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Tissue specific response to DNA damage: *C. elegans* as role model

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ABSTRACT

The various symptoms associated with hereditary defects in the DNA damage response (DDR), which range from developmental and neurological abnormalities and immunodeficiency to tissue-specific cancers and accelerated aging, suggest that DNA damage affects tissues differently. Mechanistic DDR studies are, however, mostly performed *in vitro*, in unicellular model systems or cultured cells, precluding a clear and comprehensive view of the DNA damage response of multicellular organisms.

Studies performed in intact, multicellular animals models suggest that DDR can vary according to the type, proliferation and differentiation status of a cell. The nematode *Caenorhabditis elegans* has become an important DDR model and appears to be especially well suited to understand *in vivo* tissue-specific responses to DNA damage as well as the impact of DNA damage on development, reproduction and health of an entire multicellular organism. *C. elegans* germ cells are highly sensitive to DNA damage induction and respond *via* classical, evolutionary conserved DDR pathways aimed at efficient and error-free maintenance of the entire genome. Somatic tissues, however, respond differently to DNA damage and prioritize DDR mechanisms that promote growth and function. In this mini-review, we describe tissue-specific differences in DDR mechanisms that have been uncovered utilizing *C. elegans* as role model.

1. Introduction

Environmental and cell intrinsic genotoxic agents induce a wide variety of DNA lesions that are each dealt with by specialized DNA repair, damage avoidance and damage signaling pathways, which are collectively referred to as the DNA damage response (DDR) [1]. Not only the type of lesion, but also its genomic location and the cell cycle phase influence repair pathway choice. For example, helix-distorting lesions that are repaired by nucleotide excision repair (NER), are repaired by global genome NER (GG-NER) at all positions throughout the genome, but lesions that block RNA polymerase II during transcription are efficiently removed by transcription-coupled NER (TC-NER). Furthermore, double strand breaks (DSBs) can be rejoined by non-homologous end-joining (NHEJ) in any cell cycle phase, but only in S/G2 DSBs are repaired in an error-free fashion by homologous recombination (HR). Thus far, only limited information is available on the DDR *in vivo*, in different cell types. However, studies utilizing differentiated cell types [2] indicate that DDR is also dependent on the cell type and its function and developmental stage within an organism. This cell-specific regulation of DDR is, however, less well understood.

Deficiencies in DDR mechanisms underlie various diseases characterized by neuronal and developmental failure, cancer predisposition and/or progeroid features. Although these symptoms highlight the severe impact of DNA damage accumulation on health, DNA repair deficiency does not affect all tissues equally [3]. The vast majority of studies focusing on DDR mechanisms rely on the use of *in vitro* experiments, single cell organisms or cells in culture. However, in multicellular organisms, cells may deal differently with DNA damage depending on their specific function. Therefore, to properly understand the impact of DDR-deficiency, it is necessary to take the cell type and tissue context in which DNA damage occurs into account.

The nematode *Caenorhabditis elegans* (Fig. 1) seems particularly well suited to study tissue- and development-specific DDR. Its small size and transparency, combined with its well annotated, invariant cell lineage, allow the microscopic dissection of DDR mechanisms simultaneous in different cell types *in vivo*. Somatic cells in *C. elegans* proliferate during larval development and count up to 959 post mitotic cells in the adult, forming muscular, neuronal, intestinal and

Abbreviations: BER, base excision repair; CO, crossover; DDR, DNA damage response; DSB, double strand break; FA, Fanconi anemia; GG-NER, global genome nucleotide excision repair; HR, homologous recombination; ICLR, interstrand-crosslink repair; IR, ionizing radiation; NER, nucleotide excision repair; NHEJ, non-homologous end-joining; SC, synaptonemal complex; SSA, single strand annealing; SDSA, synthesis-dependent strand annealing; TC-NER, transcription-coupled nucleotide excision repair; TLS, translesion synthesis; UV, Ultraviolet.

