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Genomic stability disorders: from budding yeast to humans

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1. ABSTRACT

Fundamental aspects of eukaryotic molecular and cellular biology are extensively studied in the budding yeast *Saccharomyces cerevisiae*. Genome maintenance pathways are highly conserved and research into a number of human genetic disorders with increased genome instability and cancer predisposition have benefited greatly from studies in budding yeast. Here, we present some of the examples where yeast research into DNA damage responses and telomere maintenance pathways paved the way to understanding these processes, and their involvement in selected human diseases.

2. INTRODUCTION

In essence, what differentiates species within nature and different individuals within a population is the DNA sequence encoded in an individual's genome. However, maintaining that information intact is a constant battle. As any chemical compound, DNA can react with its surroundings, be it water, free radicals or radiation from the sun. In fact, DNA is surprisingly reactive for a molecule that is designated to store genetic information. The need to prevent changes in the DNA sequence arising from these potential damaging agents led to the evolution of a number of DNA repair pathways that respond to different types of

DNA insults (1). Accurate repair is crucial to restore the original DNA sequence, and thus maintains the genetic integrity of that cell or individual. However, lesions are not always detected and/or accurately repaired, which leads to a relatively low basal mutation rate (2). Depending on the function of the sequence that was mutated, changes in cellular metabolism can occur that initiate the malignant transformation of that cell into a cancer cell (3). On the other hand, these mutations are, on a population level, also the driving force behind evolutionary change (4).

A number of human cancer predisposition and premature aging syndromes are characterized by deficiencies in DNA damage response pathways or telomere maintenance. Genome instability is a major cause of cancer onset and progression and many tumor suppressor genes encode proteins involved in DNA repair, telomere stability or DNA damage signaling. In this review we will briefly discuss some of the DNA repair and telomere maintenance pathways and illustrate how research in the budding yeast, *Saccharomyces cerevisiae*, has advanced our understanding of the molecular events underlying human genome instability disorders related to these pathways.

3. BUDDING YEAST AND DNA REPAIR

3.1. *Saccharomyces cerevisiae* as a model organism

The budding yeast *Saccharomyces cerevisiae* is an extensively studied model organism for fundamental aspects of eukaryotic molecular and cellular biology. This unicellular microorganism has a doubling time of as short as 90 minutes and can be grown and manipulated using efficient microbiological procedures. An important feature of yeast biology that is widely exploited in biomedical research is its relatively high recombination rate, which allows for the routine generation of knockout strains (5). This feature can also be used to generate mutant strains with targeted point mutations directly at the genomic locus of interest (6). The yeast reproductive life cycle is another aspect that consolidated this organism as a model system. Budding yeast cells are routinely studied in a haploid state, i.e. when they only have one copy of each chromosome. Haploid strains of opposing mating type can be mated, generating a diploid strain with two copies of each chromosome. This strain can then be induced to undergo meiosis and each cell will form a tetrad containing four haploid spores that randomly receive one copy of each of the parental chromosomes. Because the sibling spores are still held together by a protective cell wall, researchers can keep track of the Mendelian segregation pattern for each chromosome pair within a single tetrad, allowing for precise analysis of genetic interactions (7).

3.2. DNA damage

In humans, even under normal physiological conditions, an estimated 18,000 purine residues are hydrolysed from the DNA backbone per cell per day (8, 9). Cytosine residues spontaneously deaminate to uracil at a rate of 100 to 500 times per day in a mammalian cell (10-12). Reactive oxygen species arising from basal metabolic reactions are highly reactive with DNA and over 80 different damage products have been observed (13). Many environmental factors also add to this tally: UV radiation from the sun generates dimers between adjacent nucleotides, ionizing radiation leads mainly to double-strand breaks, and many chemical compounds react with the nitrogenous bases or the sugar-phosphate backbone to generate alkylated bases, DNA crosslinks or single-strand breaks (1). Inherent errors in DNA transactions inside the cell, such as transcription and DNA replication, can also lead to alterations in DNA structure or sequence. Likewise, telomeres shorten with each round of DNA replication and have to be extended in order to maintain their protective cap structures. Since short dysfunctional telomeres resemble a DNA double-strand break, it is also critical to prevent the DNA repair machinery from inappropriately attempting to repair this “lesion” (14).

3.3. DNA repair and telomere maintenance pathways

A number of DNA repair pathways with different lesion specificities and different repair mechanisms have evolved to accurately repair the myriad of DNA lesions a cell can incur.

The simplest and most effective form of DNA repair is the direct chemical reversal of the lesion to restore the original chemical composition of the DNA. This mechanism relies on a single enzyme directly recognizing a given type of lesion and reverting the deleterious reaction (15). DNA photolyases can reverse the two main types of UV-induced lesions, a process that requires visible light for catalysis. Interestingly, no photolyases are encoded in the human genome, although they are observed in other higher eukaryotes (16). Other classes of enzymes termed alkyltransferases can reverse a subset of alkylated base damage in the form of a suicide reaction by transferring the alkyl group to a catalytic cysteine on the protein itself (17). Methyladenine and methylcytosine can be repaired by specific dioxygenases that remove the methyl group as formaldehyde. Both alkyltransferases and dioxygenases are present throughout evolution (18).

