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Review

Systemic DNA damage responses in aging and diseases

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ABSTRACT

The genome is constantly attacked by a variety of genotoxic insults. The causal role for DNA damage in aging and cancer is exemplified by genetic defects in DNA repair that underlie a broad spectrum of acute and chronic human disorders that are characterized by developmental abnormalities, premature aging, and cancer predisposition. The disease symptoms are typically tissue-specific with uncertain genotype–phenotype correlation. The cellular DNA damage response (DDR) has been extensively investigated ever since yeast geneticists discovered DNA damage checkpoint mechanisms, several decades ago. In recent years, it has become apparent that not only cell-autonomous but also systemic DNA damage responses determine the outcome of genome instability in organisms. Understanding the mechanisms of non-cell-autonomous DNA damage responses will provide important new insights into the role of genome instability in human aging and a host of diseases including cancer and might better explain the complex phenotypes caused by genome instability.

1. The cellular DNA damage response (DDR)

The genetic information is constantly threatened by a plethora of genotoxic attacks. DNA damage can be caused by a variety of exogenous or endogenous agents. The first are environmental agents such as ultraviolet (UV) light, ionizing radiation (IR), as well as many genotoxic chemicals. The latter are by-products of cellular metabolic circuits such as oxidative respiration or events such as lipid peroxidation, which give rise to reactive oxidative species (ROS). In addition, spontaneous events constantly challenge the stability of DNA chemical bonds [1]. Depending on the source of damage, DNA can be affected in different ways, varying from single-strand breaks (SSBs), abasic sites and modified bases to highly toxic lesions such as small or bulky adducts and lesions, interstrand crosslinks (ICLs) and double-strand breaks (DSBs) (Fig. 1). Lesions might compromise DNA metabolism by interrupting replication or transcription. It is thought that DNA damage accumulation with aging results in loss of cellular functionality and ultimately degeneration of cells and tissues. Erroneous repair, however, can lead to mutations and chromosomal aberrations, which when affecting tumor suppressor genes, drive carcinogenesis. Alternatively, unrepaired DNA lesions can lead to cell malfunction or cell senescence and eventually cell death. Importantly, DNA damage compromises regenerative capacities of stem cells and disturbs tissue integrity ultimately driving multiple pathologies during the aging process. It is thus essential for the organism to preserve the stability and integrity of its genome.

The sophisticated machineries that respond to DNA damage are highly conserved throughout evolution. In addition to complex DNA repair pathways, special DNA damage-induced checkpoints temporarily halt cell cycle progression providing a time window for the cell to repair the lesions. The unscheduled cell cycle arrest in turn is associated with modulation of many of the cell's physiological circuits. Thus, the cellular response to DNA damage called 'the DNA damage response' (DDR) turned out to be a vast signaling network encompassing the repair mechanisms and numerous signaling pathways, presenting one of the most comprehensive cellular responses to a stimulus.

2. Defective DDR and human disease

The relationship between genome stability and human health is illustrated by the genome instability syndromes, typically characterized by progressive degeneration of specific tissues, cancer predisposition, chromosomal instability, and hypersensitivity to

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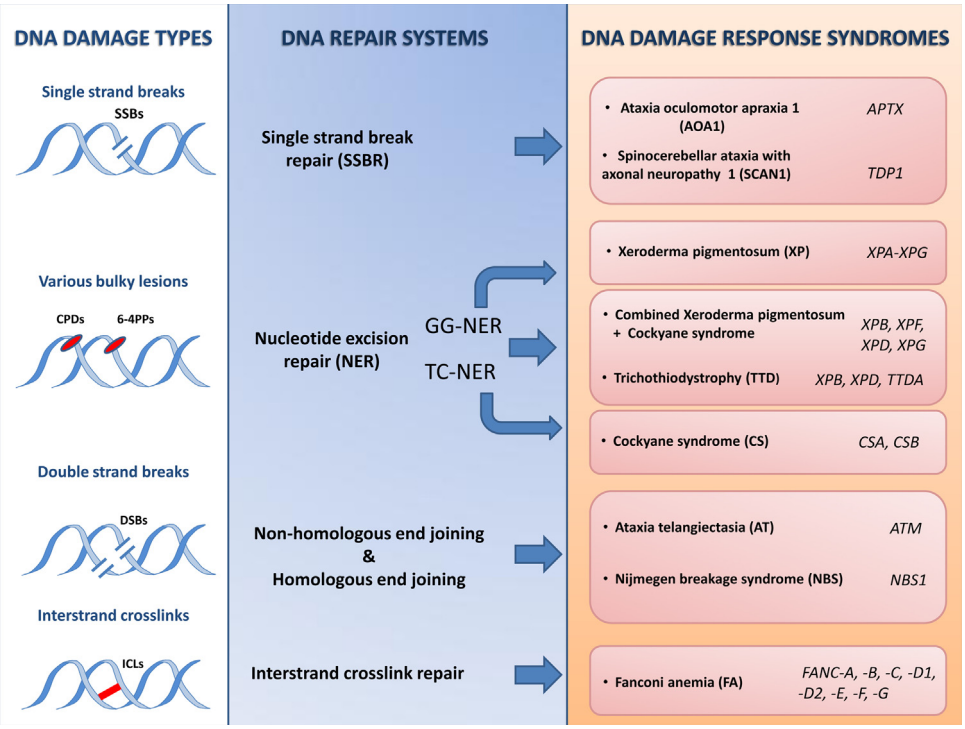