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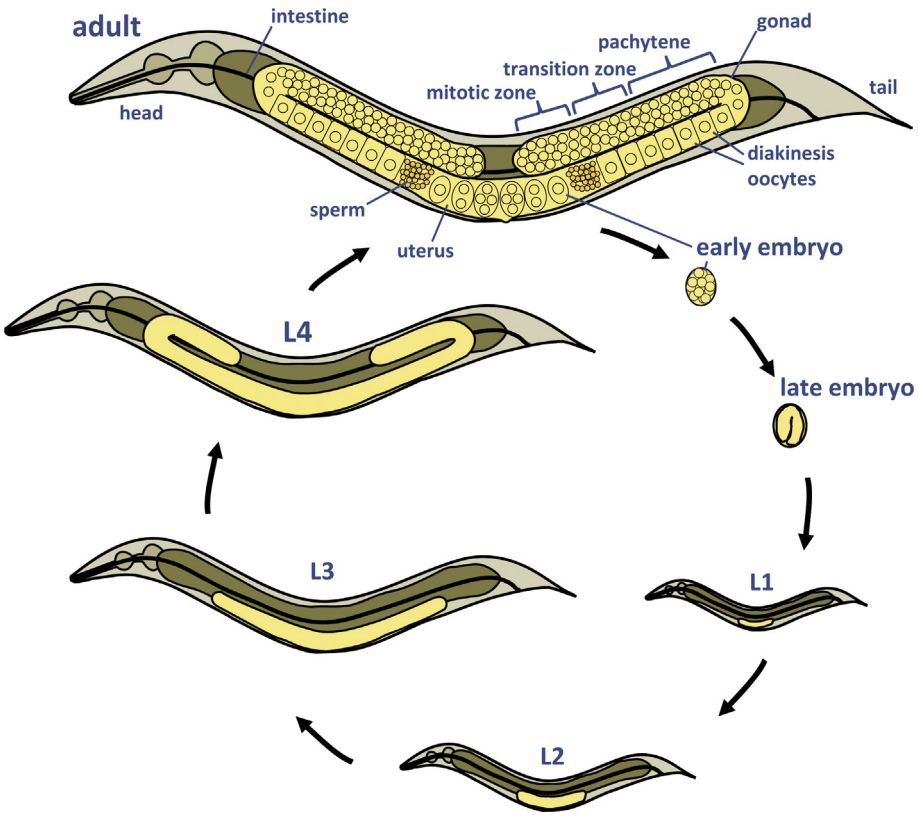

Fig. 1. *C. elegans* anatomy and life cycle.
Adult *C. elegans* produce approximately 300 eggs, which after hatching mature through four larval stages (L1–L4) to adulthood in about 3 days at room temperature. In the L1 larvae, transiently arrested germ cell precursors start proliferating to form the germ line. In the adult, the germ cells are arranged in a spatio-temporal gradient of differentiation in two gonad arms. Distal from the uterus, in the 'mitotic zone', germ stem cells proliferate, replicate their DNA and enter meiosis prophase I in the 'transition zone', when migrating proximal to the uterus. Meiotic nuclei enter pachytene before the bend of the gonad arm and then progress through diplotene and form diakinesis oocytes. The most proximal oocyte enters the spermatheca, where it is fertilized, and initiates embryogenesis as zygote upon entering the uterus. In the early embryo, rapid cell divisions occur for approximately 6 h, which is followed by an 8 h period of almost no cell divisions in the late embryo.

epidermal tissue. Furthermore, the adult contains two U-shaped gonads that harbor both male and female mitotic and meiotic germ cells that constitute an immortal and totipotent cell lineage. The self-fertilizing hermaphrodite nematode can be maintained as isogenic population and develops from egg to adult, through four larval stages, in only 3 days, making analysis fast and straightforward.

C. elegans germ cells display a strong response to DNA damage that involves evolutionary conserved DNA repair and signaling pathways [4,5]. Interestingly, this response varies depending on the developmental stage of individual germ cells. Strikingly, somatic cells in adult *C. elegans* often display a markedly different DDR, exemplified by the extreme resistance to ionizing radiation (IR). The differences between these cells types likely reflect their distinct main purpose. The germ lineage is immortal and totipotent, whereas somatic cells are disposable after successful reproduction. Genome maintenance in a perpetual cell lineage must therefore be faultless and efficiently safeguard all genetic information. Dividing and differentiated somatic cells, on the other hand, need only to maintain their genome to preserve fitness of the cell and to ensure procreation of the organism.

Here, we will discuss the different DDR systems used throughout the *C. elegans* life cycle, from germ stem cells to adult post mitotic cells, to exemplify and define the principle diversity in DDR that exists between cells in multicellular organisms. For detailed descriptions of the individual proteins and molecular mechanisms involved in the DDR systems described, we refer the interested reader to specialized reviews [6–9] and literature cited throughout the text.

