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DNA damage responses and p53 in the aging process

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Abstract

The genome is constantly attacked by genotoxic insults. DNA damage has long been established to cause cancer development through its mutagenic consequences. Conversely, DNA damage is induced during radiation- and chemotherapy to drive cells into apoptosis or senescence as outcomes of the DNA damage response (DDR). More recently, DNA damage has been recognized as a causal factor for the aging process. The causal role of DNA damage in aging and age-related diseases is illustrated by numerous congenital progeroid syndromes that are caused by mutations in genome maintenance pathways. The past two decades have brought rapid progress in the understanding of how DDR drives cancer development and causally contributes to the aging process. The DDR factor p53 turns out to not only take the centre stage during tumour development but also to play an important role in the aging process. Studies in metazoan models ranging from *C. elegans* to mammalian disease models have revealed cell autonomous and systemic DDR mechanisms that orchestrate adaptive responses that augment maintenance of the aging organism amid gradually accumulating DNA damage.

DNA damage drives the aging process

Aging is a nearly universal property of life forms ranging from single cell bacteria to humans. Fundamentally, aging is the default fate of life whose building blocks DNA, RNA, and proteins are constantly subjected to chemical alterations that impair their function. Albeit chemically more vulnerable than DNA, RNAs are usually rather rapidly turned over and the consequences of damaged RNA molecules temporarily restricted. Damaged proteins are either kept in shape by chaperones or are degraded and their amino acids recycled through the ubiquitin proteasome system or autophagy. Nonetheless, damaged proteins aggregate during aging and result in functional deterioration particularly in neurons where they give rise to dementia including the most prevalent Alzheimer's disease. The

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consequences of DNA damage, however, are much more widespread as DNA contains the information for all RNA and proteins a cell produces.

It was estimated that tens of thousands of damaging events occur each day in every single one of our cells [1]. The genotoxic attacks can originate from extrinsically inflicted radiation damage or chemicals as well as from endogenous sources such as metabolic byproducts or reactive oxygen species (ROS). Oxidative modifications and single strand breaks (SSBs) are the most frequently encountered lesions and are rapidly repaired by base excision repair (BER) and DNA ligases, respectively [2,3]. Both systems rely on redundancy of several glycosylases that initiate BER and numerous ligases, as complete failure to repair those lesions is incompatible with life. Helix-distorting lesions are removed by nucleotide excision repair (NER), a highly complex repair pathway with intriguing connections to cancer and the aging process that we will discuss further below for their conceptually instructive character [4]. Even highly cytotoxic double strand breaks (DSBs) and interstrand crosslinks (ICLs) occur on a daily basis. Those lesions are particularly dangerous because they impair the cell's ability to replicate the DNA and segregate the chromosomes potentially giving rise to aneuploidy resulting in functional distortion of the genetic programs of the cell [5]. The two major routes for DSB repair are non-homologous end joining (NHEJ) and homologous recombination (HR) but even in their complete absence there are still options to pull, through backup end joining or microhomology directed repair [6,7].

The distinction between the modes and results of NHEJ and HR make an interesting point about the constraints on genome maintenance in the context of other cellular functions. The rapid NHEJ process is employed mostly when cells are not replicating their DNA and when no undamaged repair template is available. Prior to the end joining the broken chromosome ends are resected potentially because a high-energy ionization event produces ROS that inflicts base damage adjacent to the break site as well as to aid the re-ligation. Given that only a fraction of the human genome encodes for genes the local loss of a DNA stretch might be tolerable in most instances [8,9]. Speed at the expense of accuracy is particularly important when cells rapidly divide. HR, in contrast is highly accurate as it uses the homologous sequence as repair template. However, during replication HR might also boost genome instability when replication forks collapse amid the engagement of chromosomes in the HR process [10,11]. HR is mostly employed during late S and within the G2 phases of the cell cycle [12]. Some of the most prominent tumour suppressor genes are operating in the HR process. Mutations in the *BRCA1* and *BRCA2* genes predispose to breast and ovarian cancer and are both involved in HR. Interestingly, despite the backup DSB repair pathways, a combination of HR and NHEJ deficiency renders cells highly susceptible even to endogenous levels of DNA damage. The synthetic lethality of those two pathways led the way for tumour therapies that are personalized to HR defects, resulting e.g. from a *BRCA1* mutation, and use inhibition of the NHEJ process [13]. A clinical strategy for utilizing the sensitivity of *BRCA1* deficient cells is the application of catalytic PARP1 inhibitors resulting in replication-associated DSBs that in the absence of functional HR cannot be resolved [14].

