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Review TRENDS in Genetics Vol.20 No.6 June 2004

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The tumor suppressor protein p53 controls cell cycle checkpoints and apoptosis via the transactivation of several genes. However, data from various laboratories suggest an additional role for p53: transcription-independent suppression of homologous recombination (HR). Genetic and physical interactions among p53, HR proteins (e.g. RAD51 and RAD54) and HR-DNA intermediates show that p53 acts directly on HR during the early and late steps of recombination. Complementary to the MSH2 mismatch-repair system, p53 appears to impair excess HR by controlling the minimal efficiency processing segment and by reversing recombination intermediates. By controlling the balance between the BLM and the RAD51 pathways, this direct role of p53 could maintain genome stability when replication forks are stalled at regions of DNA damage. In this article, we discuss the direct role of p53 on HR and the consequences for genome stability, tumor protection and speciation.

Faithful genome transmission requires the co-ordination of a network of pathways including CELL CYCLE CHECKPOINT (see Glossary), DNA repair-recombination and apoptosis. This network prevents the proliferation of cells bearing damaged DNA.

The tumor suppressor gene p53 (*TP53*) is the most frequently mutated gene found in tumors [1,2]. Following genotoxic stress, the p53 protein transactivates a collection of genes that control the cell cycle checkpoint and apoptosis [3]. However, studies from different laboratories have pointed to an additional role of p53: transactivation-independent negative regulation of homologous recombination (HR).

Precise control of HR is essential to ensure the stability–variability equilibrium of the genome. HR is considered as an error-free DNA repair system because it copies an intact homologous sequence (Box 1). However, HR can also become deleterious and in excess it can promote genome instability and cause disease [4]. CROSSING OVER (a product of HR) between dispersed repetitive sequences can lead to different types of genome rearrangements (Figure 1a). GENE CONVERSION (a product of HR) with the homologs can lead to loss of heterozygosity [5], whereas gene conversion with a pseudogene, which generally bears stop mutations, can inactivate a functional allele [6] (Figure 1b). Moreover, the accumulation of aberrant abortive recombination events can also be toxic [7,8].

In addition to genetic interactions, the demonstration of physical interactions between p53 and proteins that are involved in recombination or DNA-recombination intermediates reveals a direct role for p53 in the control of genome stability. But how does p53 exert this effect? In this article, we present the data showing that p53 does not work via transactivation and we discuss the consequences for genome stability control, tumor protection and speciation.

Wild-type p53 represses gene conversion independently of its transactivation activity

p53 affects spontaneous and induced HR – impact on the RAD51-gene conversion pathway

The impact of p53 on HR has been studied in human, monkey and rodent adult or embryonic cells. Different methods of p53 inactivation have been used including: (i) the deletion of p53; (ii) the inactivation by the p53-antagonist HDM2 (the human homolog of mouse double minute 2) or by viral proteins such as large T antigen from SV40 or E6 of papilloma virus; (iii) the inactivation of temperature-sensitive p53; or (iv) the expression of dominant negative mutant p53. All of these studies concluded that wild-type (wt) p53 represses HR. In apparent contrast, it has been reported that RAD51-dependent gene targeting (by HR) is independent of p53 status in ES cells [9]. However, p53 is located in the cytoplasm in ES cells and is unlikely to affect nuclear events either directly or via its transactivation activity [10].

Glossary

Cell cycle checkpoint: cellular process that stops or slows the cell cycle in conditions that are unfavorable for cell division.
Crossing over: the reciprocal exchange of genetic information (Box 1).
Gene conversion: the non-reciprocal exchange of genetic information, which does not modify the general chromosome structure (Box 1).
Heteroduplexes: duplex-hybrid DNA, generated by strand exchange (Box 1) and containing mismatches.
Holliday junctions: cruciform intermediates generated by strand exchange at initiation step of homologous recombination (Box 1).
Paralogs: genes within the same species that share structural homology – probably generated by the duplication of an ancestral gene.

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 0168-9525/$ - see front matter doi:10.1016/j.tig.2004.04.003

Box 1. Homologous recombination: roles, mechanisms and products

Homologous recombination (HR) is a fundamental process that is conserved in all organisms and involved in genome stability, molecular evolution, chromosome segregation during meiosis, DNA repair and resumption of stalled replication forks [31,64,65].

In most models, HR is initiated at a break or a nick on one DNA molecule followed by exchanges with an intact homologous DNA partner, which can be found on the sister chromatid, leading to sister chromatid exchange (SCE) on the homologous chromosome or on repetitive sequences that are dispersed through the genome. The most documented model is the double-strand break (DSB) repair model (Figure I), which accounts for DSB repair after genotoxic stress, during meiotic recombination or gene targeting.

The two products of HR are gene conversion that is associated with crossing over or gene conversion without associated crossing over (Figure I). Both types of products are initiated by the same initial step: homologous pairing and strand exchange catalyzed by RecA protein in bacteria or by RAD51 in eukaryotes [66–68].

