DNA repair*

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Abstract

The integrity of the genome is essential to the health of the individual and to the reproductive success of a species. Transmission of genetic information is in a selective balance between two opposing forces, the maintenance of genetic stability versus elimination of mutational change and loss of evolutionary potential. *Caenorhabditis elegans* provides many advantages for the study of DNA surveillance and repair in a multicellular organism. Several genes have been identified by mutagenesis and RNA interference that affect DNA damage checkpoint and repair functions. Many of these DNA damage response genes also play essential roles in DNA replication, cell cycle control, development, meiosis and mitosis. To date, no obvious DNA damage-induced checkpoint has been described in *C. elegans* somatic cells. In contrast, the DNA damage response in the germ line is characterized by two spatially separate checkpoints; mitotic germ nuclei proliferation arrest and apoptosis of damaged meiotic nuclei. Both of these responses are regulated by checkpoint genes including *mrt-2*, *hus-1*, *rad-5* and *cep-1*, the *C. elegans* ortholog of the human tumour suppressor p53. The germ line DNA damage checkpoints in *C. elegans* provide an excellent model in which to study the genes required to maintain genomic stability and to test compounds which might have tumor

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suppressing properties. In addition to single gene studies, integration of data from high-throughput screens has identified genes not previous implicated in the DNA damage response and elucidated novel connections between the different repair pathways. Most of the genes involved are conserved between worms and humans, and in humans, are associated with either oncogenesis or tumor-suppression. Thus, studies of the physical and functional interactions of the components of the repair pathways in *C. elegans* will provide information about human repair disorders and cancer predisposition.

1. Overview

The integrity of the genome is essential to the health of the individual and to the reproductive success of a species. Faithful transmission of genetic information is in a selective balance between genetic stability and mutational change as a resource for evolutionary potential. In order to maintain genome fidelity the coordinated action of surveillance and repair pathways is required. Much of our knowledge about repair has come from studies in bacteria, yeast and mammals, including human cell lines (reviewed in Sancar et al., 2004; Krogh and Symington, 2004), and it is increasingly evident that most repair functions are highly conserved. *Caenorhabditis elegans* provides an experimental model in which the repair processes required for both genomic stability and mutational change can be studied. In this Chapter, we present an overview of DNA damage response research using *Caenorhabditis elegans*. Table 1 is a summary of some DNA damage response genes identified in the *C. elegans* genome along with mutant phenotypes where known. Included in the Table are components of the pathways for nucleotide excision repair, mismatch repair, DNA damage checkpoint, non-homologous end joining, homologous recombination repair, and chromosomal structure surveillance.

Table 1. List of repair genes and mutant phenotypes

Pathway	Gene	Cosmid	Mutant phenotype	Reference
Uncloned rad mutants	*rad-1*	–	UV and gamma sensitive	Hartman and Herman, 1982
	rad-2	–	UV and gamma sensitive	Hartman and Herman, 1982
	rad-3	–	UV sensitive, reduced brood size	Hartman and Herman, 1982
	rad-4	–	UV sensitive, cold sensitive, suppressor of ndj	Hartman and Herman, 1982
	rad-6	–	UV sensitive, Dpy, reduced brood size	Hartman and Herman, 1982
	rad-7	–	UV sensitive, reduced brood size	Hartman and Herman, 1982
	rad-8	–	UV sensitive, sick, reduced brood size	Hartman and Herman, 1982
	rad-9	–	UV sensitive, sick, reduced brood size	Hartman and Herman, 1982
Nucleotide excision repair	*xpa-1*	K07G5.2	UV sensitive	Park et al., 2002
	XPB	Y66D12A.15	–	–
	XPC	Y76B12C.2	–	–
	XPD	Y50D7A.2	–	–
	XPE	M18.5	Let/Gro	Kamath et al., 2003
	XPF	C47D12.8	UV sensitive	Park et al., 2004
	XPG	F57B10.6	Emb	Piano et al., 2002
	ERCC1	F10G8.7	–	–
	csb-1	F53H4.1	UV sensitive	Lee et al., 2002