2. DDR in germ cells

Germ line specification occurs early in *C. elegans* embryogenesis after several cell divisions with the birth of the first primordial germ cell P4, which divides at about the 100-cell stage to form the Z2 and Z3 cells [10]. After hatching, in the first larval stage, Z2 and Z3 start proliferating to form the germ lineage that is arranged in a spatial/temporal distal to proximal gradient of differentiation in the adult (Fig. 1). Germ cells in the adult are contained in two U-shaped arms of a somatic gonadal compartment, which are joined together at their proximal ends to a common uterus. At the distal ends of the gonads, proliferating nuclei reside in a syncytial 'mitotic compartment' and form the germ stem cell niche. Nuclei enter prophase I of meiosis in the 'transition zone' and initiate meiotic recombination when migrating in a proximal direction toward the spermathecal, before finally entering the uterus to initiate embryogenesis.

2.1. DDR in the mitotic compartment

The response to DNA damage is separated both spatially and developmentally in the adult gonad, in which DNA damage often leads to microscopically visible changes. In the distal mitotic stem cell compartment, where nuclei proliferate before entering meiosis, DDR is characterized by an extensive and redundant usage of different DNA repair pathways and a strong checkpoint response to allow efficient and thorough repair to take place. DNA damage and replication stalling cause a transient, microscopically discernable cell cycle arrest, visible as a decreased amount of cells that are enlarged because growth but not cell division continues [5,11].

DNA damage can also be estimated by visualizing the HR recombinase RAD-51, which localizes to DSBs. Replication-blocking lesions also recruit RAD-51, but this specifically depends on its paralog RFS-1, showing that HR is activated in response to many types of lesions but may process some lesions differently [12]. Indeed, HR and not NHEJ is the major DSB repair pathway in both proliferating and meiotic germ cells [13]. DBSs are processed and recruit signaling proteins, such as the PI_3-kinases ATL-1/ATR and ATM-1 and the HPR-9/MRT-2/HUS-1 (RAD9/RAD1/HUS1; 9-1-1), complex to elicit a G2/M arrest *via* checkpoint proteins CLK-2/TEL2 and CHK-1 [5,11,14–17].

NER, base excision repair (BER) and interstrand-crosslink repair (ICLR) are also active in the mitotic germ cell compartment. In particular GG-NER repairs UV photolesions and protects germ cells against UV irradiation [18]. TC-NER is active, but is only relevant to UV survival when GG-NER is inactive. UV photolesions block replication fork progression and elicit a checkpoint response that depends on lesion processing by NER [19]. Besides NER and translesion synthesis (TLS) by POLH-1/Polymerase η, HR counteracts UV-induced replication stress [20]. Lesion processing by BER also activates checkpoint signaling, as cell cycle arrest induced by misincorporated uracil is suppressed when the uracil-DNA glycosylase UNG-1 is absent [21]. In contrast, checkpoint activation by ICLs is not dependent on processing by ICLR proteins. Rather, checkpoint activation regulates the localization of FCD-2 to damaged chromatin in mitotic germ cells after replication stress or the induction of ICLs [22,23]. In addition to FCD-2, other orthologs of Fanconi anemia (FA) proteins, including DOG-1/FANCJ, were shown to promote germ cell chromosomal integrity and survival after exposure to crosslinking agents [23–25].

Other types of genomic stress, for instance resulting from absent RecQ family helicases DOG-1 and HIM-6/BLM, induce replication stress and cell cycle arrest as well [26,27]. Besides its role in ICLR, DOG-1 was found to maintain stable inheritance of guanine rich sequences that can form secondary G-quadruplexe structures that interfere with replication [28]. In the absence of DOG-1, mutations arise at these guanine rich sites, which are exacerbated if also HR or HIM-6 is absent [27]. The formation of larger deletions at these guanine stretches is prevented by an alternative DSB end-joining pathway involving POLQ-1/polymerase θ, which joins DSBs based on single nucleotide homology [29]. This theta-mediated end-joining also acts to repair breaks that occur due to replication fork collapse in the absence of TLS, most likely to prevent excessive DNA loss [30].

The strong activation of cell cycle checkpoints and multiple, partially redundant repair pathways in response to different types of genotoxic stress suggests that the genome of proliferating germ cells in *C. elegans* is maintained in a robust and efficient manner. This seems to be corroborated by a whole genome analysis of mutation rate in the *C. elegans* germ lineage, which was found to be on average approximately one mutation per genome per generation in wild type animals and was not strikingly elevated in several single DDR mutants [31].

