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DNA REPAIR '99
The Mammalian Mre11-Rad50-Nbs1 Protein Complex: Integration of Functions in the Cellular DNA–Damage Response

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DNA-repair functions can be generally divided according to the type of DNA damage that is repaired by a given pathway and by the mechanistic scheme by which that repair is effected. The requirement for some form of DNA recombination distinguishes the repair of DNA double-strand breaks (DSBs) from nucleotide-excision repair (NER), DNA-mismatch repair, or base-excision repair. Because DSBs are repaired by DNA recombination, these lesions are extraordinarily potent inducers of genetic alteration. Given this property, it is not surprising that the formation of DSBs is critical to the initiation of programmed DNA recombination events such as immunoglobulin-gene recombination (see Maizels 1999 [in this issue]), mating-type switching, and meiotic exchange; these events occur in cell lineages that diversify their coding potential during normal differentiation. On the other hand, retrospective analysis of malignant cells often reveals the pathological outcomes that may ensue from DSB formation and repair. Loss of heterozygosity, chromosome loss, and chromosomal rearrangement are deadly forms of genetic diversification, and these events can frequently be attributed to DNA recombination events gone awry. Spontaneous genomic instability of this nature is greatly exacerbated by defects in the cell's response to DSBs, and such defects markedly predispose to the onset and progression of malignancy (Petrini et al. 1997).

In the end, the remarkable stability of genetic information is due to a complex network of functions that include DNA damage–dependent cell cycle–checkpoint regulation and DNA repair. The activation and integration of these functions implicitly depends on a detector of DSBs that transduces a signal that the lesion is present (fig. 1). The hMRE11-hRAD50-NBS1 protein complex has emerged as a central player in the human cellular DNA-damage response, and recent observations suggest that these proteins are at least partially responsible for the linking of DNA-damage detection to DNA-repair and cell cycle–checkpoint functions. This protein complex has been implicated in the activation of cell cycle–regulatory pathways, by virtue of the fact that the *NBS1* gene has been shown to be mutated in the chromosomal-instability syndrome, Nijmegen breakage syndrome (NBS) (Carney et al. 1998; Varon et al. 1998).

At the cellular level, NBS is similar to ataxia telangiectasia (AT); in the presence of ionizing radiation (IR)–induced DNA damage, both syndromes fail to suppress DNA synthesis and exhibit radiosensitivity and increased spontaneous, as well as IR-induced, chromosomal instability. Important distinction between these two autosomal recessive syndromes can be made at the clinical level; nevertheless, both are associated with combined variable immune deficiency, as well as with an extremely strong predisposition to malignancy (Shiloh 1997). Cytological analyses of the hMRE11-hRAD50-NBS1 protein complex in irradiated cells indicates that it becomes associated with DSBs early in the cellular DNA-damage response and that it remains thus associated until the bulk of DSB repair is complete (Nelms et al. 1998). These data support the hypothesis that the complex functions in the detection of DNA damage, whereas the cell cycle–checkpoint defects associated with NBS point, in addition, to a role in transduction of the ensuing signal that DNA damage is present. In the following sections, the salient features of the hMRE11-hRAD50-NBS1 protein complex will be discussed. Because two members of this complex are highly conserved between yeast and mammals, this discussion will be preceded by a brief outline of the *Saccharomyces cerevisiae* DSB-repair pathway, with particular emphasis on the functions of the yeast *Mre11* and *Rad50* homologues, *ScMre11* and *ScRad50*. The terms "recombinational DNA repair" and "DSB repair" will be used interchangeably throughout this review, reflecting the fact that DSBs must be repaired by DNA recombination.