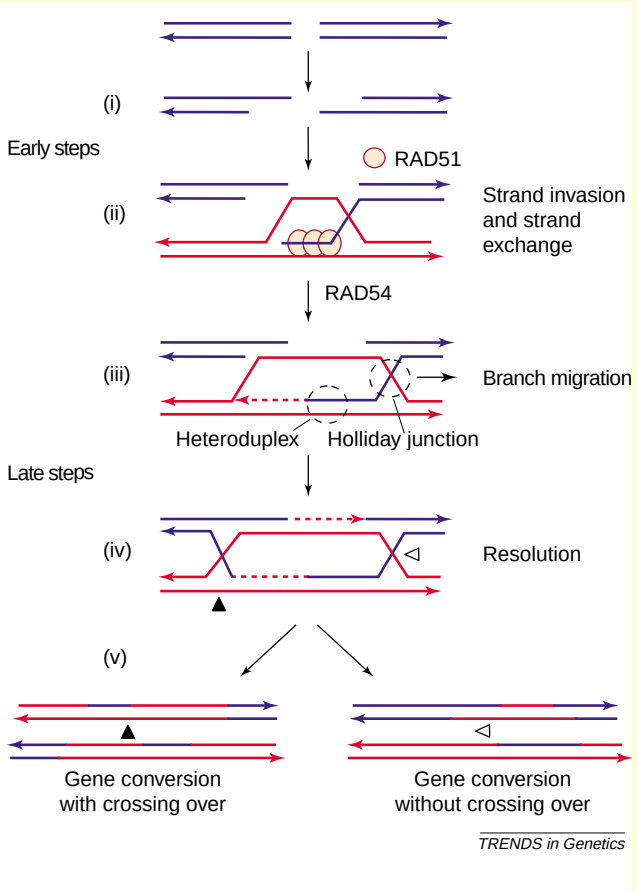

Figure I. Double-strand break (DSB) repair via homologous recombination: the DSB repair model [69]. **(i)** The DSB is processed by a single-strand exonuclease generating single-stranded tails. This process is believed to be catalyzed by the heterotrimer RAD50–MRE11–NBS1. **(ii)** The single-stranded DNA, coated with RAD51, aligns and invades a homologous duplex DNA. This step requires sequence homology but limited polymorphism is tolerated. Consequently, if strand exchange occurs between non-perfectly homologous sequences (bearing some sequence divergences), it creates heteroduplexes that can be processed by the mismatch-repair system. This step also creates cruciform junctions (Holliday junctions), which can migrate (branch migration) leading to the elongation of the heteroduplex molecule. **(iii)** RAD54 acts in the subsequent steps: polymerization is primed from the 3′ invading strand; displaced single-stranded DNA then anneals the complementary single-stranded tail. **(iv)** Polymerization fills in the gaps. **(v)** Gene conversion depends on the orientation of mismatch repair of the heteroduplex and on the sequence copied at the DSB location. Holliday junctions can be resolved according to two alternative orientations (black or white triangles). Depending on the orientation of the resolution of the Holliday junctions, the products (gene conversion) will be associated or not with crossing over. Abbreviations: NBS1, Nijmegen breakage syndrome 1; MRE11, MRE11 meiotic recombination 11 homolog.

Two main methods have been used to measure HR. The first method measures the intermolecular HR between two defective SV40 genomes with HR recreating a functional viral genome [11]. The second strategy measures intramolecular HR between tandem repeat sequences, which restores a functional reporter gene [12–18]. Most studies have been conducted in cultured cells but recently the question has been addressed *in vivo* in mice [17].

Inhibition of p53 stimulates HR between direct repeats and between inverted repeat sequences [18]. Because recombination between inverted repeats mainly involves gene conversion [19], this suggests that p53 affects gene conversion, which is a *RAD51*-dependent process in mammalian cells [20].

Double-strand break (DSB) repair

DSBs strongly stimulate HR in mammalian cells [21]. However, ionizing radiation induces DSBs but it does not stimulate significantly HR in wt-p53 cells [18,22], whereas it strongly stimulates HR when these cells contain mutant p53 [16,18]. More precisely, on an enzymatic DSB that is targeted in the recombination substrate by the