One of the most lethal forms of DNA damage, a double strand break (DSB) is a difficult lesion to repair accurately, since the continuity of the DNA strand is lost. There are two major pathways that repair DSBs: homologous recombination (HR) and non-homologous end joining (NHEJ). HR is involved not only in DSB repair, but also in the resolution of stalled replication forks during DNA replication, and in the generation of genetic diversity through mitotic and meiotic recombination (19). Recombination uses homologous sequences present in the genome as a template for repair. Although generally less error-prone than NHEJ, recombination often leads to rearrangements of genetic information and sometimes gain or loss of DNA sequences. NHEJ is a pathway by which cells directly rejoin two broken DNA ends without the need for extensive homology between the sequences (20). Often a microhomology of as little as 1-4 bp is sufficient for reannealing of the DNA strands (21). As the broken end needs to be processed to allow religation of the strands, NHEJ usually leads to loss of base pairs surrounding the original break point (20, 21).

Post-replicative repair is a process of damage tolerance that allows cells to replicate damaged DNA, but that does not by itself repair DNA lesions (22). It comprises two alternative pathways for lesion avoidance. Translesion synthesis replaces the replicative polymerase with a specialized translesion polymerase, which is able to replicate past a damaged substrate, albeit at the expense of a high mutation rate (23). Cells are also able to bypass lesions and continue DNA synthesis by a less-well understood error-free mechanism that appears to use the sister chromatid as a template (24).

The base excision repair (BER) pathway is responsible for repairing the most abundant base lesions, mostly caused by endogenous base damage and alkylating agents. This pathway is initiated by a class of enzymes termed DNA glycosylases, which each recognise a particular subgroup of lesions and excise the damaged base from the DNA backbone, forming an abasic site. Abasic sites are also a form of spontaneous DNA damage in their own right and arise from hydrolysis of bases from the sugar-phosphate backbone. A single-strand incision is then made adjacent to the abasic site to allow removal of the remaining backbone residue and gap-filling by a DNA polymerase, although the order of events and nature of the residue depend on the nature of the lesion. DNA ligase then catalyzes the rejoining of the repaired strand with the adjacent DNA to complete repair (25).

Another form of excision repair, termed nucleotide excision repair (NER) is involved in repairing bulky adducts as well as crosslinks between nucleotides or between strands, which tend to be more severe types of lesions and require more extensive processing. An inherited human disease termed Xeroderma Pigmentosum (XP) is caused by mutations in NER factors and will be our first example of the importance of budding yeast research in understanding human disease, in chapter 4.

Incorrect pairing of bases in the DNA, although not a form of DNA damage *per se*, can be an important source of mutations and is actively suppressed by a pathway termed mismatch repair, or MMR. Mismatches often arise due to errors during DNA replication or when homologous recombination occurs between sequences that are not completely identical. Defects in MMR lead to an increase in spontaneous mutation rates and underlie the human cancer predisposition syndrome hereditary non-polyposis colorectal cancer (HNPCC). The impact of yeast research in the process that led to the discovery of this connection will be discussed in chapter 5.

Understandably, DNA repair events are not isolated from the multiple other DNA transactions a cell has to maintain in order to survive and multiply, such as transcription, DNA replication and chromosome segregation. The pathways that signal the occurrence of DNA damage and modulate the cellular responses to it are termed cellular checkpoints. In chapter 6, we will discuss the input from yeast research into our current understanding of the molecular mechanisms, as well as the inherited cancer predisposition syndromes that are caused by mutations in components of these pathways.

In contrast to prokaryotes, which predominantly maintain circular genomes, eukaryotes organise their genomes in linear chromosomes (26). While allowing for an increase in genome size and complexity, linear chromosomes entail the need of a DNA end, known as a telomere. Usually, telomeric DNA is an iterative repeat of a short DNA sequence and is folded on itself in such a way as to protect the chromosome end from being degraded or fused to other DNA ends (27). Similar to DNA repair pathways, telomere maintenance mechanisms are crucial for genome stability, preventing chromosome fusions or the loss of genetic information. Insights from yeast research into telomere biology will be our fourth example, and are described in chapter 7.

