In the early 1980s, a primary hurdle on the track to understanding the function of a protein was the isolation of its gene. Over the last two decades, we have seen subsequent hurdles in the race to decipher protein function, including atomic structure resolution and the creation of viable mouse mutants, being cleared at an ever-increasing pace. The genome surveillance protein Rad50 has now leapt over these modern-day hurdles. In the last two years, rapid progress has been made in understanding structural aspects of Rad50 [Hopfner et al. 2000, 2001, 2002, de Jager et al. 2001]. In this issue of *Genes & Development*, John Petrini and colleagues report on the phenotypes of mice carrying a hypomorphic Rad50 allele named Rad50S [Bender et al. 2002].

Rad50 is part of an evolutionarily conserved protein complex containing Mre11 and Nbs1 [D’Amours and Jackson 2002] that is referred to as the Mre11 complex by Petrini and colleagues. The Mre11 complex has been implicated in diverse aspects of genome metabolism that involve DNA end processing, including cell cycle checkpoint activation in response to DNA double-strand breaks (DSBs), DSB repair, and telomere length maintenance [Haber 1998; Lombard and Guarente 2000; Petrini 2000; Zhu et al. 2000]. All three components of the mammalian Mre11 complex are essential for cellular viability [Xiao and Weaver 1997; Luo et al. 1999; Yamaguchi-Iwai et al. 1999; Zhu et al. 2001]. However, hypomorphic mutations in the human *NBS1* and *MRE11* genes cause the genome instability and cancer predisposition syndromes Nijmegen breakage syndrome (NBS) and ataxia telangiecatisia-like disorder (ATLD), respectively [Carney et al. 1998; Matsura et al. 1998; Varon et al. 1998; Stewart et al. 1999]. In addition, two different engineered reduced-function alleles of murine *Nbs1* resulted in viable mice [Kang et al. 2002; Williams et al. 2002]. No viable mutations in mammalian *RAD50* had been identified thus far. This void has now been filled by the Rad50S/S mice.

### Rad50S/S mice

To derive a viable mouse Rad50 allele, Bender et al. [2002] took their clues from genetic analyses of the *RAD50* gene from the yeast *Saccharomyces cerevisiae*. RAD50-deficient *S. cerevisiae* cells are viable but display mitotic and meiotic phenotypes. The cells are sensitive to the DNA-damaging agent methyl methanesulfonate (MMS) and are defective in the formation of viable spores. Alani et al. [1990] had isolated separation-of-function *rad50S* alleles of *RAD50* that conferred no overt MMS sensitivity to the cells, but still blocked viability of the organism at the molecular level [Bender et al. 2002]. Bender et al. [2002] mimicked three of these mutations in mouse embryonic stem (ES) cells. Two resulted in inviable cells, but one, a methionine substitution for lysine at amino acid position 22 [K22M], did support cell growth. This allele was used to derive Rad50S/S mice.

A remarkable aspect of the *Rad50* allele is its dramatically different consequence at the cellular versus the organismal level [Bender et al. 2002]. Rad50S/S mouse embryonic fibroblasts (MEFs) show almost none of the phenotypes that might be expected of perturbed Mre11 complex function [Table 1]. The cells display no growth defect, no defect in ionizing radiation-induced relocalization of the complex, and no hypersensitivity to DNA-damaging agents such as ionizing radiation and mitomycin C. In addition, although NBS and ATLD cells are defective in the ionizing-radiation-induced intra-S-phase checkpoint, Rad50S/S cells are not [Table 1]. However, even though no overt cellular phenotype of the Rad50S allele could be detected, its effect on mice is profound. Rad50S/S mice are susceptible to partial embryonic lethality. Animals that make it through birth are small, and most of them die within three months of severe anemia caused by hematopoietic stem cell depletion, whereas longer-lived animals are predisposed to cancer. How to reconcile these severe phenotypes with the subtle mutation in the Mre11 complex is a challenge, given that the complex plays pivotal roles in diverse aspects of DNA metabolism.

---

**Corresponding author.**

E-MAIL: kanaar@gen.igg.eur.nl; FAX 31-10-408-9468.