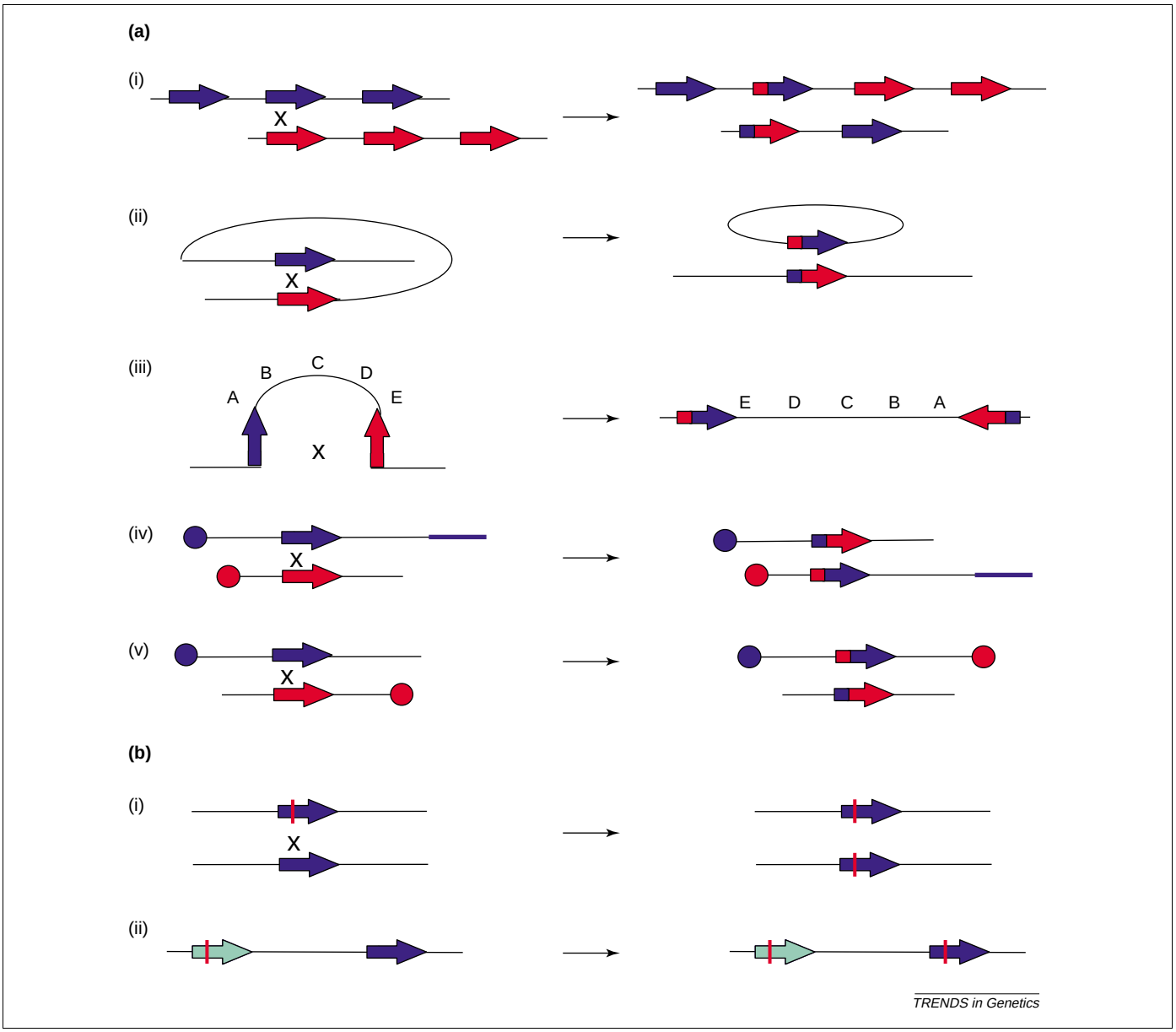

Figure 1. **(a)** Possible chromosome rearrangements resulting from crossing over (CO) between repeated dispersed sequences. **(i)** Inter-chromosomal CO or unequal sister-chromatid exchange leading to deletion and amplification. **(ii)** Intrachromatid CO between direct repeats leading to deletion and an excised fragment. The excised fragment can be eliminated or randomly re-integrated into the genome [20]. **(iii)** Intrachromatid CO between inverted repeats leading to the inversion of the intervening sequence. (**iv–v**) Interchromosomal CO. Depending on the orientation with regard to the centromeres, these events result in translocation (**iv**) or in dicentric plus acentric chromosomes (**v**). **(b)** The consequences of gene conversion between two hetero-alleles (i) or with a pseudogene (ii). The red boxes represent the mutations and the green box represents the pseudogene.

meganuclease I-SceI, wt p53 strongly inhibits HR [23]. Importantly, ionizing radiation-induced HR is controlled via a *RAD51* pathway in mammalian cells [20]. These data also identify the *RAD51* pathway as a target for HR suppression by wt p53.

p53 affects HR independently of its role in the G1–S checkpoint and in transactivation activity

Replication (in S-phase) of damaged DNA leads to genetic instability. Following genotoxic stress, p53 protein is stabilized and transactivates a collection of genes that leads to the arrest of the damaged cells in G1, prior to the S-phase. This arrest enables repair of the DNA matrix before replication, thereby avoiding genetic instability [3]. This role of genome-integrity maintenance is thus dependant on the p53 transactivation activity. Paradoxically, treatment with hydroxyurea (a replication inhibitor) stabilizes the p53 protein without triggering its transactivation activity [24], suggesting the importance of a transcription-independent role for p53 in genome maintenance during replication.

Several studies showed that the suppression of HR by p53 is a function that is separate from its G1-arrest control and transactivation activities [18,25–27].

In addition, HR is stimulated by RAD51 overexpression but this stimulation is inhibited by co-expression of a transcriptionally inactive p53 mutant, confirming both the interaction with the *RAD51* pathway and the independence of p53-transactivation activity [28,29].