DSB Repair in Yeast: The *RAD52* Epistasis Group

Eleven genes (*ScRAD50–ScRAD57, ScRAD59, ScMRE11,* and *ScXRS2*) collectively referred to as the

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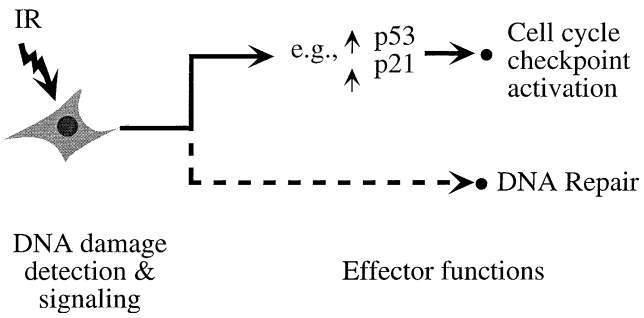

Figure 1 Cellular DNA–damage response. DSBs, induced in this example by IR, are detected, and an appropriate signal is transmitted to downstream mediators of the cellular DNA—damage response. These effectors include cell cycle–checkpoint mediators, particularly p53 and its transcriptional targets, as well as DNA-repair enzymes.

"*RAD52* epistasis group" encode proteins that mediate most DSB-repair and DNA recombination events in *S. cerevisiae* (Ajimura et al. 1993; Bai and Symington 1996; Game 1993; Ivanov et al. 1992). The repair of IR-induced DSBs in *S. cerevisiae* is usually effected by homologous recombination between a damaged site and the corresponding locus on a sister chromatid (Szostak et al. 1983). Repair involving recombination between homologues does occur, but such events are relatively rare, in both yeast and human cells (Kadyk and Hartwell 1992). DSBs can also be repaired by nonhomologous end joining in *S. cerevisiae,* although this mode of recombinational DNA repair appears to be utilized less frequently than homologous recombination (Haber 1992).

The *S. cerevisiae RAD52* epistasis group can be divided into two subgroups, with *ScMRE11, ScRAD50,* and *ScXRS2* being distinct from *ScRAD51, ScRAD52, ScRAD54, ScRAD55,* and *ScRAD57.* Mutations in *Scmre11, Scrad50,* and *Scxrs2* reduce the efficiency of nonhomologous end joining by 70-fold, whereas this process is unaffected by mutations in *Scrad51, Scrad52, Scrad54,* or *Scrad57* (Moore and Haber 1996; Schiestl et al. 1994; Tsukamoto et al. 1996). Although ScMre11, ScRad50, and ScXrs2 function in nonhomologous end joining, abrogation of this mode of DSB repair does not appear to be responsible for the IR sensitivity of the corresponding mutants. In fact, many aspects of the *Scmre11, Scrad50,* and *xrs2* mutant phenotypes argue that these proteins are also critical for homologous recombination–based DSB repair (Moore and Haber 1996; D. Bressan, B. K. Baxter, and J. H. J. Petrini, unpublished data).

The mechanistic basis of the *S. cerevisiae* Mre11/Rad50/Xrs2 protein complex's effect on these two otherwise genetically distinct modes of DNA recombination is unclear. However, an important clue may be that the DSB-repair defects in these mutants are almost exclusively manifested in cells possessing a sister chromatid—that is, in cells in the G2 phase of the cell cycle—whereas cells in G1, lacking a sister chromatid, are much less affected. This suggests that nonhomologous end joining and homologous recombination both require a sister chromatid or homologous chromosome to stabilize broken chromosomes and, thereby, to facilitate the repair process. According to this view, the lack of such a stabilizing influence abrogates nonhomologous end joining and profoundly impairs homologous recombination in *Scmre11, Scrad50,* and *xrs2* mutants (Moore and Haber 1996; D. Bressan, B. K. Baxter, and J. H. J. Petrini, unpublished data). Hence, the *S. cerevisiae* Mre11/Rad50/Xrs2 protein complex may play a structural rather than an enzymatic role in the DSB-repair process. As described below, an analogous role for the mammalian complex may explain the observation that both *RAD50* and *MRE11* are essential genes in mammals.

The Mammalian Mre11-Rad50-Nbs1 Protein Complex

To date, five mammalian *RAD52* epistasis–group homologues have been isolated. The most highly conserved of these are the *RAD51* and *RAD54* homologues, but the *MRE11, RAD50,* and *RAD52* homologues also contain local regions of impressive primary-sequence conservation. In our laboratory, my colleagues and I have established that a homologue of the ScMre11/ScRad50/ScXrs2 protein complex exists in human cells; Nbs1 (also known as "p95") has replaced Xrs2 in mammals, and, hence, this complex is referred to, throughout the present review, as the "hMRE11-hRAD50-NBS1 protein complex" (Dolganov et al. 1996; Carney et al. 1998). Xrs2 in *S. cerevisiae* and Nbs1 in mammals are notable exceptions to the rule of conservation among RAD52 epistasis–group proteins. Whereas Southern blotting indicates that the *NBS1* gene is conserved among mammals, no obvious *NBS1* or *XRS2* homologues are present in the genome databases currently available, including the nearly complete *Caenorhabditis elegans* genome sequence (Carney et al. 1998; Maser et al. 1999). In contrast, proteins with similarity to Mre11 and Rad50 are present in organisms representing all branches of the tree of life.