Article and publication are at http://www.genesdev.org/cgi/doi/10.1101/gad.1025402.
Rad50 structure

Because a specific mutation in Rad50, K22M, causes reduced function of the Mre11 complex, it is useful to consider the architecture of Rad50 and the complex. Based on its primary amino acid sequence, Rad50 has traditionally been declared a member of the structural maintenance of chromosomes (SMC) protein family, which organizes chromosomes during their replication and segregation (Nasmyth 2001; Hirano 2002; Wyman and Kanaar 2002). The amino acid sequence of proteins in this family suggests that they consist of N- and C-terminal globular domains, separated by an extended coiled-coil region (Fig. 1A). The terminal globular domains contain Walker A- and B-type ATPase domains, respectively, that reconstitute into a bipartite ATPase domain (Fig. 1B). The combination of electron microscopy, scanning force microscopy (SFM), and X-ray crystallography confirmed this predicted structure (Melby et al. 1998, Hopfner et al. 2000, Anderson et al. 2001, 2002, de Jager et al. 2001; Haering et al. 2002, Hopfner et al. 2002). However, these studies also revealed a number of highly interesting surprises.

SMC family proteins function either as homo- or heterodimers. The Mre11 complex contains a Rad50 homodimer. A previously unexpected aspect of the architecture of the coiled-coil regions is that they do not form intermolecular coiled coils, but intramolecular coiled coils that are highly flexible (Fig. 1B; de Jager et al. 2001; Haering et al. 2002; Hopfner et al. 2002). The intramolecular coiled coil forms because the predicted coiled-coil region of a single molecule folds back onto itself. In the case of Rad50 homologs, the coiled coil is interrupted by a conserved CXXC motif, where C stands for cysteine and X for any amino acid (Fig. 1A). Recently, it was shown that this motif is located at the tip of the coiled coil in an archael Rad50 structural homolog. It provides a dimerization domain, referred to as a zinc-hook, between sister chromatids. This tethering can occur through multiple interactions of the zinc-hook structures by intermolecular coordination of a zinc ion between Rad50 CXXC motifs.

Table 1. Comparison of genome instability-related phenotypes associated with mutations in the Mre11 complex in humans and mice

| Phenotype                                | Human Nijmegen breakage syndrome | Human AT-like disorder | Murine Rad50<sup>a</sup> |Murine Nbs |
|------------------------------------------|----------------------------------|------------------------|---------------------------|-----------|
| Cancer predisposition                    | Y                                | ND                     | Y                         | Y/N<sup>a</sup> |
| Cellular radiosensitivity                | Y                                | Y                      | N                         | Y         |
| Spontaneous chromosomal instability      | Y                                | Y                      | Y                         | N         |
| Radioresistant DNA synthesis             | Y                                | Y                      | N                         | Y         |
| Defective ionizing radiation-induced foci formation | Y                                | Y                      | N                         | Y         |

Y, phenotype observed; N, phenotype not observed; ND, not determined.

<sup>a</sup>Depends on specific Nbs allele (Kang et al. 2002; Williams et al., 2002)
between the two Rad50 coiled-coil arms by coordination of a zinc ion by the sulfhydryl groups of the four cysteines [Fig. 1B,C; Hopfner et al. 2002].

A molecular picture of the architecture of the human Mre11 complex and its mode of interaction with DNA is now beginning to emerge. Mre11, which has exo- and endonuclease activities (Sharples and Leach 1995; Paull and Gellert 1998; Trujillo et al. 1998), binds to the coiled-coil regions of Rad50 near the globular ATPase domain [Hopfner et al. 2001]. A dimer of Mre11 interacts with two Rad50 molecules, resulting in a large globular domain from which the coiled-coil arms emanate [Fig. 1B, de Jager et al. 2001]. An intriguing unanswered question about the architecture of the Mre11 complex is the location of Nbs1. This component interacts with Mre11 [D’Amours and Jackson 2002], but exactly how it fits in the complex is still unknown. SFM analysis of the complex between human Rad50 and Mre11 showed that it binds DNA through its globular domain with the arms protruding away. The complex oligomerizes on linear DNA and can tether DNA molecules, presumably through interactions between the tips of its coiled coils [de Jager et al. 2001; Hopfner et al. 2002]. Importantly, oligomerization requires a DNA end, allowing the complex to specifically tether broken DNA molecules either within a sister chromatid or between a broken and an intact sister chromatid [Fig. 1C].