Pathway	Gene	Cosmid	Mutant phenotype	Reference
Mismatch repair	*msh-6*	Y47G6A.11	Somatic instability and Mut	Tijsterman et al., 2002
	msh-2	H26D21.2	Microsatellite instability, Mut, reduced DD apoptosis	Degtyareva et al., 2002
	mlh-1	T28A8.7	–	Pothof et al., 2003
	pms-2	H12C20.2	–	Pothof et al., 2003
DNA damage checkpoint	*mrt-2*	Y41C4A.14	Mrt, Rad, checkpoint defective	Ahmed and Hodgkin, 2000
	hus-1	H26D21.1	Mrt, Rad, checkpoint defective	Hofmann et al., 2002
	rad-5/*clk-2*	C07H6.6	Rad, checkpoint defective	Ahmed et al., 2001
	cep-1/*p53*	F52B5.5	Rad, checkpoint defective	Derry et al., 2001; Schumacher et al., 2001
	egl-1	F23B12.9	–	Hofmann et al., 2002
	ape-1	F46F3.4	Enhanced *cep-1*-dependent apoptosis	Deng et al., 2004
	abl-1	M79.1	Enhanced radiation-induced apoptosis	Deng et al., 2004
	brc-1	C36A4.8	Him and increased germ cell apoptosis	Boulton et al., 2004
	brd-1	K04C2.4	Him and increased germ cell apoptosis	Boulton et al., 2004
	pme-5	ZK1005.1	–	–
	kin-20	F46F2.2	Rad	–
	hpr-9	Y39A1A.23	Rad	Boulton et al., 2002
	hpr-17	F32A11.2 W	Rad	Stergiou and Hengartner, 2004
	chk-1	Y39H10A.7	–	–
	chk-2	Y60A3A.12	Emb Let, Him, absent chiasma in meiosis	MacQueen and Villeneuve, 2001
Non-homologous end joining	*cku-70*	Y47D3A.4	–	–
	cku-80	R07E5.8	–	Boulton et al., 2002
	lig-4	C07H6.1	–	Boulton et al., 2002
Homologous recombination	*atm-1*	Y48G1BL.F	Radiation sensitve, checkpoint defective	Stergiou and Hengartner, 2004; Boulton et al., 2002
	atl-1	T06E4.3	Embryonic lethality, Him, Rad	Aoki et al., 2000
	rad-54	W06D4.6	Rad	Boulton et al., 2002
	rad-50	T04H1.4	Rad	–
	mre-11	ZC302.1	Germline mortality, Him, Emb	Chin and Villeneuve, 2001
	rad-51	Y43C5A.6	Embryonic lethality, Him, Rad	Takanami et al., 1998
	top-3	Y56A3A.27	–	Wicky et al., 2004
	dna-2	F43G6.1	Rad	–

Pathway	Gene	Cosmid	Mutant phenotype	Reference
Chromosome structure	*coh-2*	F10G7.4	Late embryo or larval arrest or HIM	–
	scc-3	F18E2.3	Embryonic lethal; cell division defects	–
	rec-8	W02A2.6p	Embryonic lethal; aneuploidy	–
	him-1/*smc-1*	F28B3.7	UV sensitive, high incidence of males, Emb	Hartman and Herman, 1982
	him-3	ZK381.1	High incidence males, implicated in sister repair	–
Cytokinesis checkpoint	*mdf-1*	C50F4.11	Fail to arrest metaphase to anaphase	–
	mdf-2	Y69A2AR.30	Fail to arrest metaphase to anaphase	–
	san-1	ZC328.4	Fail to arrest cell cycle during anoxia	–
	fzy-1	ZK177.6	Embryonic lethal, defective anaphase	–
	ify-1/*securin*	C27A2.3	Embryonic lethal, defective anaphase	–
	sep-1	Y47G6A.12	Prevents timely disjunction and segregation	–
	ubc-1	C35B1.1	–	–
	air-2	B0207.4	Embryonic lethal; cell division defects	–
Helicases	*dog-1*	F33H2.1	Deletion of G tracts, mutator	Cheung et al., 2002
	wrn-1	F18C5.2	Abnornmal checkpoint response, premature aging	Lee et al., 2004
	him-6	T04A11.6	Embryonic lethality, Him	Wicky et al., 2004

In addition to those listed in Table 1 are those genes involved in base excision repair, DNA glycosylation, the *rad-6* pathway, trans-lesion bypass, and those encoding editing and processing nucleases.