There are numerous instances where speed matters over accuracy. The speed argument goes particularly for cells that are engaged in replication. Even though the replicative DNA

polymerases have a low error rate due to their proofreading activity that is accomplished through their exonuclease domain, occasional errors might slip through. Mismatch repair (MMR) scans the genome post replication for such errors by detecting structural aberrations of mispaired nucleotides [15]. Some DNA lesions, for example helix-distorting lesions, cannot be circumvented by replicative DNA polymerases. In those cases translesion synthesis (TLS) polymerases take over [16]. They handle the base pairing with less stringency but keep the replication forks going even though they tend to make mistakes.

Cancer and Aging: the flip side of DNA damage

There are two principally distinct outcomes of DNA damage. Erroneous repair can lead to mutations and chromosomal aberrations both of which are causal events in cancer development. In contrast, persistent DNA damage can block transcription and replication thus hampering cellular functionality and promoting cellular senescence and apoptosis. Consequently stem cell compartments become depleted, tissues degenerate, and homeostasis declines: ultimately, persistent DNA damage drives the aging process.

Erroneous repair can result from mistakes in placing the correct nucleotides, aberrant recombination, or lesion bypass and could alter the genetic information in numerous ways. When a mutation inactivates a tumour suppressor gene such as p53, the checkpoints that control the proliferation rate of a cell lose their function [17]. When distinct sections of a chromosome are erroneously joined, the promoters might aberrantly drive the expression of an oncogene. A most prominent example for this is the *MYC* gene that is normally expressed in a highly controlled fashion to drive cell cycle entry. However, when the V(D)J recombination during B-cell maturation fails and the Eμ enhancer that normally boosts the expression of the immunoglobulin heavy chain gene is fused to the *MYC* gene the B cells are driven into uncontrolled proliferation [18]. A recent study by the Nussenzweig lab revealed that even during interphase DSBs resulting from topoisomerase 2B activity at topological domain boundaries of chromatin results in chromosomal rearrangements observed in cancers [19].

Through its mutagenic effect, DNA damage thus triggers tumour development. Importantly, the mutations need to affect genes that control the cell's DDR as a functional DDR prevents the cells from uncontrolled proliferation. The DDR controls, through DNA damage checkpoints, under which circumstances cells may enter and proceed through the cell cycle [20]. The tumour suppressor p53 plays an important role in controlling cellular proliferation in the context of DNA damage (Figure 1). Normally, p53 is a shortly lived protein whose activity is tightly regulated by various processes including transcriptional and translational control as well as posttranslational modifications (PTMs) [21]. Moreover, p53 is rapidly ubiquitylated for example by MDM2 and consequently targeted for degradation by the UPS [22,23]. However, in the presence of DNA damage, p53 is stabilized by DDR signalling. For instance, p53 is activated by several PTMs including phosphorylation on serine-15 by the phosphatidylinositol kinase-related kinases ataxia-telangiectasia mutated (ATM), and ATM and Rad3-related (ATR), or on serine-20 by the checkpoint kinase (CHK2) at the N-terminal transactivation domain, which interfere with the inhibitory interaction between MDM2 and p53, rendering p53 stabilization and accumulation. Specific DNA binding activity of p53 can

be further enhanced or fine-tuned by phosphorylation and acetylation at the DNA-binding domain and C-terminal regulatory domain, modulating the distinct cell fate decisions [24–27]. There are numerous regulative events that determine the quality of the p53 DDR response and certainly numerous more awaiting their discovery [28].