The deleterious effects of the Rad50 K22M mutation in mice invite biochemical analysis of the activities of the Mre11 complex containing this mutation. Because it is located close to the ATPase domain of Rad50, it is of interest to determine the effect of this mutation on the nucleases activities of the complex, given that ATP stimulates the endonuclease activity of the complex on DNA substrates containing 3’ single-stranded overhangs [Paull and Gellert 1999; Trujillo and Sung 2001]. Effects of the mutation on the nuclease activity could impinge on the DNA repair function of the Mre11 complex or on its involvement in DNA damage checkpoint signaling, because the nucleolytic processing of DNA lesions could be required to effectively signal them to the cell cycle checkpoint machinery [Lydall and Weinert 1995; Lee et al. 1998; D’Amours and Jackson 2001].

The Mre11 complex and S-phase progression

Deficiencies in the Mre11 complex, such as those that occur in cells derived from NBS and ATLD patients, can result in the inefficient inhibition of DNA synthesis upon ionizing radiation treatment (Table 1; Shiloh 1997; Stewart et al. 1999). This response, known as radiosensitive DNA synthesis [RDS], is indicative of the inability of cells to fully induce an intra-S-phase checkpoint (Shiloh 1997). Several recent studies provide new insights into the position of the Mre11 complex in the cascades of events that are required to protect cells from RDS. Near the top of these cascades is the ataxia telangiectasia mutated (ATM) protein kinase, which is defective in patients suffering from the genome instability, and cancer predisposition syndrome ataxia telangiectasia (AT; Khanna and Jackson 2001). In response to ionizing-radiation-induced DSBs, ATM phosphorylates Nbs1, which is required to inhibit DNA synthesis [D’Amours and Jackson 2002]. Interestingly, the extent of RDS is greater in cells from AT patients than in cells from NBS and ATLD patients, suggesting the possibility of parallel pathways leading to DNA synthesis inhibition that diverge at ATM [Falck et al. 2002]. Indeed, recent evidence suggests that one branch is formed by the ATM-dependent phosphorylation of Chk2, which results in inhibition of DNA replication origin firing through the Chk2–Cdc25A–cyclin E/Cdk2 cascade [Falck et al. 2001], whereas ATM-dependent phosphorylation of the Mre11 complex is required for a parallel branch of the intra-S-phase checkpoint [Falck et al. 2002]. An intriguing downstream substrate in the Mre11-complex-dependent branch could be SMC1, a component of the multiprotein cohesion complex required for establishment of sister-chromatid cohesion during S phase [Nasmyth 2001; Hirano 2002]. Ionizing-radiation-induced phosphorylation of SMC1 by ATM is dependent on Nbs1 and required for inhibition of DNA synthesis [Kim et al. 2002; Yazdi et al. 2002]. However, the results of Bender et al. (2002) support the argument that the checkpoint-related functions of the Mre11 complex in Rad50NS cells are not significantly affected. When Rad50NS cells were treated with ionizing radiation they were as efficient as wild-type cells in inhibiting DNA synthesis.

The Mre11 complex in DNA repair and replication

Given that mutations in the components of the S. cerevisiae Mre11 complex (in which the Nbs1-like component is encoded by the XRS2 gene) resulted in ionizing radiation sensitivity, much attention has been given over the years to defining its role in repair of DSBs. Multiple lines of evidence suggest that the complex participates in two mechanistically distinct pathways of DSB repair: homologous recombination and nonhomologous DNA end joining [Bressan et al. 1999; Lewis and Resnick 2000; Chen et al. 2001; Huang and Dynan 2002]. The former depends on a homologous DNA template, that is, the undamaged sister chromatid, to accurately restore the continuity of the broken sister chromatid, whereas the latter relies on DNA ends without any requirement for a template. Important as the role of the Mre11 complex in repair of exogenously induced DSBs might be, the complex is also pivotal in protecting cells from spontaneous chromosomal rearrangements [Chen and Kolodner 1999; Myung et al. 2001]. These latter observations are consistent with a role of the Mre11 complex in preventing genome instability during DNA replication.