2. Radiation sensitivity of *C. elegans*

In *C. elegans*, the first study of repair function was the identification by Hartman and Herman (1982) of nine Rad (radiation-sensitive) mutants, which were hypersensitive to ultraviolet light during embryogenesis. UV irradiation of the Rad mutants results in a decrease in viability. Many of these Rad mutants exhibit phenotypes in addition to their UV sensitivity suggesting that the Rad genes are involved in other biological processes in addition to their roles in the UV-induced DNA damage response (Table 1). More recently, researchers have used reverse genetic techniques such as RNA interference and PCR-mediated gene knockouts to investigate genes involved in different DNA damage response pathways such as nucleotide excision repair (Park et al., 2002; Park et al., 2004; Lee et al., 2002).

The UV sensitivity of *C. elegans* varies depending on the developmental stage of the worm (Hartman, 1984; Hartman, 1984) with wild-type animals being most sensitive to UV radiation during early embryogenesis. The UV hypersensitivity of the early stage embryo might be due in part to the rapid cell proliferation and the lack of obvious DNA damage-induced checkpoints; DNA replication progresses even after exposure to large fluences of UV radiation (Jones and Hartman, 1996).

3. DNA damage checkpoints in the germ line

In contrast to the developing embryo, activation of the checkpoint in the germ line results in obvious morphological changes that can be monitored by microscopy of live animals. (Gartner et al., 2000; Stergiou and Hengartner, 2004). In response to DNA damage, mitotic germline nuclei arrest proliferation, presumably to allow time for DNA repair. In the meiotic region of the germ line, cells with DNA damage are removed by apoptosis before oogenesis. DNA damage-induced apoptosis occurs in addition to physiological programmed germ cell death, which is hypothesized to maintain germline homeostasis. DNA damage-induced germ cell death requires the conserved apoptotic machinery (Gartner et al., 2000). However, the proapoptotic gene *egl-1*, which is required for somatic programmed cell death but not physiological germ cell death, is not absolutely required for DNA damage-induced germ cell apoptosis (Gartner et al., 2000) even though there is a *cep-1*-dependent increase in *egl-1* transcription after genotoxic stress (Hofmann et al., 2002). The specific genes involved in the germline DNA damage-induced checkpoints are shown in Figure 1 and are discussed below.

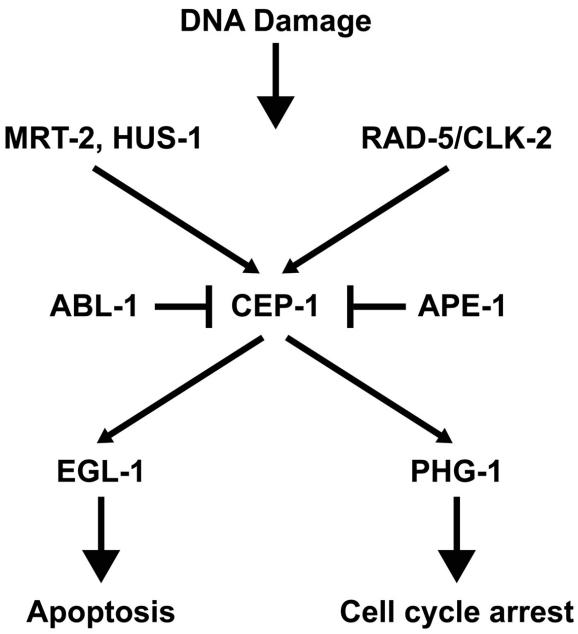

Figure 1. Diagram of the germline DNA damage-induced checkpoints.