To exemplify in a simplistic way the outcomes of the p53 response, we can turn to its most ancestral form, which is the *C. elegans* p53-like CEP-1 protein [29,30].The homology to human p53 is mainly restricted to the DNA binding domain with most of the hot spot mutations that are associated with human cancers highly conserved. Also the residues forming the zinc finger are present in the nematode form. The most well characterized function of CEP-1 is the regulation of DNA damage-induced apoptosis in meiotic pachytene cells. The pachytene is the critical meiotic phase where recombination takes place. During meiotic recombination the SPO-11 endonuclease induces DSBs that are used for the exchange with the homologous chromosome. When the cells reach the late pachytene stage all DSBs should have been properly processed and the Holliday junctions resolved. When, however, DSBs are still present the meiotic recombination has failed and those cells couldn't proceed to form genomically integer gametes. At this stage the CEP-1 mRNA gets translated as prior to this point in meiosis it has been repressed by the translational KH-motif RNA binding protein and Quaking homolog GLD-1 [31]. In addition to translational control, also the stability of CEP-1 is regulated through ubiquitylation [32]. Once CEP-1 becomes available for activation through DDR triggered by the persistent DSBs it transcriptionally induces the two proapoptotic BH3-only domain genes *egl-1* and *ced-13* [33–35]. As in mammals, the BH3-only domain proteins inhibit Bcl2 that in worms is encoded by the *ced-9* gene. CED-9 then alleviates its sequestration of the Apaf1-like CED-4, which in turn sets off the CED-3 caspase to seal the fate of the cells carrying unprocessed meiotic DSBs or those induced by ionizing radiation (IR) [36].

The apoptotic DDR regulation of p53 is highly conserved in humans where the BH3-only domain genes p53 up-regulated modulator of apoptosis *(PUMA)* and *NOXA* (named for 'damage') are induced in a similar fashion [37,38]. In addition to triggering the apoptotic demise of genomically compromised cells, p53 also induces cell cycle arrest, most well characterized by the transcriptional activation of the cyclin-dependent kinase inhibitor 1A *(CDKN1A)* gene p21 that inhibits mitotic cyclin-dependent kinases (CDKs) [39]. The cell cycle arrest is critical for allowing cells time to repair the damage, during which p53 enhances several DNA repair pathways to facilitate the clearance of DNA lesions [40]. Not only is p53 involved in the NER by transcriptionally up-regulating the xeroderma pigmentosum complementation group C (XPC) and damage-specific DNA binding protein 2 (DDB2), both of which are important damage-recognizing factors required for initiating global-genome NER [41,42], but p53 has also been implicated in the transcriptional control of the MMR component human MutS homolog 2 (hMSH2) upon DNA damage [43,44]. The expression of Fanconi anemia complementation group C (FANCC) gene, the lack of which causes an inherited DNA repair deficiency syndrome, is also closely related with the promoter abundance of p53 [45]. Beyond transcriptional regulation, p53 also modulates BER in a transcriptionally independent manner. The activities of the pivotal BER enzymes 8-oxoguanine glycosylase and AP endonuclease are augmented by direct interaction with p53 hence enhancing the efficiency of excising oxidative DNA lesions [46]. Moreover, a sub-pool

of ATM-phosphorylated p53 upon IR is found directly associated with the lesions, promoting DNA repair [47]. In parallel to the repair pathways, p53 up-regulates the p53-controlled ribonucleotide reductase (p53R2) for supplementing sufficient nucleotides during DNA re-synthesis thereby further facilitating the DNA repair process [48].

Amid unrepairable damage, however, p53 may also induce cellular senescence thus permanently withdrawing cells from cycling yet keeping them metabolically active [49]. The individual contributions of transient cell cycle arrest, cellular senescence and apoptosis to the tumour suppressor function of p53 might vary depending on the cell type and other tumour suppressor gene and oncogene mutations that may be present. However, we can again extract some conceptually instructive insights into the outcome of DDR. A failure to arrest the cell cycle either transiently or permanently amid DNA damage might fuel mutation rates and thus boost tumorigenesis. Even heavily genomically compromised cells might survive when p53 is dysfunctional.

Importantly, however, there is the other extreme of DDR. When p53 puts on the breaks too much, cells might not sufficiently proliferate to assure a physiological level of tissue regeneration (Figure 1). This can be detrimental particularly for tissues that require proliferative activity of their stem and progenitor cell compartments such as the hematopoietic system [50]. In addition, extraneous apoptosis might result in loss of tissue integrity regardless of which cell type is affected. Cellular senescence not only impairs proliferation and thus tissue regeneration and homeostasis but beyond that impacts neighbouring cells and potentially even the organism through the senescence associated secretory phenotype (SASP) [51]. SASP is a collection of heterogeneous cytokines that promote inflammation, tissue remodelling, and proliferation of recipient cells. In recent years, the contribution of senescent cells to aging has revealed the widespread physiological and pathological consequences of this cell fate. Highly pathological levels of cellular senescence have been observed in mice carrying mutations in the mitotic spindle checkpoint gene *Bubr1* [52]. When, however, either the senescence pathway was abrogated by a mutation in the *Ink4a* encoded p16 gene or cells were eliminated when the p16 promoter was fused to a caspase that consequently eliminated senescent cells, the premature aging phenotype of the *Bubr1* mutants was alleviated [53]. Moreover, even the functional decline during normal aging could be slowed down by elimination of senescent cells [54]. Currently, senolytic drugs are being tested such as Bcl-XL inhibitors that could selectively eliminate senescent cells and supposedly slow the aging process of the organism [55]. However, it is important to notice that cellular senescence might also have positive functions as for example the SASP component PDGF-A was demonstrated to support wound repair in murine skin [56].