Indeed, the dependence of genome duplication on homologous recombination in general is presently a topic of vigorous reinvestigation [Cox et al. 2000]. Evidence from genetic, cytological, and biochemical approaches points to a possible central position of the Mre11 complex in this link. S. cerevisiae rad50S and mre11 nuclease-deficient alleles are synthetically lethal with the
structure-specific endonuclease Rad27/FEN1 (Moreau et al. 1999; Debrauwere et al. 2001). Given the role of Rad27/FEN1 in processing intermediates in lagging-strand DNA synthesis, these results suggest the involvement of the Mre11 complex in this process. Furthermore, the complex plays a role in the resolution of aberrant DNA structures that arise when replication forks pass through repeated sequences (Cromie et al. 2001; Farah et al. 2002; Lobachev et al. 2002). In addition, certain DSB repair pathways that are directly coupled to extensive DNA replication, such as break-induced replication in S. cerevisiae and replication restart in phages, require Rad50 and Mre11 homologs (George et al. 2001; Signor et al. 2001). Finally, the Mre11 complex localizes to replication sites (Maser et al. 2001), and its presence is required to prevent the accumulation of DSBs during DNA replication in extracts from Xenopus laevis cells (Costanzo et al. 2001).

Cells derived from Rad50<sup>S/S</sup> mice are not sensitive to exogenously induced DSBs, yet they show increases in spontaneous levels of γ-H2AX foci, a marker for DSBs [Modesti and Kanaar 2001], and cytologically detectable chromosome breaks [Bender et al. 2002]. These phenotypes are consistent with the idea that the Mre11 complex is important for correcting problems arising during DNA replication. If so, Rad50<sup>S/S</sup> cells would be under continuous genotoxic stress, which could cause the underlying phenotype of the mice. The age-dependent attrition of cells in the bone marrow and testis can be explained in this context because these tissues contain rapidly proliferating cells derived from a small stem-cell compartment. Furthermore, interference with the ability of Rad50<sup>S/S</sup> cells to activate cell cycle checkpoints and induce apoptosis by deletion of p53 results in an increased life span of the mice and decreased tumor latency [Bender et al. 2002]. This is also in accordance with the idea that reduced function of the Mre11 complex leads to chronic genotoxicity.

Rad50S: conservation between yeast and mouse?

Based on their amino acid sequences, it is clear that components of the yeast and mammalian Mre11 complex are highly conserved. It is interesting, then, that the K22M amino acid change in Rad50 yields contrasting phenotypes in yeast and mice. The differential effect is most dramatic in meiosis: Whereas the failure to form viable spores owing to the inability to further process meiotic DSBs is a defining feature of rad50 alleles, no overt meiotic defect is observed in Rad50<sup>S/S</sup> mice [Bender et al. 2002]. However, in addition to differences in phenotypes, there are also similarities, particularly with respect to telomere metabolism. In yeast the Mre11 complex is involved in telomere homeostasis [Haber 1998]. In mammalian cells the complex has been localized at telomeres, but a biological effect on telomeres had not been shown [Zhu et al. 2000]. Now Bender et al. [2002] show that in Rad50<sup>S/S</sup> tumor cells, telomere-to-telomere fusions are increased. A more detailed analysis of the molecular nature of these defective telomeres will undoubtedly provide new insight into the mechanism of telomere maintenance in mammalian cells. Given the presence of repetitive DNA sequences at telomeres and their unusual structure [Griffith et al. 1999], the role of the Mre11 complex might be related to its role in resolving aberrant DNA secondary structures arising during replication of sequences with a high propensity to form secondary structures.

The murine Rad50<sup>S</sup> allele underscores the fact that very subtle changes in protein activity can have dramatic phenotypic consequences. It also shows that even in the context of a highly conserved protein, it is not trivial to predict the behavior of mammalian mutant alleles based on yeast genetics. Two of the mimicked yeast rad50S alleles resulted in nonviable murine ES cells, whereas a third resulted in mice on the threshold of viability. The severity of the murine Rad50<sup>S</sup> phenotype caused by a subtle mutation provides a prime example of the importance of polymorphisms in genome-surveillance proteins for conferring differences in cancer predisposition in the human population. Now that a biological effect of the mammalian Rad50<sup>S</sup> protein has been shown, it is an interesting venture to link this biological effect to one or more of the many biochemical and structural functions of the Mre11 complex. Certainly, we can expect many more surprises with regard to this protein complex in the not-too-distant future, given that the keyword “Rad50” pulls up just as many references in PubMed in the last two and half years as in the preceding 23.