Cytological Observations

Over the years, the microscopic examination of irradiated human cells has provided important information regarding the cellular DNA–damage response. The availability of immunological reagents specific for proteins that function in DSB repair has augmented this classical approach, by permitting investigators to analyze the disposition of these proteins in damaged cells (Haaf et al. 1995; Maser et al. 1997). This approach

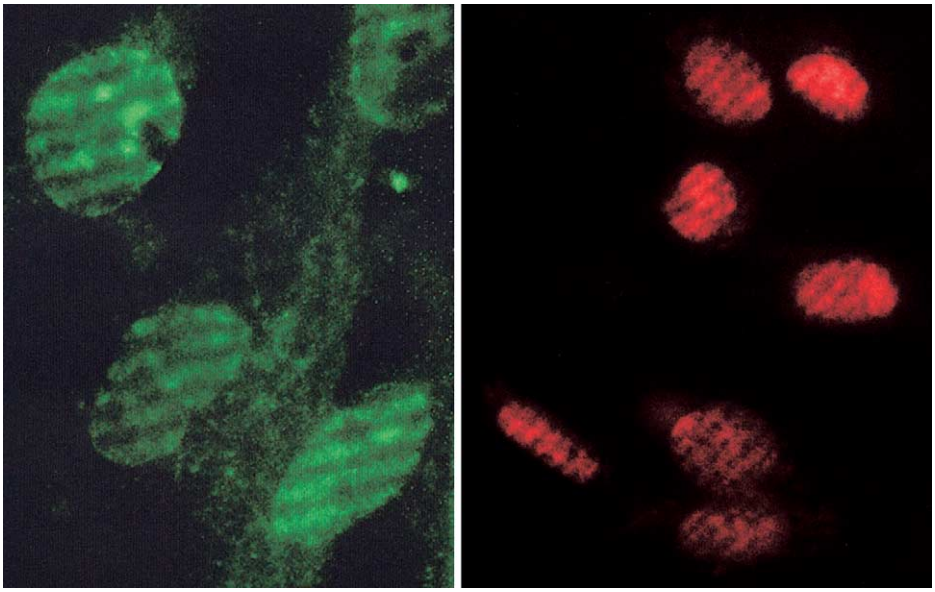

Figure 2 DNA-damage detection. Human diploid fibroblasts were irradiated through the gold masking grid, as described in the text, and were stained for DSBs (*green signal*) and hMRE11 protein (*red signal*) 30 min after irradiation. The DSB stripes dissipate ≤90 min after IR, at which time the bulk of DSB repair is complete. The hMRE11 stripes follow the same time course.

has been particularly useful for the understanding of the functions of the hMRE11-hRAD50-Nbs1 protein complex. Although gentle extraction of nuclear proteins suggests that the complex may associate preferentially with certain structures within the nucleus, the members of this rather abundant protein complex are, for the most part, uniformly distributed in the nuclei of normally growing cells. However, on the induction of DSBs by IR, a dramatic alteration in the distribution of the complex occurs. The proteins become associated in large foci, the formation of which is strictly dependent on the prior induction of DSBs—for example, nuclear foci are not induced in cells treated with UV radiation. Several lines of evidence support the interpretation that nuclear foci are indicative of the complex's functions in the cellular response to DSBs (Maser et al. 1997). One explanation for the formation of IR-induced nuclear foci is that they represent either sites of ongoing DNA repair or sites at which DNA repair has been initiated and remains unresolved.

