Brca2-deficient cells at first glance amage. The replication defect and chromosomal istability observed in Brca2-deficient cells at first glance amage. The replication defect and chromosomal
stability observed in Brca2-deficient cells at first glance
em at odds with the unrestrained proliferation
sociated with cancer. It can therefore be predicted that associated with the unrestrained proliferation
associated with cancer. It can therefore be predicted that
condary mutations—incurred at a high frequency sem at odds with the unrestrained proliferation
sociated with cancer. It can therefore be predicted that
condary mutations—incurred at a high frequency
cause of the mutator phenotype—must be selected ssociated with cancer. It can therefore be predicted that
econdary mutations—incurred at a high frequency
ecause of the mutator phenotype—must be selected uring the process of transformation to yield cancer cells, ecause of the mutator phenotype—must be selected
uring the process of transformation to yield cancer cells,
which have in some way ameliorated or compensated for
ny underlying replication and/or repair defect (Lee et al. any unity the process of transformation to yield cancer cells,
thich have in some way ameliorated or compensated for
ny underlying replication and/or repair defect (Lee *et al.*
1999). If this model is correct, the identi In an underlying replication and/or repair defect (Lee *et al.* (1999). If this model is correct, the identification and consistently undergo secondary (1999). If this model is correct, the identification and alysis of genes that consistently undergo secondary untation in BRCA2-deficient tumour cells are likely to rough valuable biological insights into the mechanism of provide valuable biological insights into the mechanism of
provide valuable biological insights into the mechanism of
provide valuable biological insights into the mechanism of
provide valuable biological insights into the

s utation in BRCA2-deficient tumour cells are likely to
rovide valuable biological insights into the mechanism of
eplication-associated recombination in mammalian cells.
Over-reliance on analogies to the bacterial RecA ovide valuable biological insights into the mechanism of
plication-associated recombination in mammalian cells.
Over-reliance on analogies to the bacterial RecA
thway in interpreting or predicting the manner in which eplication-associated recombination in mammalian cells.
Over-reliance on analogies to the bacterial RecA
athway in interpreting or predicting the manner in which
ampleonus recombination and replication may interact Over-reliance on analogies to the bacterial RecA
athway in interpreting or predicting the manner in which
omologous recombination and replication may interact
as mammalian cells is of course to be avoided. For a start athway in interpreting or predicting the manner in which

omologous recombination and replication may interact

in mammalian cells is, of course, to be avoided. For a start,

are are many simificant differences between the omologous recombination and replication may interact
 \overline{t} i mammalian cells is, of course, to be avoided. For a start,
rere are many significant differences between the activ-
ies of the enzymes involved A_s discusse It is manifest many significant differences between the activies of the enzymes involved. As discussed previously, $Rad51$ is far less proficient at promoting strand nere are many significant differences between the activies of the enzymes involved. As discussed previously, $Rad51$ is far less proficient at promoting strand ies of the enzymes involved. As discussed previously,

1Rad51 is far less proficient at promoting strand

xchange, exhibits poor ATPase activity and appears to

xchange, exhibits poor ATPase activity and appears to

xchang in Rad51 is far less proficient at promoting strand xchange, exhibits poor ATPase activity and appears to ork with the opposite strand polarity, when compared to *Pork with the opposite strand polarity, when compared to hil. Trans. R. Soc. Lond.* B (2000)