3.1. *mrt-2*, *hus-1* and *rad-5*

An exciting finding was the identification of *mrt-2*, a gene responsible for germline immortality (Ahmed and Hodgkin, 2000). *mrt-2* mutants exhibit progressive telomere shortening and accumulate end-to-end chromosome fusions. In addition, *mrt-2* mutants are defective in DNA damage-induced mitotic arrest and apoptosis in the germline (Gartner et al., 2000). *mrt-2* encodes a homologue of a checkpoint gene required to sense DNA damage in yeast (*S. pombe rad1*/*S. cerevisiae rad17*). In addition to *mrt-2*, function of the DNA damage checkpoint involves the gene *hus-1*, which when mutated results in a phenotype similar to *mrt-2* (Hofmann et al., 2002). Another checkpoint gene is *rad-5* (Gartner et al., 2000). Cloning of the *rad-5* gene (Ahmed et al., 2001) lead to the surprising result that *rad-5*(*mn159*) (from Hartman and Herman, 1982) is allelic with *clk-2*(*qm37*), a mutant implicated in regulation of biological rhythms and life-span (Benard et al., 2001; Lim et al., 2001). *rad-5*/*clk-2* regulates the S phase replication checkpoint and is homologous to *S. cerevisiae* Tel2, which has an essential function in yeast for regulating telomere length. Overexpression of human CLK2 in *C. elegans* made the cell hypersensitive to apoptosis triggered by oxidative stress or DNA replication block and gradually increased telomere length suggesting that human CLK2 may have a role in maintaining telomere length (Jiang et al., 2003). However, the role of *rad-5*/*clk-2* in the regulation of telomere length remains unclear. Studies investigating the effect of *rad-5*/*clk-2* mutations on telomere length have been contradictory (Lim et al., 2001; Benard et al., 2001; Ahmed et al., 2001). Ahmed and coworkers (2001) suggest that the differences observed in the three studies could be explained by the fact that

telomere length varies considerably between *C. elegans* strains and that telomere length can fluctuate even within isogenic lines. Cheung et al. (2004) used single telomere length analysis (STELA) and reported strain specific differences in wild type as well as mutant strains, such as the telomerase deficient *trt-1* (Cheung et al. in press).

3.2. *cep-1/p53*

p53 is a key regulator of the DNA damage-induced checkpoint in mammals (reviewed in Sancar et al., 2004). *cep-1*, the *C. elegans* homolog of p53, is required for DNA damage-induced apoptosis in the *C. elegans* germ line, but not for programmed cell death occurring during worm development nor physiological (radiation-independent) germ cell death (Schumacher et al., 2001; Derry et al., 2001). Despite the differences in the three-dimensional structure of the DNA binding domain between CEP-1 and human p53 (Huyen et al., 2004) its role in the DNA damage checkpoint appears to be conserved. Furthermore, CEP-1 can induce apoptosis in mammalian cells and this induction can be inhibited by iASPP, an evolutionarily conserved inhibitor of p53 (Bergamaschi et al., 2003).

Several genes have been identified that either regulate *cep-1* activity or are regulated by *cep-1*. The *C.elegans* iASPP ortholog, *ape-1* (apoptotic enhancer) is a conserved inhibitor of *cep-1*. *ape-1*(*RNAi*) results in an increase in *cep-1*-mediated apoptosis (Bergamaschi et al., 2003). Lettre et al. (2004) also identified *ape-1* along with several other genes in a genome-wide *RNAi* screen for genes that when knocked out resulted in an increase in germ cell death. Many of the genes identified in this screen required *cep-1* activity for the increase in germ cell death. Deng et al. (2004) studied the antagonistic effects of *abl-1*, a homolog of the conserved nonreceptor tyrosine kinase c-Abl, on *cep-1*-mediated apoptosis. Deletion of *abl-1* results in increased radiation-induced apoptosis, but not ethylnitrosourea-induced apoptosis. Thus, ABL-1 can distinguish proapoptotic signals triggered by two different DNA-damaging agents. In addition, treatment of *C. elegans* with c-Abl inhibitors results in a phenotype similar to the *abl-1* mutation, demonstrating the utility of *C. elegans* as a model to screen for potential anticancer drugs.