2.2. Meiotic recombination and DSB repair

Following chromosome duplication, proliferating germ nuclei enter prophase I of meiosis in the so called 'transition zone', proximal to the mitotic compartment (Fig. 1). Here, homologous chromosomes pair and initiate meiotic recombination. In the pachytene stage, chromosomes are fully synapsed and held together by a protein-DNA structure called the synaptonemal complex (SC). Recombination is initiated when the topoisomerase II-like protein SPO-11 induces around 11-12 DSBs per nucleus, which is on average almost two DSBs per chromosome pair [32–34]. As these DSBs are repaired by HR, one DSB per chromosome initiates the formation of an "obligate" crossover [35], which will form the physical link, or chiasma, between homologous chromosomes during bivalent formation in diplotene and diakinesis stages and is essential for chromosome segregation during the first meiotic cell division that takes place upon fertilization. Mutants that cannot induce or repair DSBs will therefore show defects in bivalent formation in diakinesis and hardly produce viable offspring (Fig. 2) [33,34]. Thus, control mechanisms must ensure that only limited DSBs are induced in the correct meiotic stage, which are evenly distributed over chromosomes. Importantly, DSB repair activity should be controlled such that only one DSB per chromosome pair is repaired *via* crossover recombination while the other DBSs do not form crossovers and are repaired by other means.

SPO-11 dependent RAD-51 foci first appear in the transition zone, corresponding to leptotene/zygotene, and disappear by late pachytene, indicating that repair of DBSs occurs in early/mid pachytene [33]. The choice for crossover formation is controlled at the level of DSB induction, through modulation of chromatin and chromosome structure, as well as by specialized crossover promoting and inhibiting factors and repair proteins. A detailed description of this intriguing control over genome editing is, however, beyond our focus and is described in detail by others [36,37]. During HR, the anti-recombinase RTEL-1 promotes non-crossover DSB repair by synthesis-dependent strand annealing by disassembling D loop-recombination intermediates [38]. In mutants defective for RTEL-1, all induced DSBs appear to be repaired by crossover formation between homologous chromosomes (Fig. 2). This indicates that in wild type worms, HR of meiotic DSBs usually takes place using the homologous chromosome and not the sister chromatid as repair template. Indeed, in wild type worms, both inter-sister repair, as well as other forms of DSB repair seems to be actively suppressed in early meiosis. In some mutants that cannot initiate homolog pairing, RAD-51 foci appear and disappear as in wild type but crossovers do not form, which suggests that HR takes place without the homologous chromosome (Fig. 2) [39,40]. Therefore, it is likely that factors that facilitate homolog pairing may prevent the use of the sister chromatid and provide the aligned homologous chromosome as repair template.

Upon progression through prophase I, the DSB repair mode changes. In early prophase, RAD-51 loading onto DSBs, either induced by SPO-11 or IR, is promoted by the MRE-11/RAD-50 complex, likely through DNA end resection [33,41]. In later mid- and late pachytene stages, however, DSBs are not repaired as interhomolog crossovers anymore and loading of RAD-51 can take place independent of MRE-11/RAD-50. Furthermore, mutants in which crossovers are not formed due to defects in SC formation show persistent RAD-51 foci in late pachytene but intact univalent chromosomes in later stage diakinesis [42,43], suggesting alternative DSB processing strategies. Upon loss of RAD-51 or the REC-8 subunit of cohesin, however, these univalent chromosomes are not intact but fragmented (Fig. 2), indicating that in late pachytene DSBs are repaired by inter-sister instead of inter-homolog HR. Loss of BRC-1/BRCA1, SMC-5 or SMC-6 in SC mutants also leads to chromosome fragmentation in diakinesis, indicating that these proteins function in this process [44,45]. Interestingly, transient SC disassembly and separation of chromosome axes are observed in late pachytene after DSB induction, which has therefore been suggested to license inter-sister HR [46]. This depends on the MYS-1/TIP60 acetyltransferase and coincides with a reduction in acetylated H2AK5, a chromatin mark that is associated with homolog-pairing. Therefore, remodeling of chromatin and chromosome structure may play a role in regulating the different DSB repair modes – first inter-homolog and then inter-sister repair – in early prophase I.