Fig. 1. Examples of distinct DNA damage repair and response defects leading to genetic disorders in humans. Various damage types including SSBs, bulky lesions, DSBs and ICLs require single strand break repair, nucleotide excision repair (NER), homologous and non-homologous end joining and interstrand crosslink repair, respectively. Defects in DNA damage response pathways lead to genome instability and consequently to complex syndromes characterized by tissue degeneration, cancer susceptibility, developmental defects, and premature aging.

DNA damaging agents [2,3]. The large variety of damage types requires specialized repair machineries. Mismatch repair (MMR) corrects errors that stem from mismatches that occurred during DNA replication, base excision repair (BER) removes small chemical alterations of bases, which could miscode and therefore result in mutagenesis. More complex damage types such as bulky lesions are resolved by nucleotide excision repair (NER), while homologous recombination and non-homologous end joining (HR and NHEJ) repair DSBs, and an elaborate enzymatic cascade repairs SSBs. The highly toxic ICLs are removed in a complex repair reaction involving the Fanconi anemia (FA) proteins [4]. While each of those repair systems is of paramount importance for human health, we will here focus on the consequences of dysfunctional NER and aberrant responses to DSBs to exemplify cell-autonomous and systemic DNA damage responses and their role in disease.

2.1. Complex consequences of DNA repair deficiencies in human disease: distinct outcomes of defects in nucleotide excision repair (NER) in development, aging, and cancer

Nucleotide excision repair deals primarily with helix-distorting DNA lesions such as UV-induced cyclobutane pyrimidine dimers (CPDs) and pyrimidine 6–4 pyrimidones (6–4PPs) that interfere with replication and transcription. These intrastrand dimers are resolved by removal of the damaged stretch of the strand and refilling of the gap by using the complementary strand as a template. The helix distortion is recognized by two different subpathways: global-genome NER (GG-NER) which scans the whole genome, and transcription-coupled NER (TC-NER) dealing with damage that blocks elongating transcription machineries. Defects in GG-NER give rise to the cancer-prone syndrome, xeroderma pigmentosum (XP). XP is characterized by pigmentation abnormalities, sun sensitivity, atrophic skin and most severely, leads to markedly elevated skin cancer. Mutations in one of seven genes (*XP-A* to *G*) that are involved in NER have been identified in XP patients. In addition, XP can be caused by mutations in *XP-V*, which instead of functioning directly in NER encodes the DNA polymerase eta that can bypass UV-induced lesions thus instead of repairing tolerates lesions during replication. By contrast, TC-NER defects do not lead to cancer susceptibility but instead cause Cockyane syndrome (CS) that is characterized by severe growth and intellectual impairment and multiple manifestations of premature aging. Mutations in the genes *CSA* and *CSB* (CS complementation group A and B) have been identified in CS patients. Specific mutations in the same two genes can give also rise to the even more severe cerebro-oculo-facio-syndrome (COFS) or the mild UV-hypersensitivity syndrome [5] with uncertain genotype–phenotype correlations. Notably, different mutations in the same gene can lead to different pathologies; for example, mutation in the *XPD* gene can lead either to XP or trichothiodystrophy (TTD). TTD patients share many similarities to CS patients, but in addition display characteristic brittle hair and nails[6]. Moreover, mutated *XPD*, *XPB*, *XPF* and *XPG* can result not only in XP but also in a very rare XP–CS combination depending on the specific mutations. Genetic mouse models were generated to further investigate the disease mechanisms underlying the distinct NER syndromes. NER-deficient mice recapitulate the UV sensitivity and develop skin cancer upon low doses of UV irradiation. Mutations in single genes, such as *Csa* or *Csb*, however, do not result in overt disease phenotypes as in the human patients [7]. Only further abrogation of NER by ablation of genes such as *Xpc* or *Xpa* recapitulate the severe growth retardation and premature aging observed in CS patients [8]. Mutations in *Ercc1*, *Xpf* or *Xpg*, in contrast, are sufficient for triggering postnatal developmental failure and accelerated tissue degeneration [9,10].

Taken together, these syndromes have established that specific molecular defects in responding to DNA damage lead to distinct pathological outcomes: mutations that increase the mutation rate, such as GG-NER defects, elevate cancer risk, while defects that ham-

per transcription-coupled repair impair developmental growth and tissue functionality, ultimately accelerating the aging process. However, the human pathologies as well as the murine models also exemplify the vast complexity of physiological outcomes of alterations in the DNA metabolism. Importantly, the DNA repair defects and cellular sensitivities to genotoxic insults alone cannot entirely explain the pathologies and physiological alteration observed in the patients or animals models of NER deficiencies.