The outcome of enhanced p53 function has been first demonstrated in two different mutant mice that express hyperactive forms of p53 [57,58]. Tyner and colleagues generated the $p53^{+/m}$ mice, in which the *m* allele comprises a truncated form of p53 containing only exons 7-11 of the p53 coding sequence. With enhanced stability and transactivation activity of the *m* allele product, $p53^{+/m}$ mice were highly protected from tumours yet at the expense of accelerated aging [57]. Further analysis of the haematopoietic stem cells (HSCs) revealed a reduced number of proliferating HSCs with age in $p53^{+/m}$ mice, confirming that increased p53 activity may lead to decreased production of progenitor and mature differentiated cells from

the stem cells thereby contributing to the aging phenotype [59]. In mice overexpressing another truncated isoform of p53, p44, signs of premature aging were observed as early as 4 months of age and, consistently, the mice displayed a low incidence of cancer [58]. The fine balance between keeping the brakes on proliferation and controlling cellular survival has been kept in mice that carry an extra copy of the p53 gene, called the Super-p53 mice [60]. These mice are protected from cancer development, likely because they are equipped with three p53 alleles that are therefore much less likely to lose heterozygocity. For extended lifespan, however, this was not sufficient and instead required an additional copy of the ARF tumour suppressor [61]. The mice with increased basal level of p53 due to low expression levels of MDM2 (*mdm2* $^{puro/\Delta 7\text{-}12}$mice) were also cancer resistant yet with a normal lifespan [62], further echoing the notion that a balanced p53 levels is of great significance for tumour suppression without accelerated aging.

When it comes to the human, previous studies have revealed a Pro/Arg polymorphism at amino acid residue [72] of p53 that alters the potential of inducing apoptosis [63–65]. A meta-analysis of the published literature has indicated that carriers of p53 Pro/Pro form, which is less potent in inducing apoptosis than p53 Arg/Arg form, had increased survival albeit higher mortality from cancer [65]. Another independent study recruiting more than 9000 participants demonstrated an higher overall survival for p53 Pro/Pro carriers, and, most importantly, a increased survival after cancer or other life-threatening disease [66]. However, contrasting results were obtained in a more recent study with even larger population [67], leaving it an open question whether hyper-active p53 plays an unfavourable role in human lifespan.

Persistent DNA damage: a driving force of aging

As DDR prevents tumourigenesis, its constitutive activation such as in hyperactive p53 mutants accelerates the aging process. The continuous activation of DDR, however, arises not only by genetic mutations that augment DDR, but can result from DNA lesions that are not repaired and thus persist. For instance critically shortened and thus unprotected telomeres are recognized as DNA-DSBs [68]. Indeed, the inability of telomerase to maintain the telomere length cause premature aging through activating the DDR and p53 [69,70]. Mice that are lacking the catalytic subunit or the RNA component of telomerase have shorter lifespan with early onset of aging phenotypes, even though in mice these phenotypes require several generations of defective telomere extension to arrive at critical telomere shortening precipitating the progeroid pathologies [71,72]. Premature replicative senescence also shortens lifespan in *Ku80*$^{-/-}$ mutant mice that lack functional NHEJ [73]. Intriguingly, the accelerated aging phenotypes of both animal models can be alleviated by the loss of p53, underlining again the pivotal role of p53 in DDR-mediated premature aging [74,75].