References

Alani, E., Padmore, R., and Kleckner, N. 1990. Analysis of wild-type and rad50 mutants of yeast suggests an intimate relationship between meiotic chromosome synapsis and recombination. *Cell* **61**: 419–436.

Anderson, D.E., Trujillo, K.M., Sung, P., and Erickson, H.P. 2001. Structure of the Rad50·Mre11 DNA repair complex from *Saccharomyces cerevisiae* by electron microscopy. *J. Biol. Chem.* **276**: 37027–37033.

Anderson, D.E., Losada, A., Erickson, H.P., and Hirano, T. 2002. Condensin and cohesin display different arm conformations with characteristic hinge angles. *J. Cell Biol.* **156**: 419–424.

Bender, C.F., Sikes, M.L., Sullivan, R., Erskine Huye, L., Le Beau, M.M., Roth, D.B., Mirzoeva, O.K., Oltz, E.M., and Pettrini, J.H. J. 2002. Cancer predisposition and hematopoietic failure in Rad50<sup>S</sup> mice. *Genes & Dev.* (this issue).

Bressan, D.A., Baxter, B.K., and Petrini, J.H. 1999. The Mre11–Rad50–Xrs2 protein complex facilitates homologous recombination-based double-strand break repair in *Saccharomyces cerevisiae*. *Mol. Cell. Biol.* **19**: 7681–7687.

Carney, J.P., Maser, R.S., Olivares, H., Davis, E.M., Le Beau, M., Yates III, J.R., Hays, L., Morgan, W.F., and Petrini, J.H. 1998. The hMre11/hRad50 protein complex and Nijmegen breakage syndrome: Linkage of double-strand break repair to the cellular DNA damage response. *Cell* **93**: 477–486.

Chen, C. and Kolodner, R.D. 1999. Gross chromosomal rearrangements in Saccharomyces cerevisiae replication and recombination defective mutants. *Nat. Genet.* **23**: 81–85.

Chen, L., Trujillo, K., Ramos, W., Sung, P., and Tomkinson, A.E. 2001. Promotion of Dnl4-catalyzed DNA end-joining by the Rad50/Mre11/Xrs2 and Hdf1/Hdf2 complexes. *Mol. Cell* **19**: 7681–7687.
The Mre11 complex and genome stability