4. YEAST *RAD*, HUMAN XP AND NER

In the early 1960s, studies in the bacterium *Escherichia coli* demonstrated that nucleotide dimers caused by UV radiation are excised from high-molecular weight DNA fractions (28, 29). Repair DNA synthesis was observed before cells resumed physiological DNA replication, suggesting an excision and re-synthesis mechanism (30, 31). This pioneering work laid the foundations for our current understanding of the nucleotide excision repair (NER) pathway. Bulky DNA adducts and crosslinks that distort the structure of the DNA helix are recognised and bound by the yeast Rad4-Rad23 (human XPC-RAD23B) complex. The pre-incision complex, comprised of the TFIIH complex, Rad14 (XPA), RPA and Rad2 (XPG) is recruited and unwinds the DNA surrounding the lesion. Ssl2 (XPB) and Rad3 (XPD) are components of the TFIIH complex and provide the helicase activities required for the pre-incision step. Rad2 (XPG) and Rad1-Rad10 (ERCC1-XPF) endonuclease activities then nick the damaged DNA strand on either side, generating a 25 to 32 residue single-stranded gap. DNA polymerases delta or epsilon, the PCNA sliding clamp and the RFC clamp loading factors are then required to fill in the gap, which is sealed by a DNA ligase (Figure 1) (32).

Mutations in many NER genes have been described in humans and can lead to a genetic cancer predisposition syndrome termed Xeroderma Pigmentosum (XP). Affected patients present with an extremely high rate of skin cancers and have a markedly reduced life expectancy as a consequence. First described in the late 19th century, XP was found to be due to defective DNA repair in the late 1960s (33, 34). For several years the actual mutations that caused the disease were unknown, but heterogeneity in the progression of disease between patients suggested the involvement of multiple genes (35). By fusing cell lines derived from different XP patients and testing for cross complementation of UV sensitivity, five XP complementation groups were identified by 1975 (36). This has now been expanded to seven groups, named XP-A through XP-G. The subsequent elucidation of the affected genes and their biochemical functions in nucleotide excision repair has benefited greatly from research in budding yeast.

Table 1. Representative examples of yeast DNA repair genes and their epistasis groupings

***RAD3* epistasis group (Nucleotide Excision Repair)**	***RAD52* epistasis group (Recombination)**	***RAD6* epistasis group (Post-Replicative Repair)**
RAD1	*RAD50*	*RAD5 (REV2)*
RAD2	*RAD51*	*RAD6*
RAD3	*RAD52*	*RAD18*
RAD4	*RAD54*	*REV1*
RAD7	*RAD55*	*REV3*
RAD10	*RAD57*	*REV7*
RAD14	*RAD59*	*MMS3*
SSL1	*XRS2*	*UBC13*
RAD25	*MRE11*	*RAD30*
RAD16		
RAD23		

Note that checkpoint components were originally included in some of the epistasis groups, but were later shown to participate in a different pathway, and have thus been excluded from this table

Table 2. Representative human and yeast NER genes and the year they were cloned

Human			**Yeast**		
Gene	Year cloned	Ref.	Gene	Year cloned	Ref.
XPA	1989	(144)	*RAD14*	1992	(145)
XPB (ERCC3)	1990	(146)	*RAD25*	1992	(147)
XPC	1992	(148)	*RAD4*	1988	(149)
XPD (ERCC2)	1990	(150)	*RAD3*	1983	(151)
XPE (DDB2)	1996	(152)	-	-	-
XPF (ERCC4)	1996	(153, 154)	*RAD1*	1983	(155)
XPG (ERCC5)	1990/93	(156, 157)	*RAD2*	1984	(158, 159)
ERCC1	1986	(55)	*RAD10*	1985	(160, 161)

Note that with the exception of XPA and XPB, human XP genes were generally identified after their yeast homologue

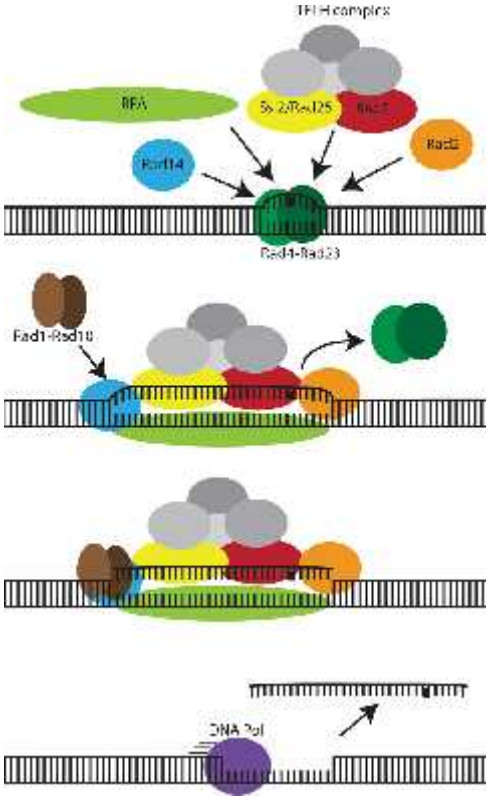

Figure 1. Schematic representation of nucleotide excision repair. The UV-induced nucleotide dimer is recognised and bound by Rad4-Rad23, which recruits the TFIIH complex, RPA, Rad2 and Rad14. Rad25 and Rad3 unwind the DNA, and the Rad1-Rad10 and Rad2 endonucleases cleave the damaged strand on either side of the lesion. The gap is then filled by a DNA polymerase (accessory factors PCNA and RFC not shown) and resealed by DNA ligase (not shown).