Box 2. The RecQ family in mammalian cells

The RecQ proteins contain a specific helicase domain conserved through evolution and define the RecQ family (Figure I). The Rec Q helicase family comprises the bacterial RecQ, the yeast Sgs1 and five members in mammalian cells: BLM, WRN, RTS (the mutated protein in Rothmund–Thompson syndrome), RecQ4 and RecQ5. WRN is a helicase affected in Werner syndrome (WS), an autosomal recessive disorder that is associated with genetic instability, cancer predisposition and with premature aging. BLM is a helicase affected in Bloom syndrome (BS), an autosomal recessive disorder that is associated with genetic instability and cancer predisposition. BS is characterized by elevated levels of sister-chromatid exchange. Both BLM and WRN have been reported to process Holliday junctions [70] and WS cells are defective in recombination intermediate processing [8].

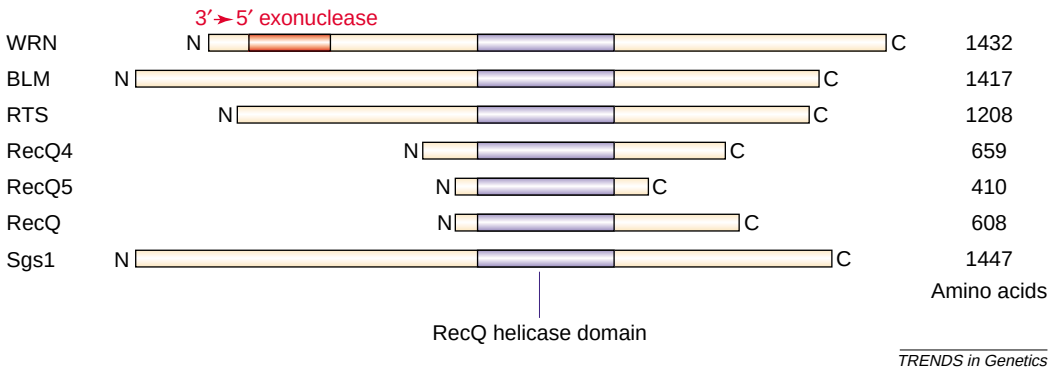

Figure I. RecQ family members. The blue boxes correspond to the conserved RecQ helicase domain. WRN possesses also an exonuclease domain (red box) absent in the other family members. The numbers on the right part indicate the number of amino acids in the corresponding protein. Abbreviations: BLM, Bloom syndrome protein; RTS, Rothmund–Thompson syndrome protein; RecQ4, RecQ protein-like 4; RecQ protein-like 5; WRN, Werner syndrome protein.

Role in stalled replication forks

HR is an efficient way of reactivating blocked replication forks [30,31]. Replication elongation inhibitors such as hydroxyurea and aphidicolin stimulate *RAD51*-dependent recombination [32], which is repressed by wt p53 [33,34].

Recently, it has been reported that the Bloom syndrome protein (BLM; Box 2) facilitates the transport of p53 to the stalled replication forks and facilitates the interaction with RAD51 [28]. The authors propose a model in which p53 controls the alternative processing of stalled replication forks (i.e. BLM or RAD51–RAD54) and by repressing HR limits HR-induced genetic instability (Figure 2).

Remarkably, both the transactivation-dependent (G1 arrest) and transactivation-independent (HR repression) roles of p53 pursue the same goal: the prevention of genetic instability resulting from the replication of damaged DNA. These two processes could thus represent back-up systems.

Requirements of p53 for HR suppression: dosage, mutations and structural domains

Low expression levels of wt p53 are sufficient for HR suppression [23]. Reciprocally, low expression levels of dominant-negative p53 are sufficient to stimulate HR [18]. Mutations in p53 stimulate HR but to a lesser degree than its complete inactivation. In addition, $p53^{-/-}$ mouse embryonic fibroblasts (MEFs) exhibit higher levels of HR than $p53^{+/+}$ MEFs. Interestingly, $p53^{+/-}$ MEFs exhibit an intermediate response, showing that p53 is haploinsufficient for HR suppression [16].