8: 1105–1115.
Costanzo, V., Robertson, K., Bibikova, M., Kim, E., Grieco, D., Gottesman, M., Carroll, D., and Gautier, J. 2001. Mre11 protein complex prevents double-strand break accumulation during chromosomal DNA replication. Mol. Cell 8: 137–147.
Cox, M.M., Goodman, M.F., Kreuzer, K.R., Sherratt, D.J., Sandler, S.J., and Mians, K.J. 2000. The importance of repairing stalled replication forks. Nature 404: 37–41.
Cromie, G.A., Connelly, J.C., and Leach, D.R. 2001. Recombination at double-strand breaks and DNA ends: Conserved mechanisms from phage to humans. Mol. Cell 8: 1163–1174.
D’Amours, D. and Jackson, S.P. 2001. The yeast Xrs2 complex functions in S phase checkpoint regulation. Genes & Dev. 15: 2238–2249.
———. 2002. The Mre11 complex: At the crossroads of DNA damage processing: Implications for repair and arrest. Cell 108: 583–596.
D’Amours, D. and Jackson, S.P. 2001. The Mre11 complex and DNA replication: Linkage to E2F and meiotic telomeres. Cell 105: 473–485.
Hopfner, K.P., Hopfner, K.P., Karcher, A., Henderson, B., Bodmer, J.L., McMurray, C.T., et al. 2002. The Rad50 zinc-hook is a structure joining Mre11 complexes in DNA recombination and repair. Nature 418: 562–566.
Huaring, J. and Dynan, W.S. 2002. Reconstitution of the mammalian DNA double-strand break end-joining reaction reveals a requirement for an Mrc11/Rad50/NBS1-containing fraction. Nucleic Acids Res. 30: 667–674.
Kang, J., Bronson, R.T., and Xu, Y. 2002. Targeted disruption of NBS1 reveals its roles in mouse development and DNA repair. EMBO J. 21: 1447–1455.
Khan, K.K. and Jackson, S.P. 2001. DNA double-strand breaks: Signaling, repair and the cancer connection. Nat. Genet. 27: 247–254.
Kim, S.T., Xu, B., and Kastan, M.B. 2002. Involvement of the cohesin protein, Smc1, in Atm-dependent and independent responses to DNA damage. Genes & Dev. 16: 560–570.
Lee, S.E., Moore, J.K., Holmes, A., Umezou, K., Kolodner, R.D., and Haber, J.E. 1998. Saccharomyces Ku70, mre11/rad50 and RPA proteins regulate adaptation to G2/M arrest after DNA damage. Cell 94: 399–409.
Lewis, L.K. and Resnick, M.A. 2000. Tying up loose ends: Non-homologous end-joining in Saccharomyces cerevisiae. Mutat. Res. 451: 71–89.
Lobachev, K.S., Gordenin, D.A., and Resnick, M.A. 2002. The Mre11 complex is required for repair of hairpin-capped double-strand breaks and prevention of chromosome rearrangements. Cell 108: 183–193.
Lombard, D.B. and Guarente, L. 2000. Nijmegen breakage syndrome protein and MRE11 at PML nuclear bodies and meiotic telomeres. Cancer Res. 60: 2331–2334.
Luo, G., Yao, M.S., Bender, C.F., Mills, M., Bladl, A.R., Bradley, A., and Petrini, J.H. 1999. Disruption of mRad50 causes embryonic stem cell lethality, abnormal embryonic development, and sensitivity to ionizing radiation. Proc. Natl. Acad. Sci. 96: 7376–7381.
Lydall, D. and Weinert, T. 1995. Yeast checkpoint genes in DNA damage processing: Implications for repair and arrest. Science 270: 1488–1491.
Maser, R.S., Mirzoeva, O.K., Wells, J., Olivares, H., Williams, B.R., Zinkel, R.A., Farnham, P.J., and Petrini, J.H. 2001. Mre11 complex and DNA replication: Linkage to E2F and sites of DNA synthesis. Mol. Cell. Biol. 21: 6006–6016.
Matsuura, S., Tauchi, H., Nakamura, A., Kondo, N., Sakamoto, S., Endo, S., Smeets, D., Solders, B., Belohradsky, B.H., Der Kaloustian, V.M., et al. 1998. Positional cloning of the gene for Nijmegen breakage syndrome. Nat. Genet. 19: 179–181.
Melby, T.E., Ciampaglio, C.N., Briscoe, G., and Erickson, H.P. 1998. The symmetrical structure of structural maintenance of chromosomes [SMC] and MukB proteins: Long antiparallel coiled coils, folded at a flexible hinge. J. Cell Biol. 142: 1595–1604.
Modesti, M. and Kanaar, R. 2001. DNA repair: Spotlight(s) on chromatid. Curr. Biol. 11: R229–R232.
Moreau, S., Ferguson, J.R., and Symington, L.S. 1999. The nuclease activity of Mre11 is required for meiosis but not for mating type switching, end joining, or telomere maintenance. Mol. Cell. Biol. 19: 556–566.
Myung, K., Datta, A., and Kolodner, R.D. 2001. Suppression of spontaneous chromosomal rearrangements by S phase checkpoint functions in Saccharomyces cerevisiae. Cell 104: 397–408.
Nasmyth, K. 2001. Disseminating the genome: Joining, resolving, and separating sister chromatids during mitosis and meiosis. Annu. Rev. Genet. 35: 673–745.
Pauil, T.T. and Gellert, M. 1998. The 3’ to 5’ exonuclease activity of Mre 11 facilitates repair of DNA double-strand breaks. Mol. Cell 1: 969–979.
———. 1999. Nbs1 potentiates ATP-driven DNA unwinding and endonuclease cleavage by the Mre11/Rad50 complex. Genes & Dev. 13: 1276–1288.
Petrini, J.H. 2000. The Mre11 complex and ATM: Collaborating
to navigate S phase. *Curr. Opin. Cell Biol.* **12**: 293–296.

Sharples, G.J. and Leach, D.R. 1995. Structural and functional similarities between the SbcCD proteins of *Escherichia coli* and the RAD50 and MRE11 (RAD32) recombination and repair proteins of yeast. *Mol. Microbiol.* **17**: 1215–1217.