In order to identify the genes involved in UV-lesion repair in eukaryotic cells, randomly mutagenised yeast strains were isolated based on their increased sensitivity to UV radiation (37-39). These so-called *rad* mutants were systematically studied and were grouped into three epistasis groups (Table 1). These groups were based on genetic interactions between different mutations, where double mutants that were exquisitely more sensitive to UV than either of the single mutants were placed in separate epistasis groups. Alternatively, when double mutants were not more sensitive to UV-irradiation than either of the single mutants, the two genes were placed in the same epistasis group (40, 41). The simplest explanation for an epistatic interaction is that the two genes encode components of the same multiprotein complex or that they act in sequential steps of the same biochemical pathway. Mutants in the *RAD3* epistasis group are defective in NER and *rad1*, *rad2*, *rad3*, *rad4*, *rad10* and *rad14* mutants were found to be completely devoid of NER functions, suggesting that these genes encode the core NER machinery (42, 43). Other mutants, such as *rad7*, *rad16* and *rad23*, displayed only partial NER defects, suggesting an accessory function of the corresponding proteins in the NER pathway (42, 43). By the early 1990s, many of the yeast genes had been cloned and characterized (Table 2). The biochemical properties of the proteins were mainly studied *in vitro* using cell free extracts or recombinant proteins and a range of plasmid substrates engineered to contain UV lesions at known locations. Rad1 and Rad10 were shown to form a stable complex with endonuclease activity (44-47), Rad2 was shown to encode a single-stranded endonuclease (48, 49), and Rad3 was found to be an ATP-dependent DNA helicase (50, 51).

Screening approaches similar to the yeast *rad* mutants were used in rodent cell lines to identify randomly mutagenised cells with increased UV sensitivity (52-54).

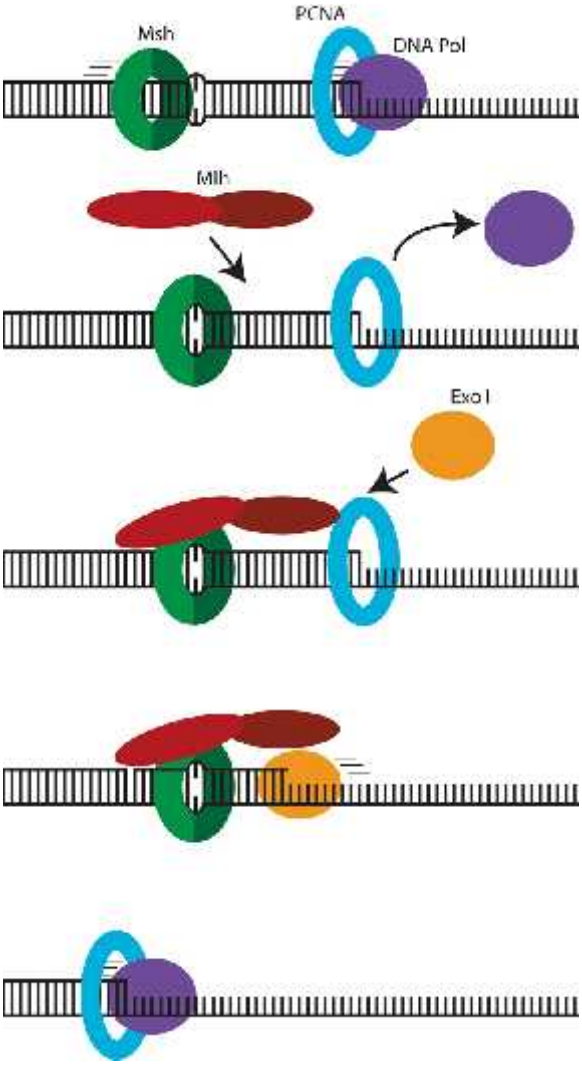

Figure 2. Representation of the mismatch repair pathway in eukaryotic cells. An Msh dimer encounters a mismatch and recruits an Mlh dimer. Based on the relative position of the mismatch to the PCNA clamp, the daughter strand is identified and nicked by Mlh on the opposite side of the mismatch. Exo1 is recruited to degrade the daughter strand until the mismatch is removed and replication of the locus is re-initiated. The RFC clamp loader complex is not shown.