In contrast to the *Drosophila* p53 ortholog, *cep-1* has also been shown to regulate DNA damage-induced mitotic germ cell arrest (B. Derry, personal communication). Furthermore, *cep-1*-mediated germline mitotic arrest is dependent on *phg-1*, a *C. elegans* homolog of the human growth arrest gene gas1. *phg-1* is required for *cep-1*-mediated mitotic arrest but not for *cep-1*-mediated apoptosis indicating that *cep-1*-mediated mitotic arrest and apoptosis can be separated (B. Derry, personal communication).

4. DNA mismatch repair

Components of the mismatch repair pathway were originally identified in bacteria as mutation-prone strains. In humans, mismatch repair deficiency predisposes to hereditary nonpolyposis colon cancer (HNPCC) and involves the proteins MSH2, MSH6, MLH1, and PMS2. *C. elegans* has orthologs to all four of these genes. Utilizing a system to screen for repeat sensitivity, Tijsterman et al. (2002) demonstrated that RNAi of *msh-2*, *msh-6*, *mlh-1* and *pms-2* results in a mutator phenotype. In this screening system, a DNA repeat puts a heat-shock promoter-driven lacZ transgene reporter gene out of frame. Mutations that result in a frameshift would result in lacZ expression. In *msh-2*, *msh-6*, *mlh-1* and *pms-2*-deficient animals, in-frame lacZ+ patches were observed as a result of somatic repeat instability (Tijsterman et al., 2002; Pothof et al., 2003). Degtyareva et al., (2002) used an *msh-2* mutant to demonstrate elevated levels of microsatellite instability. In this study, the phenotype of *msh-2* mutants was similar to wild-type worms with regard to lifespan and meiotic chromosome segregation, but *msh-2* animals had somewhat reduced fertility. In addition, the mutant worms had reduced DNA damage-induced germ-line apoptosis after genotoxic stress, linking a functional component of the mismatch repair pathway to the DNA damage checkpoint in *C. elegans*. This result is similar to that observed in mammalian mismatch repair mutants (reviewed in Buermeyer et al., 1999).

Not all mismatch repair homologs have a role in DNA repair. Similar to the situation in budding yeast, the *C. elegans* MutS family homologs, *him-14/msh-4* and *msh-5* have no apparent role in repair, but have a specialized role in crossing over during meiosis.

5. Homologous recombination repair

Double-strand breaks (DSBs) occur in response to environmental insult, such as ionizing radiation or genotoxic chemicals, or cellular sources such as oxidative damage or replication blocks in the DNA. In addition to their unwanted creation by DNA damaging events or substances, DSBs are created biologically by SPO-11 as the highly regulated initiation of meiotic recombination. The processing of both categories of DSBs utilizes many of the same proteins and mechanisms. Central to DSB repair is the RecA homolog, Rad51, which mediates functions

involving strand invasion during recombination (Shinohara and Ogawa, 1995). RAD-51 localization to DNA requires the products of the recombination genes *mre-11* and *chk-2* (Rinaldo et al., 2002; Alpi et al., 2003). *rad-51* and *mre-11* are required for both meiotic recombination and DNA repair (Takanami et al., 2000; Chin and Villeneuve, 2001; Takanami et al., 2003). It is unclear whether the checkpoint kinase, *chk-2* functions during DNA repair as well as during meiosis because of the severe meiotic phenotype of *chk-2* loss of function mutants (MacQueen and Villeneuve, 2001).

6. BRCA1 and BRCA2

BRCA1 (breast cancer) mutations are found in 45% of all familial breast cancers (Yoshida and Miki, 2004). The BRCA1 gene performs a multitude of functions in response to DNA damage, most of which are poorly understood. The *C. elegans* ortholog, *brc-1*, was identified by yeast 2-hybrid interaction of its product with BRD-1, a putative ortholog of BARD1 (Boulton et al., 2004). *RNAi* depleted *brc-1* and *brd-1* worms had a high incidence of X-chromosome nondisjunction (Him phenotype) and increased germ cell death (apoptotic phenotype). In addition, radiation treatment resulted in increased apoptotic cell death, chromosome fragmentation, and radiation hyper-sensitivity, strongly implicating *brc-1* in DNA damage response.