In HR deficient mutants, DSB repair can take place by error-prone mechanisms such as single strand annealing (SSA) or NHEJ, but this leads to the formation of deleterious chromosome fusions

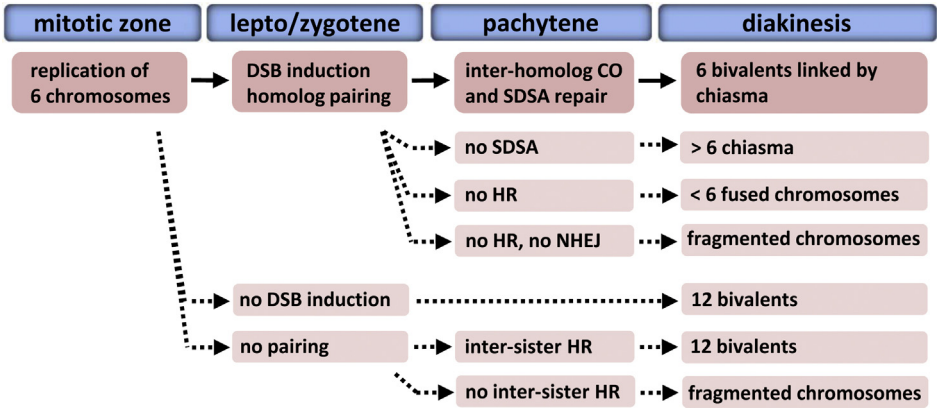

Fig. 2. Consequences of DNA repair defect in meiosis prophase I.
The depicted scheme shows the consequences of DNA repair deficiency during different stages of meiosis in *C. elegans*. In the mitotic compartment of the distal gonad, nuclei normally replicate their six chromosomes and enter meiosis prophase I at the leptotene/zygotene stage. Here, double strand break (DSB) induction and pairing of homologous chromosomes occurs. In early/mid pachytene, DSBs are repaired by interhomolog crossover (CO) and synthesis-dependent strand annealing (SDSA) repair, leading to chiasma formation to physically link homologous chromosome pairs in diakinesis. In diakinesis, condensed homolog pairs are visible as six distinct bivalent structures. Different DNA repair defects cause various defects in bivalent formation and/or chromosome structure, as depicted.

(Fig. 2) [47,48]. It is thus likely that NHEJ activity is actively suppressed or competed out by more active HR in wild type germ cells [13]. In the absence of functional nucleases COM-1/CtIP and MRE-11, RAD-51 loading is impaired and fused chromosomes appear in diakinesis [49–51]. However, additional depletion of the NHEJ Ku70/Ku80 complex restores RAD-51 loading and crossover formation if a third nuclease, EXO-1, is still present. Therefore, DSB repair pathway choice was suggested to be regulated by COM-1/CtIP and MRE-11, which promote RAD-51 loading and inter-homolog repair together with EXO-1, by preventing DNA end binding of the Ku complex. In *fcd-2* mutants in which repair by crossover formation is blocked, NHEJ-mediated chromosome fusions also appear, suggesting that the FA pathway, or FCD-2 alone, also functions to prevent illegitimate NHEJ activity [52]. Together, these data show that DSB induction as well as DSB repair are strictly controlled in early prophase I of meiosis in a spatio-temporal manner, not only to ensure that essential crossovers are formed but also that any remaining DSBs are effectively and accurately eliminated at the right time.

2.3. Apoptosis in pachytene

In wild type *C. elegans,* not all germ cells mature into oocytes but approximately half of the cells in pachytene undergo apoptosis. Excessive DNA damage or the inability to repair DNA damage leads to increased levels of apoptosis, which is restricted to late pachytene cells and not observed in the mitotic germ cell compartment or somatic tissues [5]. Inhibition of DNA damage induced apoptosis increases embryonic lethality, suggesting that apoptosis serves as a last quality check to eliminate cells that cannot form viable offspring. DNA damage is signaled by a conserved checkpoint mechanism involving many of the same proteins that activate mitotic germ cell cycle arrest, including ATM-1, ATL-1 and the 9-1-1 complex [5,11,15,17]. However, apoptosis induction additionally depends on CEP-1/p53, whose activation leads to transcriptional up regulation of the BH3-only genes *egl-1* and *ced-13* that activate the apoptotic machinery [5,15,53–55]. It is not exactly known why apoptosis only occurs in late pachytene and not for instance earlier in prophase I when DSBs are induced. One of the mechanisms involved may be the regulation of CEP-1 expression and activity, which is restricted to late stage pachytene cells, as mutations in genes that regulate its transcription or activity sensitize cells to CEP-1-dependent DNA damage-induced apoptosis [56–59]. Detailed discussions on DNA damage and germ cell apoptosis have been provided by others [9].