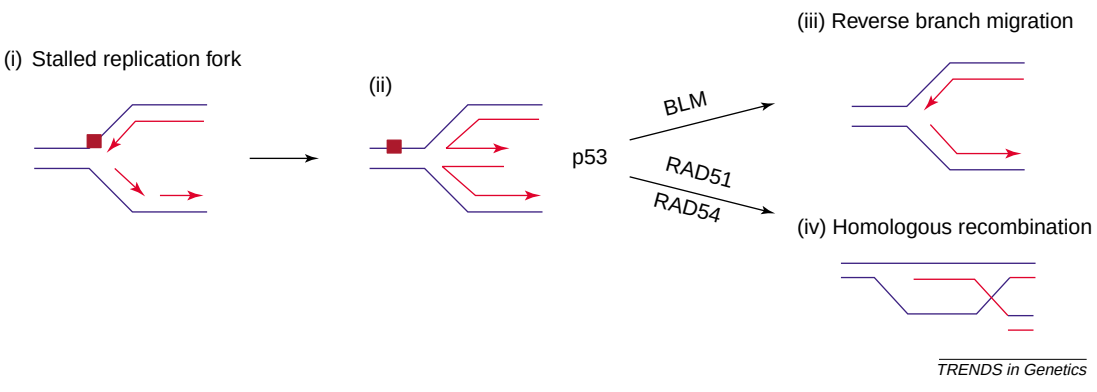

Figure 2. A model of the direct role of p53 on stalled replication forks [28]. **(i)** Replication is blocked, possibly by DNA damage (brown square), such as DNA adducts (after chemical stresses) or kinky lesions (UV-C irradiation) **(ii)** The neo-synthesized strands (in red) are complementary to each other and can thus anneal, creating a chicken foot structure. This structure is reminiscent of a Holliday junction and can branch migrate or be resolved leading to double-strand breaks (DSBs) Two alternative pathways can process such a structure: **(iii)** Bloom syndrome protein (BLM) can reverse branch migration, maintaining genome stability; **(iv)** the DSB is repaired by RAD51–RAD54 pathway leading to a recombinogenic repair. In line with this evidence, a defect in BLM results in high levels of spontaneous sister-chromatid exchange. P53 controls both process and orientates between the two alternative processes. It has thus been named a 'molecular governor' [28].

The p53 protein possesses several domains (Figure 3a). The core domain is implicated in the interaction with the p53-specific DNA-responsive elements, whereas the C-terminal domain is involved in the interaction with non-specific sequences.

A structurally intact core domain and the oligomerization domain are required for the control of HR by p53 [18,25].

By contrast, the C-terminal domain is not essential for HR suppression [25,26]. However, different activities have been attributed to the C-terminal amino acids: binding or annealing of single-stranded DNA, recognition of DNA damage or recognition of particular structures [35]. More specifically, this domain is involved in the localization of p53 to stalled replication forks [28], in the interaction with the recombination protein RAD54 [29] and in the processing of HR intermediates [25,36].

Thus, the core and the C-terminal domains of p53 might participate, using parallel pathways, in HR regulation.

Physical interactions of p53 with HR proteins and HR intermediates

In accordance with the genetic interactions and with cytological colocalization, physical interactions between p53 and the RAD51 and RAD54 recombination proteins have been shown *in vitro* and *in vivo* [28,29,37,38]. These data are thus consistent with p53 having a role in HR that is independent of its transactivation activity.

The interaction domain of p53

The domains of p53 that interact with RAD51 are located at each edge of the core region: at amino acid 94–160 and at amino acid 264–315 [38] (Figure 3a), which is consistent with the core domain being essential for HR repression. Interestingly, this core region contains cancer-mutation hotspots. The p53–RAD54 interaction domain is located in the C-terminal domain [29].

Interaction domain of RAD51

The RAD51 core domain, which is highly conserved from bacteria to mammals, contains catalytic residues for ATP binding-hydrolysis and is involved in the homo-oligomerization of RAD51, two processes essential for HR. The interaction domains have been mapped (amino acid 125–220) [38] and span the region from the first to the second ATP box corresponding to the 'RecA fold' (Figure 3b). By interacting with the 'RecA fold' of RAD51, p53 is likely to affect RAD51 activity.

p53 inhibits HR through physical interaction with RAD51

The overexpression of either wt RAD51 or mutant ^{L186P}RAD51, which exhibits reduced binding to p53, stimulates HR. P53 prevents stimulation of HR by wt RAD51 but not by ^{L186P}RAD51, suggesting that p53 represses HR through physical interaction with RAD51 [29].

Recently, molecular and biochemical support for these data has emerged. In *in vitro* reactions that used one single-stranded homologous DNA molecule and one double-stranded homologous DNA molecule, p53 inhibited the initiation of strand invasion (Box 1) promoted by human RAD51 or bacterial RecA proteins. In addition, on assembled strand-exchange intermediates (Box 1), p53 impaired branch migration promoted by human Rad51 but not by RecA, thus, exhibiting its specificity for the mammalian protein. Consistent with genetic studies mutant p53, which does not repress HR *in vivo*, failed to inhibit the *in vitro* reactions [39].

Taken together, these data indicate that physical interactions between RAD51 and p53 are necessary for