These cell lines could be cross-complemented with human genomic DNA, leading to the isolation of a human cDNA for the gene subsequently termed *ERCC1*, for excision repair cross complementing (55). Homology to the yeast *RAD10* gene confirmed the involvement of this gene in NER and the evolutionary conservation of NER pathways, but *ERCC1* was not able to complement any of the described XP cell lines (56). For a period of time, this observation led to suggestions that XP might not be caused by defects in NER components, but in another unknown repair mechanism. However, subsequent molecular cloning of the human XP genes demonstrated that they were each homologous to a yeast *rad* gene involved in NER (Table 2). Thus, the data gathered on the yeast pathway could be used to immediately assign functions for these components in human NER and enhanced our understanding of the molecular events underlying XP.

5. MATCHING MMR WITH HNPCC

As briefly mentioned earlier, DNA mismatches can potentially lead to mutations and arise when DNA polymerases mistakenly incorporate an incorrectly paired nucleotide during DNA replication or when homologous recombination occurs between sequences that are not completely identical (57). In addition, DNA polymerase "slippage" events can lead to small insertions or deletions on the daughter strand and are also detected and repaired by MMR (58). During DNA synthesis, MMR is strongly biased towards repairing mismatches in the daughter strand, maintaining the original sequence intact. Despite important differences in the way the daughter strand is detected and the origin of the single stranded nick that initiates repair, the general MMR mechanism is reasonably well conserved from *E.coli* to eukaryotes. A MutS dimer recognises a distortion in the DNA helix due to a mismatch and recruits a MutL dimer. The MutS-MutL complex then promotes the unwinding of the damaged DNA strand by a helicase, starting from a single-stranded nick generated by alternative means, depending on the location of the mismatch and the organism in question. An exonuclease degrades the damaged strand, allowing a DNA polymerase to resynthesise the DNA (eukaryotic MMR shown in Figure 2)(59).

Early studies in yeast and *E.coli* during the 1960s suggested the existence of a pathway that recognised and repaired misincorporated or mispaired nucleotides in the double-helix (60, 61). Subsequently, bacterial strains *mutH, mutL* and *mutS* were isolated based on their increased mutation rate and found to be defective in this type of repair (62, 63). While MutS was shown to be responsible for detecting the mismatch, MutL was found to bind to both MutS and MutH and activate the MutH nick endonuclease activity (64, 65). MutH is a methyl-directed nick endonuclease, that detects and nicks the unmethylated strand at hemimethylated GATC sequences (66). In *E.coli*, methylation of these DNA sequences lags behind DNA replication, which allows for temporary discrimination between parental and newly synthesized strands (67-69).

The budding yeast genome encodes several MutS and MutL homologs, but no MutH homolog, suggesting important differences in the eukaryotic MMR pathway relative to the *E.coli* system. In eukaryotes, daughter strand recognition is not methylation directed, but instead relies on interactions with the polymerase processivity clamp PCNA (59, 70, 71). In fact, methylation-directed MMR in *E.coli* is most likely an exception to the rule, given that many other prokaryotes lack the *dam* gene and are unable to methylate GATC sequences (72). While bacterial MutS functions as a homodimer, the eukaryotic MutS homologues form heterodimeric complexes with slightly different lesion specificities, increasing the range of detection of mismatch events in these organisms. Msh2, for

Table 3. Human and yeast MutS and MutL homologs

Human			Yeast		
Gene	**Year first HNPCC mutation identified**	**Ref.**	**Gene**	**Year cloned**	**Ref.**
MSH1	-		*MSH1*	1992	(162, 163)
MSH2	1993	(84, 85)	*MSH2*	1992	(162, 163)
MSH3	2011	(165)	*MSH3*	1993	(164)
MSH4	-		*MSH4*	1994	(166)
MSH5	-		*MSH5*	1995	(167)
MSH6	1997	(169)	*MSH6*	1996	(168)[1]
MLH1	1994	(90, 91)	*MLH1*	1994	(170)
PMS1	1994	(92)	*MLH2*	1996	(168)[1]
MLH3	2001	(171-173)	*MLH3*	1996	(168)[1]
PMS2	1994	(92)	*PMS1*	1985	(174)

[1]Although not considered "cloning" in the strictest sense, the sequencing of the yeast genome revealed these additional MutS and MutL homologs based on homology. Note that cloning of many of the genes and identification of the first HNPCC mutations occurred within a fairly short period of time in the early 90s.

MutS homolog 2, is the predominant nuclear MutS homolog in eukaryotes and forms heterodimers with Msh6 or Msh3 (73). The Msh2-Msh6 dimer preferentially detects one base pair mismatches, while the Msh2-Msh3 dimer binds to small insertions or deletions. The Msh4-Msh5 dimer has important functions in meiosis by modulating meiotic recombination outcomes (74). Interestingly, yeast Msh1 functions as a homodimer, similar to bacterial MutS, but is localized exclusively to mitochondria (75). Yeast MutL homologues also form heterodimeric complexes. Mlh1/Pms1 is the main MutL dimer, while Mlh1/Mlh2 and Mlh1/Mlh3 perform minor functions (32) (Table 3).