2.2. The cellular response to DNA double-strand breaks (DSBs)

The DDR is most vigorously activated by DSBs. Following induction by this highly cytotoxic DNA lesion, the DDR mounts up as a vast signaling network that activates not only DSB repair mechanisms but in addition sets in motion numerous pathways, which rapidly modulate many physiological processes [4,11–16]. DSBs can be induced by ionizing radiations, radiomimetic chemicals, or endogenous reactive oxygen species [17]. They also accompany physiological genomic transactions such as meiotic recombination [18,19] and the rearrangement of antigen receptor genes in the adaptive immune system [20]. DSBs are ultimately repaired via direct NHEJ or through HR-mediated recombination between sister DNA molecules. The NHEJ process can be divided into several subpathways [21–24]. HR is also involved in resolving replication fork breakdown and, together with the Fanconi proteins, removes interstrand crosslinks (ICLs). These lesions are challenging to repair as both strands are damaged. HR is more accurate as it takes place in S and G2 phases of the cell cycle when the DNA is replicated and therefore a second copy of the sequence is available, whereas NHEJ occurs throughout the cell cycle including the G1 phase when no undamaged copy is present that could be used as a template. However, DSB repair constitutes just one branch of the larger DSB response, which also activates special cell cycle checkpoints, modulates gene expression, alters protein turnover and activity, and affects many other cellular circuits. This extensive network is based on a group of *bona fide* DDR players, but it also turns to other arenas of cellular metabolism to temporarily recruit numerous players to the DDR where they undergo specific post-translational modifications (PTMs) [12,13,16,25–27]. The DSB response begins with *sensor*/*mediator* proteins which are rapidly recruited to the damaged DNA sites where they form large structures at nuclear foci [28] in a finely regulated manner [12,13]. While chromatin is reorganized around the break site and the DSB ends are processed in preparation for repair, a signal, whose physical identity is not entirely clear, is sent to the *transducers*—powerful protein kinases that subsequently relay the signal to numerous downstream *effectors* involved in a multitude of pathways.

2.3. Mutations that abrogate the DDR lead to complex diseases involving tissue degeneration, cancer susceptibility and accelerated aging

The primary transducer of the DSB response network is the protein kinase, ATM [14,16,29], and its activity is markedly enhanced in response to DSBs. Full and timely activation of ATM is dependent on the MRE11-RAD50-NBS1 (MRN) complex – a central DSB sensor [30,31] – and is accompanied by a flurry of PTMs on the ATM molecule, including several autophosphorylations and acetylations [14,16,32–36]. Activated ATM then phosphorylates numerous players in various pathways of the DSB response [16,36–39]. Among others, ATM phosphorylates checkpoint kinase 2 (CHK2), which is activated by this phosphorylation, and p53, which is activated and stabilized. Both are involved in the induction of senescence and apoptosis [40]. ATM's substrates include other protein kinases, which are activated via their ATM-mediated phosphorylation, and in turn phosphorylate their own targets. Hence, this phosphorylation network is multi-layered [39]. ATM also impacts tumor suppression through the senescence regulator ARF [41], which in turn impacts NF-κB and p53 through the DDR kinases ATR and CHK1 [42]. It was recently proposed that ATM might be involved in many DNA repair pathways and other aspects of genome stability by virtue of its ability to phosphorylate key players in these pathways, in addition to its cardinal role as the mobilizer of the DSB response [43]. Thus, ATM probably tends to the daily wear and tear of the genome, beyond its response to DSBs. While ATM's role in the DSB response is its most extensively studied function, ATM has recently emerged as a homeostatic protein kinase that is active in other stress responses and in several metabolic circuits [16,44,45]. Notable among them are redox balance [44,46], glucose and lipid metabolism, mitochondrial homeostasis and peroxisome-associated autophagy [16,44,45,47–51].

ATM belongs to a family of PI-3 kinase-like protein kinases (PIKKs) [52,53]. This family includes, among others, the catalytic subunit of the DNA-dependent protein kinase (DNA-PKcs), which is involved in the NHEJ pathway of DSB repair and probably also in other genotoxic stress responses [54,55] and ATR, which responds primarily to stalled replication forks [11,56]. Evidence suggests a considerable degree of redundancy and collaboration between these three PIKKs, which preferably phosphorylate Ser or Thr residues followed by Gln (S/TQ motif) [11–13,53,57].