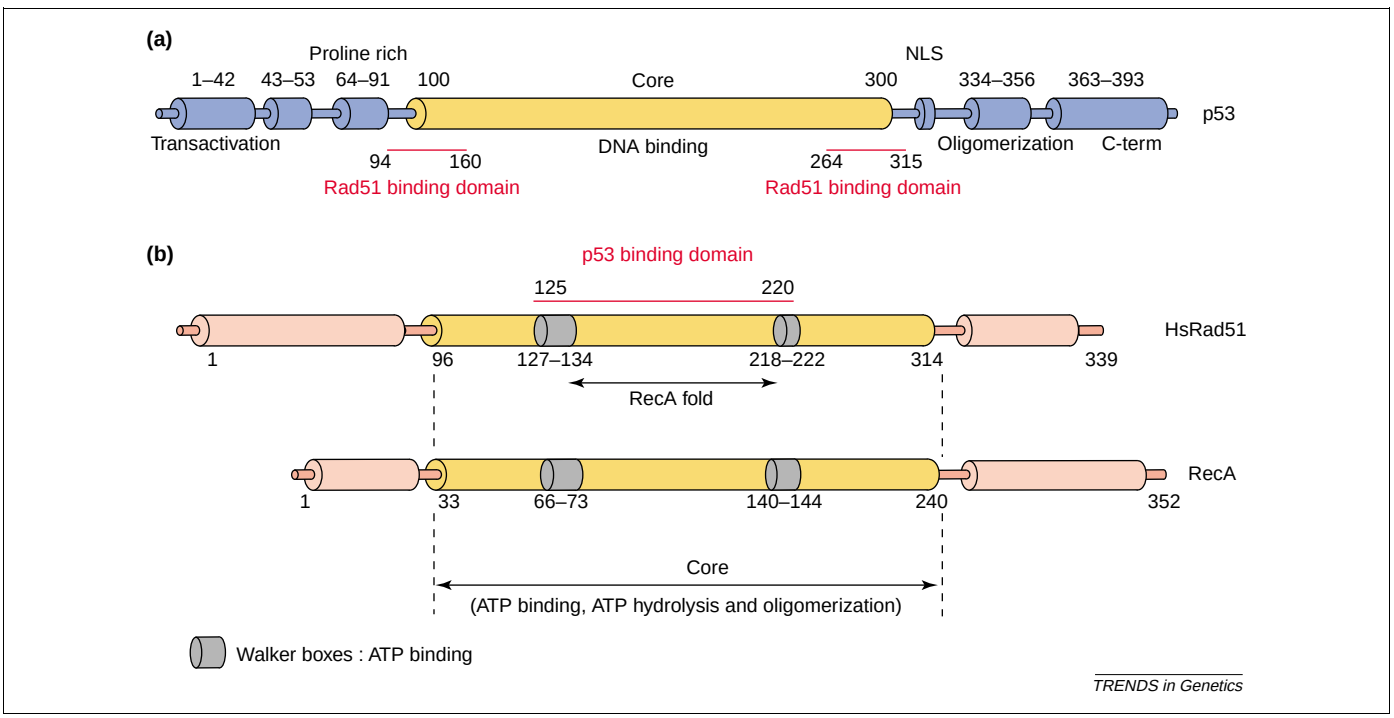

Figure 3. Structural domains of p53 and RAD51. **(a)** Functional domains of p53. The RAD51 binding domains are indicated. **(b)** Human HsRAD51 and bacterial RecA. The evolutionarily conserved core domain is shown in yellow. The gray boxes correspond to the ATP-binding sites. The 'RecA fold' and the p53-binding domain are indicated. The numbers correspond to the amino-acid residue positions. Abbreviation: NLS, nuclear localization sequence.

the inhibition of strand exchange and HR. These results are consistent with the location of the p53–RAD51 interaction domains.

Interactions with other proteins of the HR complex

RAD51 is assisted in HR regulation by many partners in elaborate proteins complex(es). In addition to five RAD51 PARALOGS, RAD51 also interacts with many other proteins that also control HR and for which physical interactions with p53 have been described (Figure 4a). Thus, p53 could act on HR via an interaction with one or several of the RAD51 partners.

Moreover, it has been proposed that the highly ordered chromatin structure has a role in HR regulation by p53 [40]. In addition to the protein interactions, several studies show the binding of p53 protein to recombination intermediates, which results from the strand-exchange process, such as HETERODUPLEXES and HOLLIDAY JUNCTIONS (Box 1).

p53 binds to HR intermediates: a comparison with the MSH2 mismatch repair system

MSH2, which is implicated in hereditary nonpolyposis colorectal cancer, and p53 have many common and parallel characteristics. MSH2, in association with a related protein MSH6, has a pivotal role in the repair of the mismatched bases that occur during replication. Inactivation of mismatch repair (MMR) results in a mutator phenotype and in tumor predisposition [41]. Because MMR corrects heteroduplexes that have mismatches this system reverses gene conversion products, which results in HR downregulation. Thus, both MSH2 and p53 have roles in tumor suppression and in HR suppression.

Immunoprecipitation and immunocytofluorescence have revealed physical interactions and colocalization of p53 and MSH2, which overlap RAD51 foci during the S phase of the cell cycle. [42]. Moreover, both p53 and MSH2 interact with the same kinds of HR intermediates, as discussed in the following sections.

(i) Heteroduplexes. Similarly, MSH2 and p53 associate with duplex DNA to form complexes that become highly stable after encountering mismatches [43]. However, p53 and the MMR factor do not exhibit the same affinity for different mismatches. For instance, the C–C mismatch was the best recognized by p53 and the worst recognized by human heterodimer hMSH2–hMSH6. By contrast, the G–T mismatch was the best recognized by hMSH2–hMSH6 and the worst recognized by p53 [44]. However, the two systems can also cooperate because hMSH2–hMSH6 enhances p53 binding to DNA substrates that have bulged bases [45].