Another prominent example for demonstrating the link between persistent DNA damage and premature aging comes from the autosomal genetic disorder Fanconi Anemia (FA) that is characterized by progressive bone marrow failure due to functional decline of hematopoietic stem and progenitor cells (HSPCs). In addition to their sensitivity to ICLs [76,77], FA cells are hyper-sensitive to oxidative stress with excessive levels of oxidative DNA damage [78,79]. Ceccaldi et al. further demonstrated that the unresolved DNA damage leads to constitutive

activation of p53 resulting in a p21-dependent G0/G1 cell-cycle arrest in HSPCs from FA patients. Remarkably, the depletion of p53 or p21 could alleviate the defects in HSPCs [80]. Another example of the important role of p53 in controlling the DDR in HSPCs is provided by a mouse mutant that expresses the hypomorph *p53*^{515C} allele in an *Mdm2* deficient background. Here, p53 activation amid high ROS levels lead to exacerbated cell cycle arrest, senescence and apoptosis in HSPCs [81].

Not only in genetic diseases caused by mutations in genome stability factors, but also during normal aging, the ability of maintaining genome integrity declines especially in highly regenerative tissues such as the hematopoietic system. By comparing transcription profiles of purified HSCs from mice aged 2 to 21 months, Chambers and colleagues have reported that with age genes associated with stress response were up-regulated, while genes involved in maintaining genome integrity including DNA repair genes were down-regulated [82]. Consistent with this observation, the efficiency of DNA repair in aged HSCs is limited, leading to gradual accumulation of DNA damage and thereby attenuating the self-renewal and tissue regenerative capacity of HSCs [83–86].

For understanding the role of persistent DNA damage in the aging process, congenital NER deficiencies have been particularly illuminating. NER recognizes helix-distorting lesions that are most prominently formed when short wavelength UV light links adjacent bases to form cyclobutane pyrimidine dimers (CPDs) and 6-4 pyrimidine-pyrimidone photopruducts (6-4PPs) [87]. Indeed, CPDs are the primary instigator of UV-induced skin carcinogenesis [88]. The lesions are recognized either by the scanning of global-genome (GG-) NER or when RNA polymerase II (RNAPII) stalls at a lesion and transcription-coupled (TC-) NER is activated. Both pathways then trigger a common NER pathway that verifies the damage, unwinds the double helix, incises on either side of the lesion, excises the stretch containing the damage, resynthesizes the gap and finally ligates the remaining gap.

Congenital defects affecting one or the other recognition pathway couldn't possibly be more distinct [89]. Xeroderma pigmentosum (XP) patients display pigmentation abnormalities, atrophic skin, and a several thousand fold elevated skin cancer susceptibility [90]. Cockayne syndrome (CS) patients, on stark contrast suffer from postnatal growth retardation, neurological defects and display numerous manifestations of premature aging but remain cancer free [91,92]. A number of NER genes are associated with XP but most clearly those involved in GG-NER show the most distinctive skin phenotypes and cancer susceptibility, while XP mutations associated with factors operating in the common NER pathway typically display in addition neurodegenerative symptoms [93]. CS patients, in contrast, carry mutation in the *CSA* or *CSB* genes that operate in the initial steps of TC-NER. NER deficiencies are highly complex –on the molecular as well as on the pathological level– and not restricted to XP and CS alone, however, they are highly instructive as to the distinct outcomes of DDR [4]. While GG-NER defects are mutagenic when unrepaired lesions pass through replication where they might result in replicative errors or genome instability when replication forks collapse, TC-NER defects result in stalling of RNAPII. At high levels of RNAPII stalling transcription is blocked and cells might no longer fulfil their function or might even apoptose. Therefore, while mutagenic DNA lesions fuel cancer development, persistent

DNA lesions drive the aging process by hampering the DNA metabolism as replication and transcription are blocked.

Intriguingly, cells respond to transcription-blocking lesions already when they are detected at very low levels. Regardless of whether cells proliferate or are terminally differentiated, in response to those lesions they reduce the expression levels of genes that are involved in the somatic growth axis, particularly the Insulin-like growth factor-1 receptor (IGF-1R) and growth hormone receptor (GHR) [94]. Both receptors are central elements of the somatic growth axis and their reduction has been established as *bona fide* longevity assurance mechanism that extends lifespan in mice that lack the pituitary or the *GHR* gene [95–97]. Also progeroid ("premature aging-like") mice that carry defects in NER show reduced somatic growth gene expression and dampened IGF-1 levels [98–100]. It is likely that cells respond with attenuating the somatic growth axis to assure the survival of the organism when DNA damage accumulates [101]. Indeed, stress resistance –a feature strongly correlated with longevity– was observed in cells experiencing transcription-blocking lesions as they became exquisitely resistance to oxidative stress [102], similarly to mice with reduced *IGF-1R* gene dosage [103].