Prototypic genome instability syndromes resulting from defective response to DSBs are ataxia-telangiectasia (A-T) and Nijmegen breakage syndromes (NBS) [58]. A-T, which is caused by null mutations in the *ATM* gene, includes progressive neurodegeneration—primarily of the cerebellum, immunodeficiency, oculocutaneous dilated blood vessels (telangiectasia), cancer predisposition and acute sensitivity to ionizing radiation and other DSB-inducing agents [59]. NBS shares with A-T the immunodeficiency, cancer predisposition and extreme sensitivity to ionizing radiation (IR), but has distinct neurological manifestations—microcephaly and intellectual impairment [60]. NBS is caused by hypomorphic mutations in the *NBS1* gene, which encodes the NBS1 component of the MRN complex.

Also defects in repairing ICLs lead to cancer-susceptibility and segmental (*i.e.*, tissue specific) progeroid features in FA patients. FA is manifested by pancytopenia, which is triggered by increased apoptosis in hematopoietic cells as well as leukemia resulting from high levels of chromosomal aberrations [61]. Therefore FA gives rise to both cancer and accelerated-aging phenotypes such as stem cell exhaustion. Mutations in genes encoding key players in SSB repair give rise to disorders involving primarily various patterns of neurodegeneration [62]. Also mutations in several RecQ helicases cause syndromes that are characterized by cancer susceptibility and, due to the relatively late onset of the disorders, some of the most recognizable features of accelerated aging. Werner, Bloom, and Rotmund–Thomson syndromes are caused by mutations in the WRN, BLM, and REQL4 helicases that are important for genome maintenance during replication and recombination repair [63]. In contrast, structural defects in the nuclear lamina result in progeroid features without markedly elevating the cancer risk in Hutchison–Gilford progeria syndrome (HGPS) or mandibuloacral dysplasia (MAD), which are caused by mutation in the *LMNA* or *ZMPSTE24* genes [64].

Recent evidence suggests that variation in DDR efficiency also contributes to a variety of metabolic diseases [65], and ATM was specifically implicated in critical metabolic circuits, such as redox balance, glucose and lipid metabolism, mitochondrial and peroxisomal homeostasis [16,45,47–50,66]. Notably, in mice, loss of one or two *Atm* alleles aggravates the metabolic syndrome of apoE-deficient animals [67–69], and murine Atm was implicated in regulation of adipocyte differentiation [48].

Taken together, defects in the DNA damage response machinery have provided insight into the complexity of the organism's systemic responses to DNA damage, which cannot be explained by cell-autonomous consequences of DNA damage alone. This is exemplified by the specificity of the phenotypes described above, as different mutations sometimes even in the same genome maintenance gene can lead to diverse disease features. The phenotypic complexity is also reflected in the pathologies in mouse disease models, some of which have been engineered to carry the exact same disease causing mutations that are found in human patients.

3. Non-cell autonomous DNA damage responses

An important DDR factor that is activated by ATM in response to DSBs is the p53 protein. p53, once coined as the "guardian of the genome", functions as a tumor suppressor protein by inducing transient cell cycle arrest, which can lead to cell senescence or cell death in response to DNA damage or oncogenic growth signaling [70]. Roughly half of all human tumors carry mutations in the *TP53* gene encoding p53. While loss of p53 function fuels aberrant cell proliferation and thus tumorigenesis, constitutive p53 activity can result in premature tissue degeneration as it prevents cell proliferation necessary for stem cell renewal and triggers aberrant apoptosis ultimately leading to tissue degeneration. The effects of increased activity of p53 were studied in mice that express a constitutively active *Tp53* alleles [71,72]. The animals exhibited reduced cancer frequencies but significant decrease in lifespan and signs of accelerated aging. Therefore, the balance of p53 levels and activity are critical in terms of cancer predisposition and in lifespan. Indeed, a "super-p53" mouse that carried an extra copy of p53 was more cancer protected than mice with only two copies of the p53 genes [73]. Addition of an extra copy of the gene encoding the tumor suppressor ARF ("super-Arf-super-p53" mouse) led to further protection from cancer and the mice outlived wild-type mice [74]. Intriguingly, p53 activity was shown not only to be a key factor in the DDR but also to have cell-non-autonomous consequences by promoting clearance of damaged cells through the activation of the innate immune system [75,76]. Indeed, the DDR also has non-cell autonomous consequences through the senescence-associated secretory phenotype (SASP) [77].

3.1. Aging, cell senescence and the DDR

It is becoming clear that individual differences in maintaining genome stability are responsible for a substantial part of the vast variation in aging and associated diseases [3,78–83]. This is vividly exemplified by the segmental (tissue-specific) accelerated aging observed in several genome instability syndromes in humans and mouse models of DNA repair deficiencies [3,84–86]. On the other hand, evidence mounts of the intimate connection between the organism's aging and cell senescence. Cellular senescence, which can be induced by various stresses, has been implicated in development, wound healing, tissue repair and aging [87–92]. It is now well established that senescent cells accumulate during aging [77,80,88,91,93–95] and are involved in many age-related pathologies, including, ironically, cancer [88,90]. Strikingly, cell senescence may lead to different outcomes – suppression of malignancy or acceleration of aging – depending on the context and persistence of senescent cells *in vivo* [88,90,91]. Thus, cellular senescence is an example of the antagonistic pleiotropy theory that poses that processes that are beneficial early in life may be harmful later. We will in this context particularly focus on the non-cell-autonomous consequences of cellular senescence that have emerged in recent years.