Strand invasion generated by RAD51 (Box 1) produces a three-strand intermediate, a structure for which p53 exhibits high affinity particularly when it contains mismatches [46]. In contrast to hMSH2–hMSH6, a preferential recognition of C–T versus G–T mispairing has been observed for p53. *In vivo* HR experiments, designed to generate heteroduplexes with distinctly mispaired regions, showed that inhibition of HR by p53 was dependent on the type of mismatch that was present in the heteroduplex and correlates with the affinity of the *in vitro* binding of p53 to artificial recombination intermediates [46].

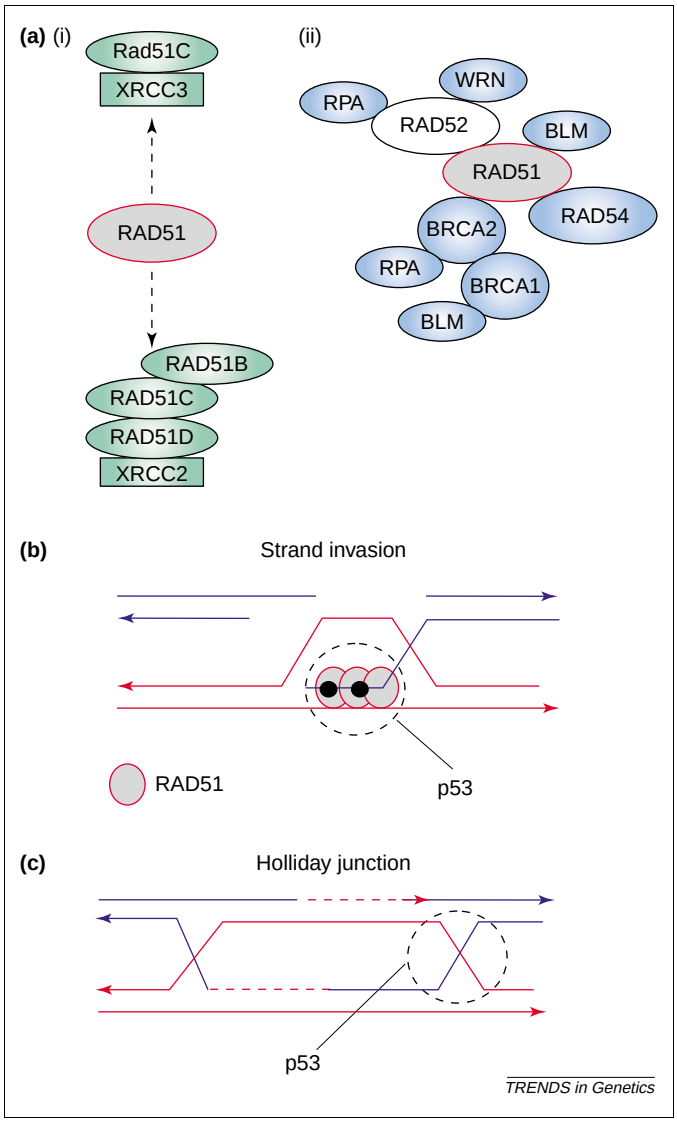

Figure 4. Targets of p53 for homologous recombination (HR) control. **(a)** HR protein complexes in mammalian cells. **(i)** Five paralogs of RAD51 (XRCC2, XRCC3, RAD51B, RAD51C and RAD51D), in two different complexes act on HR. However, no physical interactions between these paralogs and RAD51 or p53 have been clearly demonstrated. **(ii)** RAD51 also interacts physically with proteins controlling HR. Those shown in blue have been shown to interact physically with p53. **(b)** After strand exchange, which is promoted by RAD51, the heteroduplex contains mismatches (black dots), p53 (or MSH2) reverses this intermediate. **(c)** P53 could also act on the Holliday junction. Abbreviations: BRCA1, breast cancer 1 early onset; BRCA2, breast cancer 2 early onset; BLM, Bloom syndrome protein; MSH2, mutS homolog 2 colon cancer nonpolyposis type 1; RPA, replication factor A; WRN; Werner syndrome protein; XRCC2, X-ray repair complementing defective repair in Chinese hamster cells 2; XRCC3, X-ray repair complementing defective repair in Chinese hamster cells 3.

A $3' \rightarrow 5'$ exonuclease activity has also been reported for p53 [47]. Three-stranded intermediates represent good substrates for this activity, particularly when they comprise mismatches, and seem to be stimulated by RAD51. The authors suggest that the RAD51–p53 interaction has a role in targeting p53 to mismatched heteroduplexes and that p53 downregulates HR by nucleolytic degradation of heteroduplexes containing mismatches [48].

(ii) Holliday junctions. *In vitro,* p53 protein interacts with Holliday junctions [36]. In parallel, the human

hMSH2–hMSH6 dimer also interacts with Holliday junctions and facilitates the binding of p53 to these junctions [45].

Consistent with these data, p53 interacts with the two RecQ family helicases, BLM and the Werner syndrome protein (WRN) [49–53]. In addition, the C-terminal region (residue 373–383) is required for interaction with BLM and WRN and for modulation of their branch migration activities [53]. In *in vitro* reactions, p53 inhibits the helicase activity of BLM and WRN on a four-arm 50-mer X-junction that is supposed to mimic Holliday junctions. Interestingly, p53 cancer-hotspot mutants (residue 273 or 248), which do not repress HR, show a lack of (273H) or a decreased (248W) inhibitory effect on the helicase activity of BLM or WRN.