RecA. Eukaryotic DNA replication undoubtedly occurs in
a more complicated molecular and cellular milieu than in RecA. Eukaryotic DNA replication undoubtedly occurs in
a more complicated molecular and cellular milieu than in
prokaryotes, necessitating the action of additional mola more complicated molecular and cellular milieu than in
prokaryotes, necessitating the action of additional mol-
ecules for which there may be no counterparts in the prokaryotes, necessitating the action of additional molsimpler system. For similar reasons, analogies to yeast may ecules for which there may be no counterparts in the
simpler system. For similar reasons, analogies to yeast may
also be of limited value. Homologues to p53, BRCA1 or
RRCA2—all known to interact with mRad51—do not simpler system. For similar reasons, analogies to yeast may
also be of limited value. Homologues to p53, BRCA1 or
BRCA2—all known to interact with mRad51—do not
appear to exist in yeast. Mammalian cells contain a multialso be of limited value. Homologues to p53, BRCA1 or BRCA2—all known to interact with mRad51—do not appear to exist in yeast. Mammalian cells contain a multi-plicity of Rad51-like proteins. Yeast $\overline{RAD52}$ but not BRCA2—all known to interact with mRad51—do not
appear to exist in yeast. Mammalian cells contain a multi-
plicity of Rad51-like proteins. Yeast *RAD52*, but not
RAD51 RAD55 or *RAD57* appears to be essential for the appear to exist in yeast. Mammalian cells contain a multiplicity of Rad51-like proteins. Yeast *RAD52*, but not *RAD51*, *RAD55* or *RAD57*, appears to be essential for the formation of recombination intermediates associat plicity of Rad51-like proteins. Yeast *RAD52*, but not *RAD51*, *RAD55* or *RAD57*, appears to be essential for the formation of recombination intermediates associated with replication (Zou $\&$ Rothstein 1997) Many of th replication (Zou & Rothstein 1997). Many of these discreformation of recombination intermediates associated with
replication (Zou & Rothstein 1997). Many of these discre-
pancies will ultimately be resolved by biochemical studies
to elucidate the activities of the mammalian enz replication (Zou & Rothstein 1997). Many of these discre-
pancies will ultimately be resolved by biochemical studies
to elucidate the activities of the mammalian enzymes
involved in homologous recombination and to define t pancies will ultimately be resolved by biochemical studies
to elucidate the activities of the mammalian enzymes
involved in homologous recombination and to define their
inter-molecular interactions, an effort now underway to elucidate the activities of the mammalian enzymes
involved in homologous recombination and to define their
inter-molecular interactions, an effort now underway in involved in homologous recombination and to define their
inter-molecular interactions, an effort now underway in
several laboratories. Despite these limitations to a model
for mRad51/Brca2 activity based on bacterial paral inter-molecular interactions, an effort now underway in
several laboratories. Despite these limitations to a model
for mRad51/Brca2 activity based on bacterial parallels, its
formulation does provide a useful framework for several laboratories. Despite these limitations to a model
for mRad5l/Brca2 activity based on bacterial parallels, its
formulation does provide a useful framework for further
work in which informative predictions can be ma for mRad5l/Brca2 activity based on bacterial parallels, its formulation does provide a useful framework for further work in which informative predictions can be made for experimental analysis. formulation does provide
work in which informa
experimental analysis.
While this review is fo ork in which informative predictions can be made for
perimental analysis.
While this review is focused on the functions of BRCA2
DNA repair in relation to its interaction with mRad51

While this review is focused on the functions of BRCA2 in DNA repair in relation to its interaction with mRad51, While this review is focused on the functions of BRCA2
in DNA repair in relation to its interaction with mRad51,
it bears reiteration that this exceptionally large nuclear
protein is very likely to have multiple functions in DNA repair in relation to its interaction with mRad51,
it bears reiteration that this exceptionally large nuclear
protein is very likely to have multiple functions within a
cell that may or may not be relevant in this c it bears reiteration that this exceptionally large nuclear
protein is very likely to have multiple functions within a
cell that may or may not be relevant in this context. For
example functions in transcription activation protein is very likely to have multiple functions within a cell that may or may not be relevant in this context. For example, functions in transcription activation (Chapman cell that may or may not be relevant in this context. For
example, functions in transcription activation (Chapman
& Verma 1996; Fuks *et al*, 1998) and transcription-
counled DNA repair (Gowen *et al*, 1998) have been example, functions in transcription activation (Chapman & Verma 1996; Fuks *et al.* 1998) and transcription-
coupled DNA repair (Gowen *et al.* 1998) have been
ascribed to both BBCA1 and BBCA2. The relationship of & Verma 1996; Fuks *et al*, 1998) and transcription-
coupled DNA repair (Gowen *et al.* 1998) have been
ascribed to both BRCA1 and BRCA2. The relationship of
these nutative roles to the phenotype of Brca²-deficient coupled DNA repair (Gowen *et al.* 1998) have been
ascribed to both BRCA1 and BRCA2. The relationship of
these putative roles to the phenotype of Brca2-deficient ascribed to both BRCA1 and BRCA2. The relationship of
these putative roles to the phenotype of Brca2-deficient
murine cells is uncertain, and their potential contribution
to chromosome instability and cancer predisposition these putative roles to the phenotype of Brca2-deficient
murine cells is uncertain, and their potential contribution
to chromosome instability and cancer predisposition
remains to be fully explored murine cells is uncertain, and
to chromosome instability a
remains to be fully explored.
Finally it remains unclear to chromosome instability and cancer predisposition
remains to be fully explored.
Finally, it remains unclear to what extent the study of