The hallmark of cellular senescence is an irreversible arrest of cellular proliferation. The main pathways that lead to this cell cycle arrest are governed by two tumor suppressor axes: the p53–p21 axis and the $p16^{INK4a}$-pRB axis. Importantly, rather than a finite, static end point, the senescent state is complex and dynamic due to a senescence-associated secretory phenotype (SASP)—the secretion, by senescent cells, of a suite of cytokines, growth factors and proteases that promote tissue repair and regeneration or inflammation [87,90,91]. The SASP is a plastic phenotype, and its composition varies with genotype, cell type and senescence stimulus. Chronic presence of senescent cells and a persistent SASP cause local and systemic inflammation, which fuels a variety of age-related diseases. Evidence for this has been obtained in a number of mouse models [90,92,96–98]. The role of cellular senescence in aging is particularly well illustrated in mice with defective BubR1 protein - a component of the mitotic checkpoint for spindle assembly [99]. These mice display multiple progeroid features and vastly elevated amounts of senescent cells. The causal role of cellular senescence in the progeroid phenotype of these animals was demonstrated by the addition of mutant $p16^{Ink4a}$ gene that abrogated the senescence program thus alleviating the pathology of the *BurbR1* mutant mice [100]. Intriguingly, elimination of senescent cells in these mice by expressing a caspase-8 transgene under the control of a $p16^{Ink4a}$ promoter attenuated the aging phenotype [96]. Strikingly, these results suggested that clearance of senescent cells is sufficient to reverse age-related pathology.

SASP might also stimulate the growth of tumors, by secreting for example factors such as amphiregulin and growth-related oncogene (GRO)α and high levels of IL-6 and IL-8. For instance, it was observed in xenograft studies, that senescent fibroblasts stimulated progression and hyperproliferation of premalignant epithelial cells resulting in formation of xenograft tumors [101]. This stimulation was shown to be in part due to SASP factors released by senescent cells, particularly matrix metalloproteinases (MMPs) [102].

Among the most potent inducers of the SASP are genotoxic stresses and conditions that lead to persistent DNA damage signaling [103]. Indeed, several DDR players, including ATM, NBS1 and CHK2, are involved in establishing and maintaining the SASP [104]. Thus, the senescence response, and particularly the SASP, is a strong candidate for linking aging phenotypes and age-related rises in genotoxic stress [105,106]. The Janus face of SASP, with beneficial aspects as opposed to its role in detrimental inflammatory and degenerative events is further exemplified in recent findings suggesting the involvement of cell senescence in embryonic development. Senescent cells were found in many tissues throughout the embryo and in known signaling centers in embryonic patterning, including the apical ectodermal ridge (AER) and the neural roof plate [107,108]. Moreover, SASP was recently found to be involved in tissue repair and wound healing, by inducing myofibroblast differentiation through the secretion of a SASP factor, platelet-derived growth factor AA (PDGF-AA) [87]. Impairment in the wound healing process is generally observed in healthy older individuals [109]. SASP was suggested to play a role in repairing of wound tissue by preventing fibrosis. For instance, senescent hepatic stellate cells (HSCs) accumulate in damaged liver and prevent liver fibrosis by inducing collagen degradation and upregulation of secreted matrix metalloproteinases, which have fibrolytic activity [110]. It was also proposed that the matricellular protein CNN1, expressed during wound healing, induced fibroblasts into senescence and restricts fibrosis by upregulating antifibrotic genes [111].

DDR can thus play a health-promoting role mainly by suppressing tumorigenesis but also by cell-non-autonomously supporting wound healing and preventing fibrosis through the SASP. During embryogenesis growth cues secreted by senescent cells might support tissue development. In contrast, chronic DDR could trigger systemic inflammation and tissue degeneration. Particularly

studies that elevated tumor suppressor gene dosage or eliminated senescent cells could promote health and might potentially support extended healthspan during aging.