Unrepaired SPO-11 or IR-induced DSBs and many other types of DNA damage cause increased apoptosis [4,5]. UV-induced apoptosis is mediated by the same checkpoint mechanism that signals DSBs but is absent in NER mutants [18,19]. Similarly, apoptosis induction by misincorporated uracil is not observed in the absence of the uracil glycosylase UNG-1 or APN-1, which is the endonuclease that processes apurinic/apyrimidinic sites generated by UNG-1 [21,60]. This shows that both NER and BER are functional in pachytene and indicates that active lesion processing by these pathways leads to checkpoint signaling. Remarkably, this is in sharp contrast to the response of UV-irradiated mammalian somatic cells, in which apoptosis is strongly induced in the absence of functional NER. In GG-NER *C. elegans* mutants, UV damage furthermore causes an expansion of the pachytene region without the formation of diakinesis oocytes, confirming that GG-NER maintains DNA integrity in the germ line [18]. Also, ICL-induced agents induce apoptosis, but similar as in mitotic germ cells this may occur independent of lesion processing by ICLR proteins [61]. ICL-induced apoptosis is increased in *fcd-2* mutants, suggesting that these types of lesions are otherwise repaired in pachytene by ICLR. Interestingly, elevated apoptosis levels in *fcd-2* mutants are dependent on LIG-4, indicating that NHEJ generates the substrate that induces checkpoint activation and apoptosis in the absence of FCD-2 [52]. Taken together, in the immortal *C. elegans* germ lineage, genome maintenance critically depends on error-free, *i.e.*, HR, and whole genome caretaking, *i.e.*, GG-NER, DNA repair pathways. It will be interesting to find out whether repair of lesions other than DSBs can take place any time during early meiotic prophase I and also after cells have exited the pachytene stage. Possibly, repair is only allowed to take place before apoptosis can be induced, which serves as a last resort to eliminate cells damaged beyond repair. The tight spatial temporal control of DSB repair modes, due to the importance of the forming and resolution of the crossover, could imply that perhaps other repair pathways may similarly be controlled in a developmental manner to ensure proper progression of meiosis. This is, however, currently not known.

3. DDR in embryogenesis

Upon pachytene exit, germ nuclei progress through diplotene and diakinesis and enter the spermatheca at ovulation, after which

oocytes are fertilized and complete meiosis I and II (Fig. 1). Shortly after this, the first embryonic cell divisions occur, producing 550 cells in 6 h (early stage embryos), which is followed by an 8 h period with almost no divisions (late stage embryos) [13]. As cell cycle progression in early embryos needs to occur rapidly, with alternating M and S phases without clear gap phases, there is little time for DNA repair. An ATL-1/CHK-1 mediated checkpoint mechanism functions in asynchronous timing of some of the earliest embryonic cell divisions [62]. Unscheduled cell cycle delay because of replication failure, by interfering with replication itself or after extensive DNA damage accumulation, also activates the ATL-1/CHK-1 checkpoint, causing developmental defects [14,62,63]. Therefore, checkpoint activation by DNA damage is actively suppressed, which may explain that in *C. elegans* early embryonic growth is overall relatively resistant to DNA damage induction [64]. This surprising phenomenon of resistance to DNA damage and avoidance of checkpoint activation is mediated by TLS, which replicates damaged DNA preventing replication fork stalling [65,66]. TLS allows growth to continue and seems more important than DNA repair in this developmental stage. POLH-1/polymerase η mediates the embryonic resistance to many types of DNA damage, including those induced by UV, IR and cisplatin, and acts synergistically with POLK-1/polymerase κ in resistance to lesions induced by methyl methanesulfonate [66]. The PIAS SUMO E3 ligase GEI-17 regulates the activity of POLH-1 and possibly POLK-1, by SUMOylation, preventing its degradation until damaged DNA has been replicated [66,67]. In contrast to its importance in early embryogenesis, TLS appears less important in later development.