The consequences of this type of DDR have been recently studied in the nematode *C. elegans* where the mechanisms of longevity have been most extensively investigated. Here, the FOXO transcription factor DAF-16, which is normally kept inactive by insulin-like signalling but –consistently with the IGF-1R dampening in mammals– is activated upon transcription-blocking DNA lesions, promotes the animals' developmental growth and maintains the integrity and functionality of tissues in adult animals even when the DNA damage persists [104]. DAF-16 comprises a *bona fide* longevity assurance factor and its involvement in DDR suggests a distinct mechanism of adaptations to genome instability: DNA damage tolerance by augmented maintenance of tissues, which is particularly relevant for cell types that are not proliferating such as the adult nematode's cells outside of the germline that are entirely postmitotic. Therefore, there appear to be two types of longevity assurance mechanisms: DNA repair systems that prevent and delay the accumulation of DNA damage and lifespan regulators that determine the threshold to which DNA lesions are tolerated before they become detrimental. The latter are regulated by transcription factors such as DAF-16 that mediate gene expression programs that comprise stress resistance genes as well as developmental growth programs [104].

Intriguingly, the consequences DDR are not confined to the genomically compromised cell alone. Somatic growth signalling for instance is mediated through the secretion of IGF-1 and GH that have endocrine activities and SASP factors exert non-cell-autonomous effects [50]. Also p53 has non-cell-autonomous consequences when for example it regulates the cytokine secretion of tumour cells that determine whether they are cleared by macrophages [105]. In *C. elegans* innate immune factors that are induced in response to DNA damage in germ cells trigger a systemic stress resistance program that elevates somatic endurance thus extending reproductive lifespan to allow offspring generation once genome stability in the germ cells is reconstituted [106]. It will be highly important to gain more insights into the non-cell-autonomous regulation of DDR and which role p53 might play in this process.

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Alleviating DNA damage responses

Experiments discussed above particularly on additional p53 gene dosage as well as p53 ablation in a number of DNA repair deficiencies associated with exacerbated replicative senescence have indicated that a balance of DDR is important for cancer suppression and longevity and this balance could potentially be targeted for promoting health in old age (Figure 1). Also modulations of the consequences of DNA repair defects on cellular metabolism have been suggested to alleviate pathologies resulting from genome instability. *Xrcc1* mutant micethat are defective in single-strand break repair show highly elevated protein poly ADP-ribosylation (PARylation) levels and develop neurological disorders characterized by ataxia. Interestingly, genetic ablation of *Parp1* could restore ADP-ribose levels and reduce neuronal loss and alleviate the ataxia. One consequence of PARP1 activity is that excessive PARylation could dampen the NAD^+ levels resulting in defective mitophagy, which could be alleviated by replenishment of NAD^+ thus improving the health of progeroid NER and ATM mouse models [107,108]. Elevated NAD^+ levels have numerous consequences on cellular metabolism and could also promote longevity through Sirtuin-mediated activation of the mitochondrial unfolded protein response and FOXO signaling [109]. In addition, NAD^+ could also alleviate PARP1 inhibition mediated by the NAD^+ binding protein DBC1 [110]. It is thus conceivable that intervention strategies could promote longevity and healthspan through affecting the activity of genome maintenance systems.

Concluding remarks

DNA damage is invariably occurring as a result of a plethora of endogenous and exogenous genotoxic insults. A complex arsenal of DNA repair mechanisms efficiently removes the lesions and ensures the maintenance of the soma during lifespans that were relevant for supporting offspring generation during the evolutionary history of a species. The capacity to keep genomes of somatic cells intact vanishes thereafter, leading to functional decline of cells and tissues. It is an intriguing and yet incompletely understood question how germ cells retain the levels of DNA repair accuracy that has allowed maintaining the gene pool of a species for many hundreds of millions of years. The aging organism responds to DNA damage by cell-autonomous and systemic DDR. The p53 gene is not only a most important tumour suppressor but also an orchestrator of an extensive network of DDR factors that are relevant for adaptation to DNA damage in the aging organism. Studies in metazoan model systems have begun to shed light on how signalling pathways and endocrine axes respond to the build-up of DNA damage with aging. Approaches such as combining proteome assessments with studies of PTMs and metabolic alterations have begun to shed new light on the complexity of DDR and the consequences of persistent DNA damage in the aging organism [111]. It will be pivotal to further explore how longevity assurance mechanisms respond to DNA damage and how they influence the aging phenotype and the aetiology of aging-associated diseases.