3.2. Link between DNA damage and the innate immune system

Cell senescence is thought to also play a key role in inducing tissue degeneration in part mediated through chronic inflammation [77]. It is widely accepted that chronic inflammation is an important contributing factor in aging and aging-related diseases. This concept was strengthened by previous studies, which identified an elevated expression of inflammatory genes in progeroid and normal aged mice [112]. Moreover, studies in a NER-deficient mouse model with mutated *Ercc1* gene [83] identified a link between the unresolved DNA damage and lipodystrophy. This was mediated by a chronic auto-inflammatory response which responded to unrepaired DNA damage in an ATM-dependent manner [79]. At the systemic level, a remarkable link has been shown between DNA damage responses and activation of the immune system in order to promote the clearance of damaged cells. An important example is the activation of the ATM-NF-κB essential modulator (NEMO; IKK) axis by DSBs. DNA damage causes activation of ATM mediated by the induction of DSBs and SUMOylation of NEMO. ATM is then mediating the phosphorylation of NEMO which leads to the cIAP1-dependent monoubiquitination of NEMO. This allows the translocation of ATM and NEMO to the cytoplasm where ELKs and TRAF6 are polyubiquitinated and NEMO is monoubiquitinated. This induces in turn the activation of IKK *via* TANK1. The activation of IKK leads to the phosphorylation of IκBα which causes the polyubiquitination and degradation of IκBα and the release of the active NF-κB dimer [113]. In Hutchinson-Gilford progeria syndrome (HGPS) activation of ATM and NEMO resulted in an elevated secretion of inflammatory cytokines. Inhibition of NF-κB signaling could attenuate progeroid features in HGPS as well as in progeroid *Ercc1* mutants mice, supporting the idea that inflammatory responses play a major role in the aging-associated pathologies [114,115]. Moreover the link between DDR and activation of immune responses has been demonstrated in cells that were exposed to viral infection or genomic instability, leading to the expression of ligands, major histocompatibility (MHC) class I-like cell surface ligands (MICA and RAET-1 families), which bind and activate the immune receptor NKG2D present on a variety of immune cells such as NK cells, γ/δ T cells, CD8+ T cells and NKT cells [116]. The ligand induction requires the DDR kinases ATM, ATR or Chk1: blocking ATM, ATR or Chk1 inhibits ligand induction. This was tested in several murine tumor cell lines and showed as a consequence a decrease in the RAE1 levels [117]. In addition, the DDR also activates the immune system through the activity of the interferon (IFN)- regulatory factor (IRF) family of transcription factors. In particular, IRF1 induces the expression of a variety of immune system genes. Interestingly, in response to genotoxic stress, IRF-1 expression is up-regulated in an ATM-dependent manner [118,119]. Moreover, another IRF factor, IRF3, is also involved in the activation of an innate immune response in response to DNA damage, and this process is mediated by type I IFN response such as expression of IFNα and IFNβ [116]. Cytosolic DNA sensing mechanism involve sensors such as DNA-dependent activator of IRFs (DAI), which binds dsDNA and activates in turn the TANK-binding kinase 1 (TBK1)-IRF3 to regulate type I IFN response as well as absent in melanoma (AIM2), which acts through the inflammasome pathway to promote the release of interleukin (IL)-1β [79]. In order to activate the TBK1-IRF3 pathway, stimulator of IFN genes (STING) is necessary to accompany TBK1 to the endosomal compartments for the activation of IRF3/IRF7 [120,121]. Another important signaling pathway functioning upstream of STING is based on activation of cyclin-GMP-AMP (cGAMP) by direct cytosolic binding of DNA to cGMP-AMP synthase (cGAS). cGAMP has been shown to activate IRF3 by interaction with STING [122]. A recent study showed that DNA damage accumulation caused by ATM deficiency or by exogenous genotoxic stress triggers the activation of type I IFNs. This was demonstrated to prime the innate immune system for enhanced anti-viral and anti-bacterial responses. The induction in IFNs production is mediated through activation of the STING pathway [123]. Not only ATM but also p53 was demonstrated to impact components of the immune system when intercellular cell adhesion molecule-1 (ICAM-1) was demonstrated to by directly induced by p53 independently of NF-κB signaling [124]. Remarkably, another recent study has identified an alternative regulator of senescence, GATA4, previously known as a regulator of development during embryogenesis. The activation of the GATA4-mediated senescence pathway is triggered through inhibition of autophagy. GATA4 can therefore induce cell cycle arrest and senescence as well as activation of NF-κB contributing to the maintenance of the SASP. This novel pathway is dependent on ATM and ATR but independent of p53 and $p16^{INK4a}$. An increase of GATA4 levels during human aging and in normal aging mice was suggested to play a role in driving the aging-dependent inflammation [125]. Moreover NF-κB signaling has also been implicated in the local UV response in the skin. NF-κB signaling together with mitogen-activated protein kinase (MAPK) activation is triggered in response to UV-induced DNA lesions leading to a complex response, which includes both apoptosis and innate immune activation. The skin resident Langerhans immune cells, in contrast, migrate to the lymph nodes to mediate a systemic immune suppression that counteracts the inflammation at the site of UV injury of the skin [126].