The choice of DSB repair pathway in the embryo is for a large part dictated by the developmental and proliferation status of cells. Proliferating cells in the early embryo mainly depend on HR, whereas the uniformly arrested somatic cells in the late embryo mainly depend on NHEJ [13]. Following specification of the germ and somatic cell lineages, cells also change repair strategies. In particular, primordial germ cells likely rely on error-free and whole genome caretaking DNA repair pathways. Somatic cells arrest in G1 phase in late stage embryos, but the Z2 and Z3 germ line precursor cells are transiently arrested in G2 phase in early and late stage embryos [68]. Because homologous repair templates are available in G2, error-free repair of DSBs *via* HR is possible despite the growth arrest. Indeed, IR-treatment of late stage HR defective embryos leads to germline proliferation defects and sterility, whereas IR-treatment of NHEJ defective late stage embryos only causes various somatic developmental defects [13]. Similarly, UV-irradiation of GG-NER but not of TC-NER deficient embryos (HL and WV, unpublished results) and young larvae [69] leads to germline development failure. UV irradiation of late stage TC-NER deficient embryos only causes somatic growth delay and arrest [18], indicating that TC-NER is more important to somatic cells. Thus, these data suggest that DNA repair accurately maintains the whole genome in the germ cell lineage in the embryo, which is similar to germ cell DDR in adult animals but contrasts DDR in somatic cells.

4. DDR in somatic cells

During embryonic and larval development, *C. elegans* somatic cells follow an invariant lineage and cannot be replenished by stem cells when fatally damaged. Remarkably, somatic cells in larvae and adult worms are much more resistant to IR than germ cells and do not activate ATM in response to DNA damage. This peculiar feature is likely due to transcriptional repression of checkpoint signaling proteins, including ATM-1, ATL-1, CHK-1, CHK-2 and CEP-1, in the majority of somatic cells [70]. Thus, it may be that *C. elegans* retains damaged somatic cells, which may preserve partial function as supporting tissue of the germ cells and early embryos, rather than to discard them. Somatic cells do express many different DNA repair genes, albeit at lower levels than germ cells [71], and multiple complementary DSB repair pathways are highly active in dividing somatic cells during development, including HR, NHEJ, SSA and microhomology-mediated end joining [72]. However, limited DSB repair was observed in postmitotic cells in adult animals suggesting repair declines with age.

NER proteins are also expressed in developing larvae and in young and aging adult animals but at a lower level than in embryos [71,73]. UV photolesions, particularly in active genes, are efficiently repaired throughout development but NER capacity declines with age as well [73,74]. In contrast to IR, UV irradiation leads to larval growth delay and even arrest in NER mutants. This is likely due to transcription inhibition, which is effectively induced by UV but not by IR. Loss of transcriptional competence after UV irradiation, as observed in NER mutants, is associated with degradation of the large RNA polymerase II subunit [75]. UV-induced arrest is therefore specifically observed in TC-NER mutants but not in GG-NER mutants [18,76], indicating that maintenance of active genes rather than the entire genome is crucial to somatic cell function.

5. Systemic responses of DNA damage

DDR is not only determined by the cellular context, but can also be influenced in a cell-non-autonomous manner and/or by the environment. Signals originating from somatic tissues, for instance, can promote DNA damage-induced germline apoptosis [77,78]. Environmental cues sensed by *C. elegans* might similarly influence DDR, likely to regulate development, tissue maintenance and reproduction. For instance, HIF-1, a transcription factor responsive to environmental hypoxia, triggers TYR-2 tyrosinase secretion from the ASJ sensory neurons which increases DNA damage tolerance in pachytene germ cells by suppressing DNA damage induced apoptosis [79]. Also dauer larvae, which form as a specialized diapause stage in response to unfavorable environmental conditions, show increased UV resistance [75]. In line with this, mutations in genes that control the entrance into the dauer larval stage, *i.e.*, the insulin/IGF-1 receptor *daf-2* and its downstream PI_3 kinase *age-1,* increase UV resistance as well and alleviate UV-induced developmental arrest [69,80]. This is dependent on the DAF-16 FOXO transcription factor, which is activated by persistent transcription-blocking lesions. Together with the GATA transcription factor EGL-27, activated DAF-16 transcriptionally promotes maintenance and developmental growth of somatic tissues [69].