To examine this aspect of the complex's role in the cellular DNA–damage response, my colleagues and I have developed a method to induce DNA damage in discrete subnuclear regions of irradiated cells. The principle of the approach is to damage discrete regions within the nucleus and to subsequently monitor the presence of DSBs and DSB-repair proteins at those sites. This method relies on synchrotron-generated ultrasoft x-rays (1.34 keV) and microfabricated irradiation masks. The irradiation masks, fabricated with x-ray lithography, consist of gold stripes, 1.85 μm wide, with 1.35 μm of separation. Irradiated cells thus absorb ultrasoft x-rays in 1.35-μm-wide stripes separated by 1.85-μm gaps that remain essentially unirradiated. DSBs induced in stripe-irradiated cells are visualized by means of bromodeoxyuridine (BrdU) labeling with terminal deoxynucleotidyl transferase, in a fashion analogous to that used to detect apoptotic cells. Nuclei observed 30 min after irradiation display parallel stripes, corresponding to BrdU incorporation at DNA ends. Stripe-irradiated fibroblasts are subsequently stained with hMRE11 antisera. We found that hMRE11—and, therefore, the hMRE11/hRAD50 protein complex—associated with DSBs at the earliest time points examined and dissipated as DSBs were repaired (fig. 2; see also Nelms et al. 1998). These observations suggest that the complex may be a primary detector of DNA damage, and they thereby place the hMRE11-hRAD50-NBS1 protein complex's functions at the earliest stage of the cellular DNA–damage response.

Linking DSB Repair and Cell-Cycle Checkpoints

NBS1 was simultaneously identified in two laboratories: on one hand, a Herculean positional-cloning effort led to the isolation of the gene mutated in patients with NBS (Varon et al. 1998); on the other hand, a search for the human Xrs2 homologue led to the direct protein sequencing of p95, the 95-kD protein associated with hMRE11 and hRAD50. In addition, a two-hybrid

screen for hMRE11 interacting proteins identified the gene encoding p95, a gene now known as "*NBS1*" (Carney et al. 1998). Most patients with NBS carry the same mutant allele, a 5-bp deletion in exon 6 of chromosome 16; this mutation appears to be null (Varon et al. 1998). NBS1 is constitutively associated with hMRE11 and hRAD50. Null mutants of murine *MRE11* in embryonic stem cells are inviable (Xiao and Weaver 1997), and *mrad50* mice die very early in embryogenesis (G. Luo, M. S. Yao, C. F. Bender, A. R. Bladl, A. Bradley, and J. H. J. Petrini, unpublished data). In this context, it is surprising that patients with complete inactivation of the *NBS1* gene are viable. However, the existence of truncated protein products in these NBS cells has not been rigorously excluded; my colleagues and I currently are examining this issue is in our laboratory.

The implication of *NBS1* in NBS strongly supports the hypothesis that the hMRE11-hRAD50-NBS1 protein complex functions in the detection and signaling of DNA damage. In principle, the abrogation of DNA-damage detection and the ensuing signal-transduction events is likely to disrupt the activation of downstream functions in the cellular DNA–damage response, including DNA damage–dependent cell cycle–checkpoint functions and DNA repair. NBS cells, as well as cells from patients with AT, exhibit defects in the cellular response to IR, in a manner that suggests just such an abrogation. Notably, cells from both groups of patients fail to suppress DNA synthesis after treatment with IR, a phenomenon termed "radioresistant DNA synthesis" (Shiloh 1997). The similarity of the NBS and AT cellular phenotypes suggests that the corresponding gene products function in the same pathway. Indeed, persistence of the radioresistant DNA–synthesis phenotype in heterodikaryons of AT and NBS fibroblasts has led to speculation that the *ATM* and *NBS* gene products are physically associated (Stumm et al. 1997).

Cells from patients with NBS and from patients with AT are sensitive to killing by IR and exhibit increased levels of spontaneous as well as IR-induced chromosomal fragility. Interestingly, the spontaneous chromosomal aberrations seen in both AT and NBS cells frequently involves loci, on chromosomes 7 and 14, that correspond to sites of antigen receptor–gene rearrangement (van der Burgt et al. 1996). AT cells are slow to induce p53 at the G1/S checkpoint, whereas this induction is much less affected in NBS cells, consistent with the somewhat controversial interpretation that the IR-dependent G1/S checkpoint is normal in NBS cells (Jongmans et al. 1997; Yamazaki et al. 1998). Finally, albeit to varying extents, both AT and NBS cells exhibit defects at the DNA damage–dependent G2/M checkpoint after treatment with IR (Shiloh 1997).