Shiloh, Y. 1997. Ataxia-telangiectasia and the Nijmegen breakage syndrome: Related disorders but genes apart. *Annu. Rev. Genet.* **31**: 635–662.

Signon, L., Malkova, A., Naylor, M.L., Klein, H., and Haber, J.E. 2001. Genetic requirements for RAD51- and RAD54-independent break-induced replication repair of a chromosomal double-strand break. *Mol. Cell. Biol.* **21**: 2048–2056.

Stewart, G.S., Maser, R.S., Stankovic, T., Bressan, D.A., Kaplan, M.I., Jaspers, N.G., Raams, A., Byrd, P.J., Petrini, J.H., and Taylor, A.M. 1999. The DNA double-strand break repair gene hMRE11 is mutated in individuals with an ataxia-telangiectasia-like disorder. *Cell* **99**: 577–587.

Trujillo, K.M. and Sung, P. 2001. DNA structure-specific nuclease activities in the *Saccharomyces cerevisiae* Rad50·Mre11 complex. *J. Biol. Chem.* **276**: 35458–35464.

Trujillo, K.M., Yuan, S.S., Lee, E.Y., and Sung, P. 1998. Nuclease activities in a complex of human recombination and DNA repair factors Rad50, Mre11, and p95. *J. Biol. Chem.* **273**: 21447–21450.

Varon, R., Vissinga, C., Platzer, M., Ceresaletti, K.M., Chrzanowska, K.H., Saar, K., Beckmann, G., Seemanova, E., Cooper, P.R., Nowak, N.J., et al. 1998. Nibrin, a novel DNA double-strand break repair protein, is mutated in Nijmegen breakage syndrome. *Cell* **93**: 467–476.

Williams, B.R., Mirzoeva, O.K., Morgan, W.F., Lin, J., Dunnick, W., and Petrini, J.H. 2002. A murine model of Nijmegen breakage syndrome. *Curr. Biol.* **12**: 648–653.

Wyman, C. and Kanaar, R. 2002. Chromosome organization: Reaching out to embrace new models. *Curr. Biol.* **12**: R446–R448.

Xiao, Y. and Weaver, D.T. 1997. Conditional gene targeted deletion by Cre recombinase demonstrates the requirement for the double-strand break repair Mre11 protein in murine embryonic stem cells. *Nucleic Acids Res.* **25**: 2985–2991.

Yamaguchi-Iwai, Y., Sonoda, E., Sasaki, M.S., Morrison, C., Haraguchi, T., Hiraoka, Y., Yamashita, Y.M., Yagi, T., Takeuchi, M., Price, C., et al. 1999. Mre11 is essential for the maintenance of chromosomal DNA in vertebrate cells. *EMBO J.* **18**: 6619–6629.

Yazdi, P.T., Wang, Y., Zhao, S., Patel, N., Lee, E.Y., and Qin, J. 2002. SMC1 is a downstream effector in the ATM/NBS1 branch of the human S-phase checkpoint. *Genes & Dev.* **16**: 571–582.

Zhu, J., Petersen, S., Tessarollo, L., and Nussenzweig, A. 2001. Targeted disruption of the Nijmegen breakage syndrome gene NBS1 leads to early embryonic lethality in mice. *Curr. Biol.* **11**: 105–109.

Zhu, X.D., Kuster, B., Mann, M., Petrini, J.H., and Lange, T. 2000. Cell-cycle-regulated association of RAD50/MRE11/NBS1 with TRF2 and human telomeres. *Nat. Genet.* **25**: 347–352.
## Genome instability and $\text{Rad50}^S$: subtle yet severe

Martijn de Jager and Roland Kanaar

*Genes Dev.* 2002, 16:
Access the most recent version at doi:10.1101/gad.1025402

| References | This article cites 59 articles, 22 of which can be accessed free at: [http://genesdev.cshlp.org/content/16/17/2173.full.html#ref-list-1](http://genesdev.cshlp.org/content/16/17/2173.full.html#ref-list-1) |
| License    | |
| Email Alerting Service | Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article or [click here](http://genesdev.cshlp.org/content/16/17/2173.full.html#ref-list-1). |