Studies with bacterial *mut* strains, and yeast *mlh1*, *pms1* and *msh2* mutants showed that MMR is critical for the stability of short repeat sequences, such as poly $(GT)_n$, also termed microsatellites (76, 77). Frameshift mutations in these sequences are associated with slippage of the DNA polymerase and are independent of the inherent polymerase proof-reading activity or homologous recombination (76, 77). Interestingly, higher microsatellite instability had also been an important observation in studies with cell lines derived from patients suffering from the cancer predisposition syndrome hereditary non-polyposis colorectal cancer (HNPCC) or Lynch syndrome (78-82). HNPCC affected individuals have an increased lifetime risk of developing colorectal cancer (up to 80%) as well as an early onset of disease relative to the general population. These patients also face an increased risk of endometrial, ovarian, gastric, renal or bowel cancers (83).

In 1993, an incredibly quick succession of reports described the cloning of human *MSH2* and the immediate demonstration of its involvement in HNPCC (84-87). The disease-causing mutation in an affected family was mapped to chromosome 2p (87). Using a degenerate primer technique, based on the yeast *MSH2* sequence, the human *MSH2* gene was cloned and mapped to the same locus on chromosome 2p (84). Sequencing of the *MSH2* locus in HNPCC affected vs non-affected individuals confirmed the presence of a mutation only in affected individuals (84, 85). Subsequently, other HNPCC kindreds with mutations in *MLH1*, *PMS1* and *PMS2* were also described, cementing the view that HNPCC is a mismatch repair disease (88-92) (Table 3).

6. KEEPING A CHECK ON CANCER

Cells need to signal the occurrence of DNA lesions in order to orchestrate a cellular response that keeps the consequences of this damage limited to a minimum. In contrast to NER and MMR, where studies in *E.coli* pioneered the field, the bacterial "checkpoint" response (known as SOS response) is completely different from the eukaryotic checkpoint responses, and research undertaken in budding yeast paved the way to understanding these pathways.

When studying cells treated with DNA damaging agents, researchers soon observed that this leads to an arrest in cell cycle progression. However, this was initially attributed to a secondary effect of DNA damage itself, rather than the existence of a cellular pathway that enforces that arrest. As discussed previously, yeast *rad* mutants were isolated based on increased UV sensitivity and assigned to epistasis groups. One such mutant, *rad9*, was found to continue cycling after exposure to ionizing radiation, dying a few cell divisions later as a microcolony of aberrant cells (93). Interestingly, the viability of *rad9* mutants could be rescued if cells were artificially arrested in G2 with microtubule poisons and then released back into the cell cycle (93). Screens for other mutant strains that fail to establish cell cycle arrests led to the identification of the checkpoint kinases Mec1 (mitotic entry checkpoint-1), and Rad53, as well as the sensory components Rad17, Rad24 and Mec3 (94) (NB: *RAD9*, *RAD17*, *RAD24* and *RAD53* were initially assigned to *rad* epistasis groups, but have not been included in Table 1, since they are not part of any of the pathways the epistasis groups describe.)

Further research identified other checkpoint components and elucidated the architecture of the signaling cascade, as we understand it today. A number of sensory pathways detect the occurrence of DNA damage or replication stress and activate the central checkpoint kinases Mec1 and/or Tel1. Activation of the Mec1-Ddc2 kinase complex occurs in response to extended stretches of single-stranded DNA (ssDNA) and requires the activities of Dpb11, the ssDNA binding protein RPA, the checkpoint

Table 4. Checkpoint components in yeast and humans and their functions

Human	Yeast	Function	Reference[1]
RPA	RFA	Sensor (binds to ssDNA)	(175, 176) - 1988 - H
TopBP1	Dpb11	Sensor (Mec1/ATR activation)	(177) - 1995 - Y
Rad17-RFC	Rad24-RFC	Sensor (clamp loader)	(178) - 1997 - Y
Rad9-Hus1-Rad1	Ddc1-Rad17-Mec3	Sensor (checkpoint clamp)	(179) - 1998 - Y
ATR-ATRIP	Mec1-Ddc2	Signaling Kinase	(94) - 1994 - Y
Mre11-Rad50-Nbs1	Mre11-Rad50-Xrs2	Sensor (binds to DSB)	(180) - 1995 - Y
ATM	Tel1	Signaling Kinase	(113, 114) - 1995 - H/Y
53BP1, MDC1	Rad9	Mediator	(93) - 1988 - Y
Claspin	Mrc1	Mediator	(98) - 2001 - Y
Chk2/Chk1	Rad53	Effector Kinase	(181) - 1994 - Y
Chk1	Chk1	Effector Kinase	(182) - 1997 - H

[1]References acknowledge the first yeast or human study to imply a given gene/whole complex in the checkpoint response and/or the first time a given protein is assigned the described function. (Y) for budding yeast or (H) for human are used to identify in which of the two organisms this function was first identified.