The systemic role of an innate immune response that is triggered upon cell-type specific genome instability has recently been demonstrated in the nematode worm *Caenorhabditis elegans*. Adult worms are comprised of postmitotic somatic tissues and a germline, which is undergoing continuous mitotic and meiotic cell divisions. While the somatic tissues are highly radioresistant, germ cells are sensitive to DNA damage. Conserved DNA damage checkpoints halt the cell cycle of mitotically dividing germ cells and trigger *C. elegans p53 (cep-1)* mediated apoptosis in meiotic pachytene cells [97–99]. Interestingly, somatic tissues response to DNA damage in germ cells through a phenomenon naimed "germline DNA damage-induced systemic stress resistance" (GDISR) [127]. Endogenous and/or exogenous DNA damage triggers an innate immune response through the activation of extracellular signal-regulated kinases 1/2 (ERK1/2) MAPK homolog MPK-1 (mitogen-activated protein kinase-1). The putative secreted immune peptides lead to the activation of the ubiquitin-proteaosome system (UPS) in somatic tissues, which then promotes somatic endurance to multiple forms of stress such as elevated temperature. Moreover, the study showed that a similar response was triggered upon intestinal pathogen infection, which leads to the activation of p38 homolog PMK-1 (P38 MAP Kinase family-1) and also results in systemic stress resistance [127].

Recent studies revealed numerous unexpected interactions between genome maintenance responses and DDR-mediated innate immune system. Thus, the DDR induces complex systemic responses that not only trigger tissue inflammation but also support tissue maintenance and repair (Fig. 2).

3.3. The somatotropic axis and genome instability: endocrine adjustments to DNA damage accumulation in aging

Despite the physiological differences between humans and mice, progeroid mouse models based on mutations in DDR genes can provide insights on how mammals respond to unrepaired DNA damage. The developmental growth defects observed in defective NER mutants $Ercc1^{-/-}$, $Csb^{m/m}/Xpa^{-/-}$ and $Xpd^{TTD}/Xpa^{-/-}$

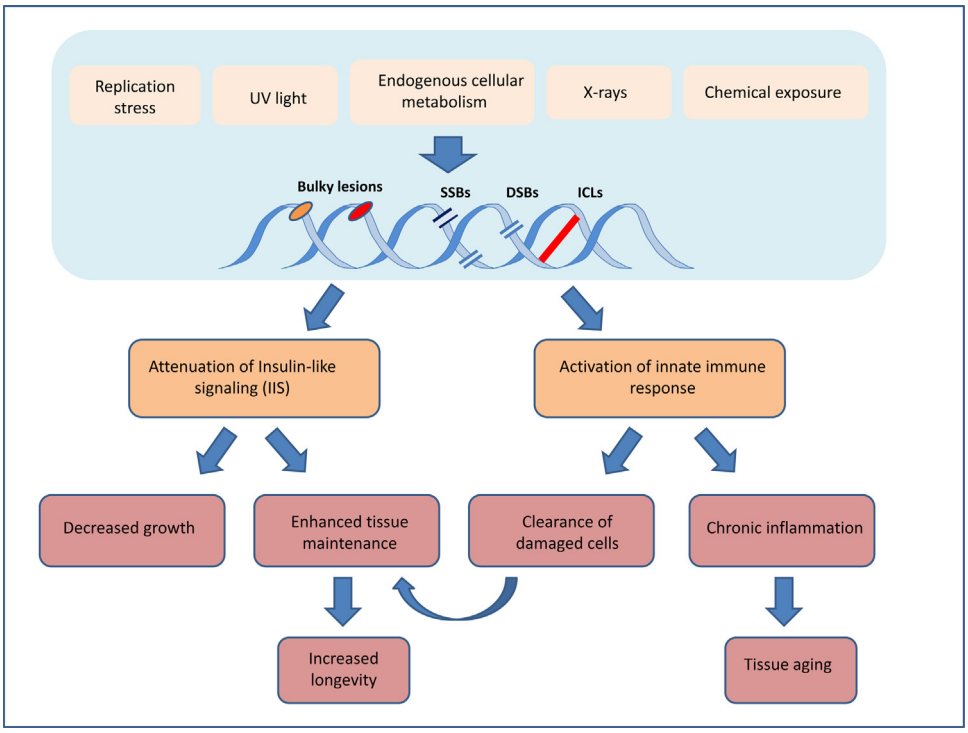

Fig. 2. Systemic responses to DNA damage. Various endogenous and exogenous genotoxic stressors damage the DNA. Cell-non-autonomous DNA damage responses, such as attenuation of Insulin-like signaling (IIS) and activation of innate immune responses result in consequences of DNA lesions beyond the genotoxically insulted cells. Attenuation of IIS leads to decreased growth as well as to enhanced tissue maintenance, which promotes survival of the aging organism. Innate immune responses can promote clearance of damaged cells, thus contributing to tissue repair and maintenance. However, chronic inflammation can severely damage tissues thus contributing to functional decline and tissue degeneration.