Control of the minimal efficiency processing segment (MEPS): impact on genome stability and on speciation

Impact on genome stability

Recombination between repeat sequences could represent a potential danger for genome integrity. However, repeat sequences and non-coding sequences exhibit frequently sufficient divergences to prevent an excess of recombination. Efficient HR requires a segment of uninterrupted homology between the two recombining molecules: the minimal efficiency processing segment (MEPS).

In mammalian cells, the MEPS comprises 200–300 bp [54]. Importantly, studies on the stability of repetitive sequences propose that p53 creates a threshold for the length of homology for recombination [15]. Remarkably, p53 is more active in suppressing HR when the homology segment is <200 bp [23]. Thus, we propose that p53 might constitute an additional method of securing genome maintenance by controlling the MEPS.

Speculation: impact on speciation?

Recombination between the genomes of two closely related species should be impaired by the sequence divergences, which represent a genetic barrier. However, the genetic barrier between *Escherichia coli* and *Salmonella typhimurium*, which are separated by 100–150 million years and show 15% divergence, has been overcome by the inactivation of the MMR system [55]. It has been suggested that neutral polymorphisms might function as genetic barriers enabling the participation of MMR in speciation [55,56]. If in a complementary and parallel way to MSH2, p53 is part of an anti-HR system (by mismatch correction and controlling the MEPS), it is tempting to speculate that it might also participate in speciation.

Control of HR by p53 and tumor protection?

The transactivation activity of p53 has a pivotal role in at least two tumor prevention processes: cell cycle checkpoint and apoptosis. *In vivo*, a transactivation-deficient mouse model showed the importance of the transactivation activity of p53 in tumor prevention [57]. Nevertheless, the authors discussed preliminary results that showed potentially fewer tumors with the mutant transgenic mice than with the p53 null mice. However, these data might be not significant because the mice were not sufficiently old to enable a definitive conclusion. Moreover, the authors demonstrated a constitutive accumulation of the mutant protein. Based on experiments cited previously, this accumulation should repress HR in an unregulated way. Because inhibition of RAD51-dependent HR stimulates tumorigenesis [58], it is not possible from these experiments to evaluate the relative parts of the transactivation or the HR repression roles of p53 in tumor protection. Remarkably, precise control of HR equilibrium is essential for genetic stability because both HR stimulation and repression lead to genome instability.

The treatment of mice with a chemical compound that inhibits the transcriptional and apoptosis functions of p53 did not lead to tumor formation, even after the mice were irradiated [59]. More directly, null p21 mouse models are defective in G1 checkpoint control and do not develop spontaneous malignancies [60]. It is thus tempting to speculate that p53 can also be involved in tumor protection, via an additional mechanism.

HR can lead to genome rearrangements via recombination between dispersed repetitive sequences (Figure 1). Moreover, increased levels of RAD51 protein, which stimulates HR and chromosome instability [61], have been reported in tumor cells [62]. Therefore, the control of HR excess represents a good candidate for this additional p53 tumor protection process. If it was not relevant, one might predict that a significant portion of p53 tumor mutants have retained the ability to repress HR, which based on published data does seem to be the case [14,18,23]. By contrast, the ^{A135V}p53 mutant, which retains its HR suppression function [26], is not tumorigenic under all conditions and retains the tumor suppressing activity of wt p53 in some circumstances [63].

Conclusions

As 'guardian of the genome', p53 appears to wear several hats. First, it controls cell cycle and apoptosis indirectly via its transcription activity. Second, it regulates genome plasticity by controlling HR directly at both the initial and the late stages via its interactions with HR proteins and intermediate structures (Figure 4). The raison d'être of both roles is the same: preventing the damaged DNA matrix from participating in replication to secure genome stability.

Two mechanisms can account for the repression of RAD51-dependent HR at a molecular level: (i) inhibition or reversion of strand exchange, at an early stage of HR; and (ii) recognition and reversion of HR intermediates, at a late stage of HR (Figure 4b,c). Each of these two mechanisms involves different domains of p53: the core domain for the early steps and the C-terminal domain for the late steps.

The MMR system and p53 show a common anti-HR activity; both have been shown to correct mismatches with complementary specificities and to bind to cruciform junctions. They might represent complementary backup systems to avoid recombination excess, which can lead to translocation or gene inactivation (Figure 1).

However, the impact of HR stimulation (and the role of p53 in such a process) on tumorigenesis remains to be evaluated directly. Nevertheless, the direct role of p53 in genome plasticity control sheds new light on an important

dimension of the complex function(s) of p53 in the cellular response to DNA damage. Precise characterization of the interactions between p53 and HR that are involved in human diseases and the consequences for chromosomal stability and tumorigenesis constitutes a major and exciting challenge for future studies.

Acknowledgements

We apologize for research that has not been cited due to space limitation. We thank D. Marsh for correction of the manuscript. This work was supported by a collaborative program from Institut Curie/CEA-DSV, ARC and EDF.

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