Collectively, the NBS cellular phenotype can be best explained by the failure of mutant cells to detect or signal the presence of DNA damage. It is perhaps telling that, whereas nuclear foci of hMRE11, hRAD50, and NBS1 are induced by IR treatment of normal cells, focus formation is completely abolished in NBS cells. This finding supports the hypothesis that the defective DNA-damage response is at least partially attributable to disruption of the complex's damage-recognition function (Carney et al. 1998). Thus, the hMRE11-hRAD50-NBS1 protein complex appears either to be a component of or to function in close proximity to a primary sensor of DNA damage. Furthermore, it is likely that the complex acts in the same DNA damage–response pathway as does the product of the *ATM* gene.

Recombinational DNA Repair

Given the strong conservation of *Mre11* and *Rad50,* it is likely that the mammalian proteins' functions in DSB repair are similar to those of their *S. cerevisiae* counterparts. However, analysis of the mammalian Mre11-Rad50-Nbs1 protein complex has been limited by the lethality of null mutations in *mMre11* (Xiao and Weaver 1997) and *mRad50.* Cultured blastocysts from *mRad50*-nullizygous embryos are acutely sensitive to killing by IR, supporting the expectation that these mutant embryos are DSB-repair deficient, but the extremely limited cellularity of blastocysts precludes direct assessment of repair in the nullizygous cells (G. Luo, M. S. Yao, C. F. Bender, A. R. Bladl, A. Bradley, and J. H. J. Petrini, unpublished data). Surprisingly, DSB repair in NBS cell lines is not profoundly affected by Nbs1 deficiency (Nove et al. 1986). Since NBS1 is much less conserved than Rad50 or Mre11, it is conceivable that this protein's role in the complex is distinct from the presumptive DSB-repair functions of hRAD50 and hMRE11. However, the extent to which the mammalian Mre11-Rad50-NBS1 protein complex is functionally analogous to the *S. cerevisiae* Mre11/Rad50/Xrs2 protein complex remains an open question. Certainly, the derivation of hypomorphic (as opposed to null) *mmre11* and *mrad50* models will help to address this issue.

It is clear that the DNA damage–recognition functions of the mammalian Mre11-Rad50-NBS1 protein complex are not essential, since they appear to be abrogated in NBS cells. This implies that Mre11 and Rad50 mediate additional functions that are essential and that must remain intact in NBS1-deficient cells. The nature of these functions is also an open question. Studies of the yeast complex suggest that the *S. cerevisiae* Mre11/Rad50/Xrs2 protein complex is required for the establishment or maintenance of sister-chromatid interactions (D. Bressan, B. K. Baxter, and J. H. J. Petrini, unpublished data) (Fabre et al. 1984; Ivanov et al. 1992; Moore and Haber 1996). The stage at which $mRad50^{-/-}$ embryonic development fails coincides with a dramatic in-

crease in the rate of cellular proliferation. The death of nullizygous embryos at this stage may imply that mRad50 deficiency abrogates sister-chromatid associations required for the repair of DSBs that arise at the replication fork.

Genomic Instability and Malignancy

Genomic instability is frequently observed in human cancer-predisposition syndromes (Cleaver 1989; German 1983; Jackson 1995; Kolodner 1995; Timme and Moses 1988). Among such syndromes are Bloom syndrome, AT, and congenitally acquired deficiencies in NER and DNA-mismatch repair. The finding that the chromosomal-instability syndrome, NBS, is attributable to defects in *NBS1* directly implicates the hMRE11/hRAD50 protein complex as a factor that protects normal tissues from malignancy (Carney et al. 1998). Since chromosomal rearrangements and changes in chromosome number are common features of malignant cells, errors in recombinational DNA repair have long been proposed to play an important role in neoplasia (Rowley 1994). The implication of NBS1 and the hMRE11/hRAD50 protein complex in NBS confirms this prediction, thus constituting the first direct link between deficiency in a recombinational DNA–repair protein complex and genomic instability associated with predisposition to malignancy.

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