DNA damage therefore not only influences individual cell function but may also affect the fitness of an organism in a cell non-autonomous manner. On the organismal and population level, DNA repair defects cause a growth delay, reduced health and decreased replicative lifespan, which is due to DNA damage and mutation accumulation and corresponds to the degree of DNA repair deficiency [27,81–83]. Excessive DNA damage, in particular in the absence of repair, furthermore reduces tissue functionality and post mitotic adult lifespan [60,71]. In TC-NER deficient mouse models, DNA damage accumulation causes upregulation of stress responses [3]. Surprisingly, this seems to protect against renal-ischemia reperfusion-induced oxidative stress [84]. Similarly in *C. elegans*, loss of NER and BER causes a compensatory transcriptomic modulation of growth and stress response pathways, particularly antioxidant defenses, which appears to depend on active signaling by DNA damage detection proteins [81,85,86]. Such adaptive hormetic responses may promote survival and partially compensate the negative effects of DNA repair deficiency [87] and could be

responsible for life span extension observed when NER is absent in long lived *daf-2* mutant animals [81]. Indeed, endogenous and exogenous DNA damage induction in the germ line triggers a systemic stress response that activates the innate immune system *via* the ERK MAP kinase MPK-1, which increases stress resistance in somatic cells [88]. Such a response may serve to strengthen somatic tissue function to extend reproductive lifespan until damage in the germ line is repaired.

6. *C. elegans* as role model

Due to its genetic tractability and defined lineage commitment, *C. elegans* is a valuable model to discover DDR mechanisms which otherwise might not have been easily identified. An important additional advantage of the worm is that DDR can be studied in the context of a whole organism. As elaborated above, research in *C. elegans* indicates that the cellular and developmental context is of major influence on the response of a cell to DNA damage. Germ cells show DDR strategies aimed at error-free protection of the whole genome and elimination of damaged cells. DDR in somatic cells, on the other hand, is focused at somatic maintenance, *i.e.*, continuation of growth and function. One of the questions is how this correlates to cell-type specific differences that may exist in higher organisms and whether such differences play a role in hereditary DDR deficiency diseases and/or different forms of cancer. Some studies indeed indicate that similarly different DDR strategies are employed in mammals. For instance, murine astrocytes display reduced checkpoint signaling but retain DNA repair ability by NHEJ upon terminal differentiation from neural stem cells [89]. Furthermore, several mammalian cell types lose the ability to repair UV lesions at a global genome level but retain repair of active genes upon *in vitro* differentiation [2].

In spite of the potential benefits of *C. elegans*, some DDR mechanisms appear to be less complex or even absent in the worm. DNA damage in mammalian cells elicits intricate signaling networks involving extensive chromatin modification and ubiquitylation and phosphorylation events but many of the important players, such as for instance histone variant H2AX and signaling proteins MDC1 and RNF8, have not been identified by sequence analysis in *C. elegans*. Additionally, certain repair proteins appear to be absent, such as for instance some regulators of NHEJ and the FA core complex. This provokes the question why an organism can apparently do without these elaborate signaling or repair complexes whereas they seem important to others. It is possible that some orthologs have so far escaped detection as their conservation is not directly evident from the sequence level or because other proteins act as functional orthologs. A functional homolog of the essential mammalian TC-NER gene CSA was for instance only recently described. This protein was hitherto not noticed because it is almost completely composed of WD40 domains that are found in many related proteins as well [76].

Although DDR appears less complex in *C. elegans*, this reduced complexity can be considered an advantage when it comes to understanding the basic principles of DDR mechanism regulation. In addition, the intricate contextual environment in which DDR proteins and pathways function and the crosstalk between different DDR processes may be more easily understood in less complex animal models. An important aspect of DDR is the regulation of chromatin structure, but how chromatin modifications and remodeling contribute to DDR is not yet well understood. Starting with genetic screening in *C. elegans*, recently the ISWI-family of ATP-dependent chromatin remodelers was shown to regulate both mammalian DSB repair and TC-NER [18,90–93]. These studies point to an evolutionary conserved function of such chromatin remodelers in DDR and suggest that *C. elegans* is an adequate model to study the relation between chromatin and DDR. Notably, chromatin organization changes drastically *in vivo*, when germ cells progress through meiosis and somatic cells differentiate. Thus, it will be especially interesting to study the causal relation between changing chromatin environments and DDR during development. With the identification of new genes and mechanisms, in combination with the recent advance in genome editing techniques such as CRISPR/Cas9, which allow the introduction of site-specific mutations and the affinity or fluorescent tagging of endogenous genes, *C. elegans* will therefore be a valuable asset to understand full DDR regulation *in vivo*.

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