remains to be fully explored.
Finally, it remains unclear to what extent the study of
BRCA2 will enlarge our understanding of breast cancer
pathogenesis in general. Somatic BRCA2 mutations do Finally, it remains unclear to what extent the study of
BRCA2 will enlarge our understanding of breast cancer
pathogenesis in general. Somatic BRCA2 mutations do
not occur in non-familial breast cancers, which account BRCA2 will enlarge our understanding of breast cancer
pathogenesis in general. Somatic BRCA2 mutations do
not occur in non-familial breast cancers, which account
for over 90% of incidence undermining (but not entirely pathogenesis in general. Somatic BRCA2 mutations do
not occur in non-familial breast cancers, which account
for over 90% of incidence, undermining (but not entirely not occur in non-familial breast cancers, which account
for over 90% of incidence, undermining (but not entirely
excluding) the conjecture that a common pathway
involving the molecule will be dysfunctional in sporadic for over 90% of incidence, undermining (but not entirely excluding) the conjecture that a common pathway involving the molecule will be dysfunctional in sporadic as well as familial tumours. Moreover, RRCA9 is widely excluding) the conjecture that a common pathway
involving the molecule will be dysfunctional in sporadic
as well as familial tumours. Moreover, BRCA2 is widely
expressed and appears to have important functions in involving the molecule will be dysfunctional in sporadic
as well as familial tumours. Moreover, BRCA2 is widely
expressed and appears to have important functions in
cellular processes such as DNA repair and transcription as well as familial tumours. Moreover, BRCA2 is widely
expressed and appears to have important functions in
cellular processes such as DNA repair and transcription
apparently fundamental to all tissues. Why should expressed and appears to have important functions in
cellular processes such as DNA repair and transcription
apparently fundamental to all tissues. Why should BRCA2 mutations therefore result in predisposition to apparently fundamental to all tissues. Why should
BRCA2 mutations therefore result in predisposition to
breast and ovarian cancer in particular? These are
important gaps in our current understanding (Venki-BRCA2 mutations therefore result in predisposition to
breast and ovarian cancer in particular? These are
important gaps in our current understanding (Venki-
taraman 1999) which cannot easily be resolved without important gaps in our current understanding (Venkitaraman 1999), which cannot easily be resolved without important gaps in our current understanding (Venki-
taraman 1999), which cannot easily be resolved without
invoking additional—and perhaps tissue-specific—
functions for BRCA2 which remain to be identified functional functions for BRCA2 which remains the resolved with invoking additional—and perhaps tissue-specify
functions for BRCA2 which remain to be identified.

I functions for BRCA2 which remain to be identified.
I am indebted to current members of my laboratory for many I am indebted to current members of my laboratory for many
helpful and stimulating discussions. Our research is supported
by the Cancer Research Campaign, the Medical Research I am indebted to current members of my laboratory for many
helpful and stimulating discussions. Our research is supported
by the Cancer Research Campaign, the Medical Research
Council and the Leukaemia Research Fund The ge helpful and stimulating discussions. Our research is supported
by the Cancer Research Campaign, the Medical Research
Council and the Leukaemia Research Fund. The generosity of
the late Dr F. A. Zöellner in endowing the Urs by the Cancer Research Campaign, the Medical Research
Council and the Leukaemia Research Fund. The generosity of
the late Dr F. A. Zöellner in endowing the Ursula Zöellner
Professorship of Cancer Research is gratefully ack Council and the Leukaemia Research Fund. The generosity of

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