clamp Ddc1-Rad17-Mec3 and the clamp loader complex Rad24-RFC. Tel1 activation depends on the Mre11/Rad50/Xrs2 complex and occurs predominantly after DSBs or at short dysfunctional telomeres. Both Mec1 and Tel1 phosphorylate their downstream targets on serine-glutamine (SQ) or threonine-glutamine (TQ) motifs, which are often clustered together in SQ/TQ cluster domains (SCD) (95). Another hallmark of checkpoint components is the presence of phospho-dependent protein-protein interaction domains, such as forkhead associated (FHA) or BRCA1 C-terminus (BRCT) domains (96, 97). Mediator proteins such as Rad9 or Mrc1 are then required for Mec1/Tel-dependent phosphorylation and activation of the downstream kinases Rad53 and Chk1 (98, 99). These kinases, in turn, phosphorylate further downstream targets involved in a plethora of functions, establishing the checkpoint response (Table 4) (100, 101).

These signaling cascades ensure that cell cycle progression is delayed while repair is underway in order to avoid conversion of an easily repairable lesion to a more deleterious one, such as chromosome rearrangements or chromosome loss (102, 103). The original concept of the checkpoint response envisioned a pathway responsible only for this DNA damage-dependent cell cycle delay (104). However, it is now well established that checkpoint functions are much broader, involving activation and recruitment of DNA repair factors to the site of damage, activation of transcriptional responses, telomere-related functions and, in some cases, induction of apoptosis (105). Checkpoint responses are also critical for faithful DNA replication and stabilize stalled replication forks that otherwise collapse into recombination-prone structures (106). A constitutively activated checkpoint response has been observed in pre-cancerous lesions and is proposed to act as a barrier to further hyperproliferation and genome instability arising from replication stress in these cells (107, 108). This selective pressure results in the outgrowth of cells with spontaneous mutations in checkpoint components, leading to an increased potential for new mutations and rearrangements in these cells (109). Consistently, the checkpoint response is an important tumour suppressor pathway and many many mutations in checkpoint components have been observed both in sporadic cancers (110), as well as in familial cancer predisposition syndromes, such as Ataxia Telangiectasia (AT), Seckel Syndrome and Nijmegen Breakage Syndrome (NBS)

AT affected individuals develop an uneven gait (ataxia), have dilated blood vessels (telangiectasia), progressive cerebellar degeneration, as well as increased radiation sensitivity, immunodeficiency, chromosomal instability and increased cancer susceptibility (111). AT cells are characterised by “radioresistant DNA synthesis”, an inability to suppress DNA synthesis after ionizing radiation, similar to the phenotype observed in yeast *rad9* mutants (112). Positional cloning of the ATM gene, for “AT mutated”, revealed a PI-3 kinase homologous to yeast Tel1, confirming the involvement of ATM in the cellular checkpoint response (113, 114).

Seckel Syndrome is characterized by proportionate short stature, mental retardation, and a typical ‘bird-like’ facial appearance (115). While the disorder is genetically heterogeneous, and mutations in centrosome components have also been described, the best-studied Seckel variants contain a mutation in the ATR gene. Similar to budding yeast Mec1 and fission yeast Rad3, ATR (ATM and Rad3-related) is the checkpoint kinase involved mainly in DNA replication stress responses and has important functions during DNA synthesis even in the absence of exogenous DNA damage (116). Consistently, complete loss of ATR function is incompatible with life, and the identified Seckel mutation occurs at a splice-site of the ATR gene, leading to greatly reduced, but detectable, expression of the full-length transcript (117).

Nijmegen Breakage Syndrome affected individuals present similar phenotypes to both AT and Seckel Syndrome, including mental retardation, bird-like facial features, microcephaly, growth retardation, immunodeficiency and cancer predisposition (118). Similar to AT, NBS patients are sensitive to radiation, which compromises cancer treatments, while radioresistant DNA synthesis and increased genomic instability are observed on the cellular level. Identification of the *NBS1* gene revealed its homology to budding yeast *XRS2*, a component of the Mre11/Rad50/Xrs2 (Nbs1) complex, (119, 120). Consistently, mutations in the other two components of the MRN/MRX complex have also been identified and lead to AT and NBS-like disorders, supporting the notion that this

complex, similar to its yeast counterpart, is involved in ATM/Tel1 activation (121, 122).

Nonetheless, while yeast models have without doubt accelerated our understanding of human DNA damage responses and checkpoint disorders, one should not ignore the shortcomings imposed by the extent of evolutionary change that occurred from yeast to humans. The human checkpoint response contains an additional checkpoint outcome, DNA–damage induced apoptosis, mediated by p53, and important DNA repair pathways, such as the Fanconi anemia pathway or the BRCA1/2 pathways, are completely absent in budding yeast.