Recently, a BRCA2-related gene has been identified and shown to be involved in double-strand break repair by homologous recombination like its mammalian counterpart. Martin et al. (2005) demonstrated that the defect in HR is due to inefficient RAD-51 nuclear localization and a failure to recruit RAD-51 to DSBs.

7. The *dog-1* and RecQ helicases

C. elegans was the first organism in which a mutant phenotype was observed resulting from the loss of a G-tract interacting helicase, implicated in repair. The *dog-1* (deletion of G tracts) gene encodes a putative helicase required to maintain homopolymeric dC/dG tracts (Cheung et al., 2002). In humans, loss of function of the orthologous BRCA1-interacting protein BACH1 results in breast cancer susceptibility (Cantor et al., 2001; Cantor et al., 2004). Whereas in mouse, loss of function of a related gene, Rtel (regulator of telomere length) showed telomere loss and displayed many chromosome breaks and fusions (Ding et al., 2004).

In humans, Bloom's syndrome is an autosomal-recessive human disorder caused by mutations in the BLM RecQ helicase and is associated with loss of genomic integrity and an increased incidence of cancer. The *C. elegans* homolog most similar to the BLM helicase is *him-6*, which when mutated results in enhanced irradiation sensitivity, a partially defective S-phase checkpoint, and reduced levels of DNA-damage induced apoptosis (Wicky et al., 2004). *him-6* and *top-3* are needed to prevent the accumulation of double-strand breaks in normally proliferating germ cells, and act in partially redundant pathways downstream of *rad-51*.

A third helicase, the *C. elegans* Werner's Syndrome RecQ helicase, WRN-1, is implicated in the DNA damage checkpoint (Li et al., 2004; Lee et al., 2004). Lee et al. (2004) showed that WRN-1 defects are accentuated by gamma-irradiation, implying that they are derived from spontaneous or induced DNA damage. Irrespective of gamma-irradiation, pre-meiotic germ cells had an abnormal checkpoint response to DNA replication blockage. These observations suggest that WRN-1 acts as a checkpoint protein for DNA damage and replication blockage. The authors point out that the *wrn-1*(*RNAi*) phenotypes are similar to those of Werner syndrome; for example, premature aging and reduced body size, suggesting that *C. elegans* may be a useful model for this human disease.

8. DNA damage repair and genomics

A broad perspective on genes involved in DNA repair has been gained using high throughput, genome-wide analysis of RNAi phenotypes in *C. elegans* (Piano et al., 2002 Kamath et al., 2003 Pothof et al., 2003; Lettre et al., 2004; van Haaften et al., 2004). As part of a large scale analysis of protein-protein interactions, known proteins implicated in replication, nucleotide excision repair, mismatch repair, base excision repair, non-homologous end joining, homologous recombination and checkpoint pathways were used in yeast 2-hybrid experiments to identify physical interactors in the predicted proteome (Boulton et al., 2002; Li et al., 2004). Results from this study illustrate how sensors, transducers and mediators are shared when generating different responses like chromatin remodeling, altered gene expression and DNA replication (Figure 2). In a striking way, data from *C. elegans* demonstrates that many of the pathways are interrelated, and that pathway components exhibit previously unrecognized links between repair mechanisms and checkpoints.