were associated with a systemic suppression of the growth hormone/insulin-like growth factor 1 (GH/IGF-1) somatotropic growth axis [8] [10,128]. This systemic response to genomic instability was not only observed in NER-deficient mice but also in other progeroid models, specifically in mice deficient of Sirtuin 6 – a chromatin-associated member of the sirtuin family of NAD-dependent protein deacetylases, with a role in BER – and animals deficient of Zmptse24 —a metalloprotease required for lamin A processing [129]. Insulin-like signaling (IIS) was the first genetic pathway demonstrated to regulate the lifespan of animals [130]. In mammals, growth hormone (GH), produced in the pituitary gland binds to the growth hormone receptor (GHR) present in the liver and also in other peripheral tissues, thereby inducing the synthesis of insulin-like growth factor 1 (IGF-1). This, in turn, promotes body growth due to its potent mitogenic effects [131]. Ames and Snell dwarf mice fail to develop the pituitary gland and are therefore unable to secrete GH, and this results in growth retardation and exceptional longevity [132]. Also *Ghr* knockout and overexpression of the IGF-1 antagonist Klotho and to a lesser extend heterozygocity of *Igf-1 receptor* phenocopied the extended longevity of the Ames and Snell dwarf mice [132–134]. A decrease in GH and IGF-1 has also been observed during normal aging in mice, rats, and humans. As the attenuation of the somatotropic axis leads to a longevity phenotype, it was suggested that dampening of the somatotropic axis exerts a protective role by promoting tissue maintenance at the cost of growth [135]. For instance, this was observed in the $Igfr^{+/-}$ heterozygous animals, where it was shown that attenuation of somatotrophic axis was linked to increased resistance to oxidative stress [133]. However, in progeroid animals, the attenuation of the somatotropic axis in response to DNA damage accumulation is taking place very early in their life thus hampering their normal developmental growth. Indeed, IGF-1 injections into HGPS mouse models allowed the animals to overcome their developmental growth retardation [136].

The growth promoting function of the somatotropic axis also supports the growth of tumor cells as IGF-1 is a potent mitogenic factor and most cancer cells are critically dependent of IGF-1R mediated signaling [137]. The dampening of the somatotropic axis might thus suppress tumorigenesis in DNA repair defective animals as well as during aging. Indeed, Ames dwarf mice and the *Ghr* knockout mice showed a reduction in occurrence of fatal neoplastic disorders [138,139]. Mechanistically, it was demonstrated that persistent DNA lesions that lead to stalling of transcription complexes and are the culprit in progeroid mice, such as $Ercc1^{-/-}$, $Csb^{m/m}/Xpa^{-/-}$, trigger the attenuation of the receptors of GH and IGF-1 leading to IGF-1 resistance and elevated oxidative stress resistance and thus defining instigating events in the shift from growth to somatic maintenance amid DNA damage accumulation with aging [140]. A recent study has discovered a similar mechanism in *C. elegans*, where it was shown that transcription-blocking lesions induce the attenuation of insulin/insulin-like signaling (IIS) leading to activation of the critical IIS effector, the FOXO transcription factor DAF-16 [141]. The longevity effect of the IIS pathway is highly conserved throughout organisms. For instance, in *C. elegans,* inhibition of IIS results in the doubling of the organism's lifespan. In the nematode, *daf-2* encodes the homolog of the IGF-1R and insulin receptor (IR) and a decrease in its activity as well as mutations in its downstream target PI3 kinase, *age-1*, were shown to induce an increase in the organism's lifespan [142,143]. Inhibition of IIS affects the nematode's lifespan by inducing changes in gene expression mediated by the activation of the FOXO transcription factor DAF-16, which upon IIS inactivation enters the nucleus and regulates the expression of a variety of stress-response genes [143]. Therefore, mutation in *daf-16* entirely reverts the longevity phenotype observed by blocking the IIS [144]. A direct link between DNA

damage and IIS was identified in *C. elegans*: DAF-16/FOXO is activated upon transcription-blocking UV-induced lesions in somatic tissues. DAF-16 activity leads to elevated tolerance to DNA damage as it allows proceeding of developmental growth and the maintenance of tissues even when completely NER deficient animals are incapable of repairing the DNA lesions. The DNA damage response of DAF-16 is specified by the GATA transcription factor EGL-27 that by interacting with DAF-16 induces developmental growth genes. The capacity of DAF-16 to response to DNA damage, however, declines with aging ultimately rendering the animals defenseless against increasing damage loads. Intriguingly, the attenuation of IIS and the resulting activation of DAF-16 could counteract the detrimental effects of genome instability by elevating DNA damage tolerance leading to enhanced tissue maintenance and extended longevity [141] and might thus provide an interesting opportunity for future therapies that aim at preventing age-related pathologies despite the invariant accumulation of DNA damage with aging.

4. Concluding remarks

Intense research over the past decades has provided deep insights into the mechanisms of DNA repair and the cellular response mechanisms through which DDR facilitates the repair process and prevents tumorigenesis. Insights from human DDR disorders and a variety of model systems including *C. elegans*, *Drosophila melanogaster* and mammalian disease models have recently disclosed new perspectives on the consequences of DDR on the systemic level. The mediators of those cell-non-autonomous DDR include endocrine adjustments and the secretory properties of senescent cells that impact a variety of processes including metabolism, immunity, regeneration and tissue maintenance. Further mechanistic insights emanating from research in various biological model systems will result in a better understanding of how genome instability impacts aging and age-related diseases.

Conflict of interest

The authors declare no competing interests.

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