7. HAPPY ENDINGS

Last but not least, telomeres play important roles in maintaining genome stability by ensuring complete replication of the genome and preventing chromosomal fusions. Gradual telomere shortening occurs naturally in somatic cells as a result of the "end replication problem". This phenomenon, which leads to replicative senescence, acts as a suppressor of tumorigenesis but at the same time contributes to the onset of aging-related diseases. On the other hand, short telomeres are also associated with certain human disorders. An example is Dyskeratosis Congenita (DC), a rare progressive congenital disorder caused by mutations in genes encoding one or more subunits of the reverse transcriptase telomerase. Patients with DC have short telomeres due to reduced telomerase activity and are characterized by cutaneous pigmentation defects, bone marrow failure, pulmonary fibrosis and predisposition to cancer. DC can be inherited in multiple ways. The most severe form of DC is a mutation in DKC1, which encodes the protein dyskerin that functions to stabilize the telomerase RNA component. As DKC1 maps to the X chromosome, this form of DC is inherited in an X-linked pattern. The milder forms of DC carry mutations in either the RNA component TERC or the catalytic component TERT. Since prokaryotes lack telomeres due to the circular nature of their chromosomes, much of our understanding of telomeres has been derived from studies carried out in the yeast model.

Telomere extension by telomerase is the primary mechanism used by a majority of cancer cells to acquire unlimited proliferation capacity. However, in the absence of telomerase, cancers are sometimes able to maintain telomeres via recombination-dependent pathways, collectively termed alternative lengthening of telomeres (ALT). ALT pathways were first discovered in yeast (123), where telomerase-negative strains senesce after approximately 50 to 100 cell divisions. At this point, a small subpopulation is able to escape senescence (123). These cells are called post-senescence survivors. Two different types of survivors were observed. Type I survivors are defined by the amplification of subtelomeric Y' elements while type II survivors are characterized by long heterogeneous telomeric tracts (123, 124), thought to arise either by intermolecular or intramolecular recombination. The generation of survivors depends on homologous recombination since deletion of the recombination gene *RAD52* eliminates all survivors (123). It was later discovered that separate pathways generate the two different types of survivors and subsequent studies have identified genes that are involved in each pathway. Generally, type I survivors arise by a *RAD51*-dependent pathway (124-126) while type II survivors are dependent on components of the Rad50-containing MRX complex (123-127). Simultaneous deletion of *RAD50* and *RAD51* abolishes the formation of all survivors (125). Following the discovery of ALT pathways in yeast, a similar mechanism was also observed in mammalian cells (128) including cancer cell lines (129-131). ALT cells closely resemble yeast type II survivors in that both arise from the recombination-dependent amplification of telomeric repeats and are very heterogeneous in length (132). Nonetheless, there are indications that similar to the yeast system, more than one pathway may exist in mammals. For example, mouse stem cells were shown to amplify both non-telomeric and telomeric sequences (133), similar to type I survivors. Understanding the ALT pathways would have high clinical significance because it supports proliferation in the ~15% of human cancers that are telomerase-negative.

Critically short telomeres can be perceived as a DSB and may inappropriately activate DNA repair pathways (134), suggesting significant overlap between telomeres and the DNA damage response. One example of the convergence between telomeres and DNA damage responses is the "healing" of DSBs by *de novo* telomere addition. *De novo* telomere addition was first observed in yeast (135) and *Tetrahymena* (136) when telomeric repeats were added to linear plasmids. This was further supported by evidence of *de novo* telomere addition to yeast artificial chromosomes (137) as well as an HO endonuclease-generated DSBs within the yeast genome (138). Sequence analysis at the breakpoint led to the discovery that new telomeres are added adjacent to telomeric seed sequences by telomerase (138, 139). The yeast system is particularly advantageous in this context as it allows for the efficient analysis of factors that affect *de novo* telomere formation next to a HO-inducible breakpoint (140). Chromosome healing has also been observed in mammalian cells (141-143), but the molecular details here remain largely elusive. Thus, this may be another scientific frontier where budding yeast studies may lead the way for better understanding of a similar process in mammalian cells in the future.

8. CONCLUSION

Although far from complete, this review highlights the importance of basic research in model organisms as a crucial scientific tool for the understanding of human disease. Since the inherent reactivity of the DNA molecule is invariable and the overall genome architecture is maintained, it is not surprising that genome maintenance pathways are conserved throughout eukaryotic evolution from single-celled microorganisms to humans. This allows for extensive and more exploratory studies to be conducted at a faster pace and with less infrastructural requirements in model organisms such as budding yeast before studying the corresponding pathway in mammalian systems.

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Abbreviations: DSB: double-strand break, NHEJ: non-homologous end joining, HR: homologous recombination, UV: ultraviolet, BER: base excision repair, XP: xeroderma pigmentosum, NER: nucleotide excision repair, MMR: mismatch repair, HNPCC: hereditary non-polyposis colorectal cancer, ssDNA: single stranded DNA, AT: ataxia telangiectasia, NBS: nijmegen breakage syndrome, ALT: alternative lengthening of telomeres

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