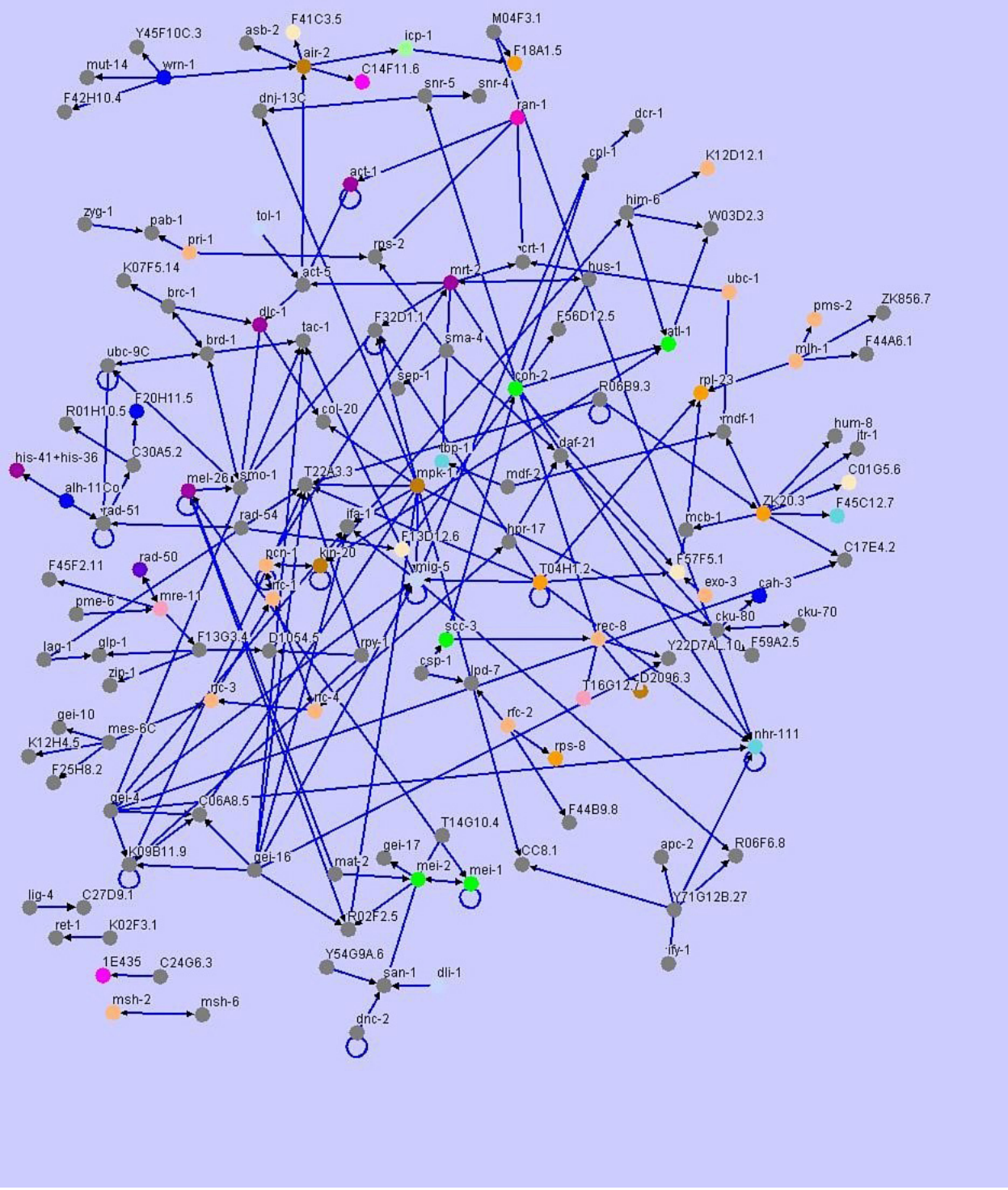

Figure 2. Yeast 2-hybrid data from Li et al. (2004) showing interactions between DNA damage proteins and chromosomal components. Data has been visualized by Maja Tarailo from the University of British Columbia, using Osprey, a software platform for visualizing complex interaction networks. Colours denote Gene Ontology (GO) terms.

9. Summary

C. elegans has proven to be a useful model with which to investigate the factors maintaining genome stability. Genes have been identified by mutagenesis and *RNAi* that affect DNA damage checkpoint and repair functions

resulting in hypersensitivity to radiation. To date no obvious DNA damage-induced checkpoint has been described in the soma. In contrast, the DNA damage response in the germ line is characterized by two spatially separate checkpoint responses; mitotic germ nuclei proliferation arrest and *cep-1*-mediated apoptosis of damaged meiotic nuclei. In addition to single gene studies, integration of data from high-throughput screens has identified genes not previously implicated in the DNA damage response and elucidated novel connections between the different repair pathways.

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