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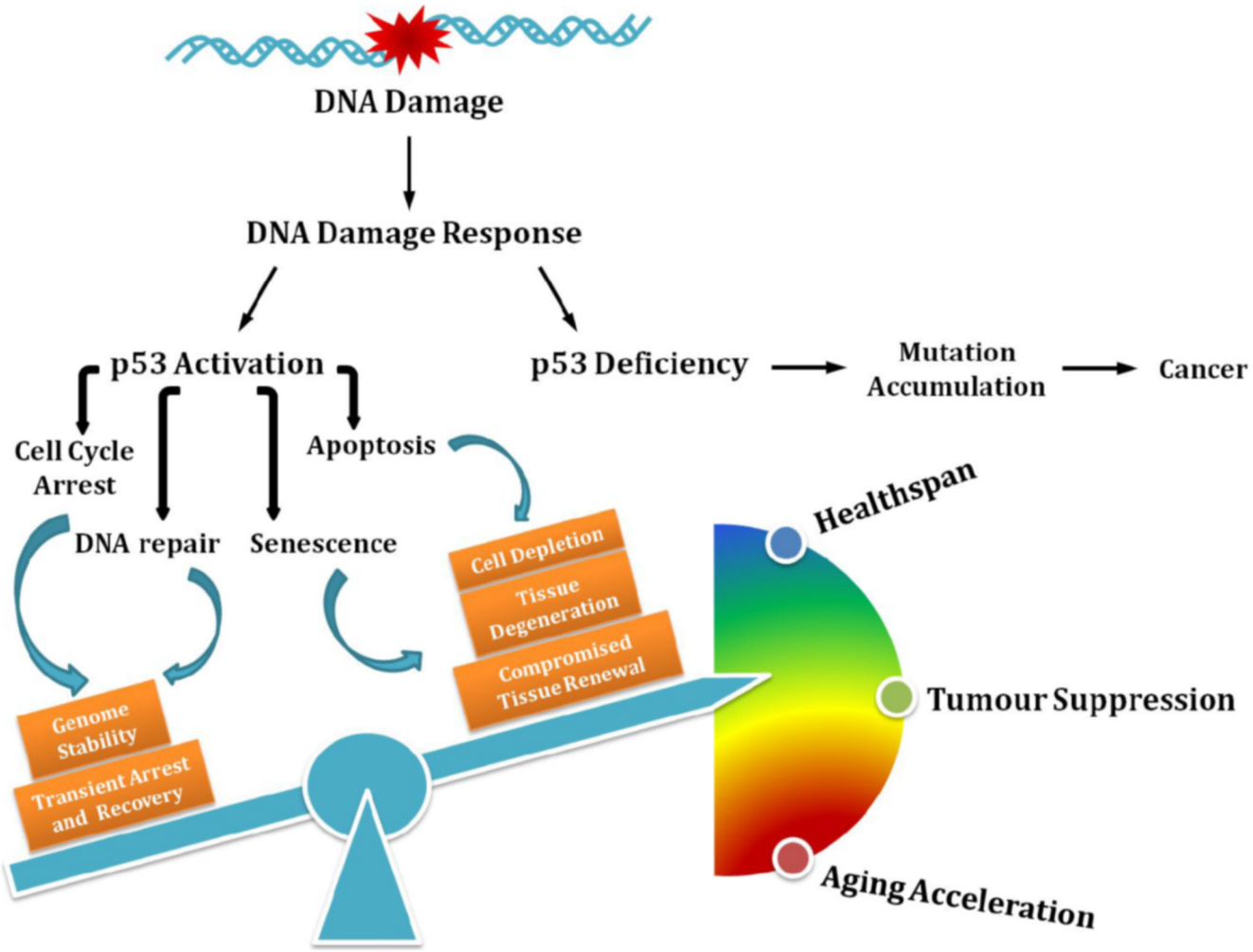

Figure. The influence of p53-mediated cell fate decision on cancer development and the aging process.

Defective p53 leads to accumulation of mutations that drive carcinogenesis; on the contrary, p53 regulates diverse outcomes of the DNA damage response, the fine-tuning of which balances healthspan, tumour suppression, and accelerated aging.