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The p53 network: Cellular and systemic DNA damage responses in aging and cancer

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Abstract

Genome instability contributes to cancer development and accelerates age-related pathologies as evidenced by a variety of congenital cancer susceptibility and progeroid syndromes that are caused by defects in genome maintenance mechanisms. DNA damage response pathways that are mediated through the tumor suppressor p53 play an important role in the cell intrinsic responses to genome instability, including a transient cell cycle arrest, senescence and apoptosis. Both senescence and apoptosis are powerful tumor suppressive pathways preventing the uncontrolled proliferation of transformed cells. However, both pathways can potentially deplete stem and progenitor cell pools, thus promoting tissue degeneration and organ failure, which are both hallmarks of aging. p53 signaling is also involved in mediating non-cell autonomous interactions with the innate immune system and in the systemic adjustments during the aging process. The network of p53 target genes thus functions as an important regulator of cancer prevention and the physiology of aging.

p53 at the crossroad of cancer and aging

Preservation of genomic integrity is crucial for the survival and reproduction of all life on earth. Genome integrity is constantly threatened by a variety of genotoxic insults, with tens of thousands damaging events occurring in every single cell on a daily basis ¹. Erroneous repair can result in mutations potentially leading to altered gene function, which in turn can give rise to cancer development. Persistence of lesions can lead to cellular senescence and apoptosis eventually resulting in tissue degeneration ². Specifically cellular senescence has been shown to serve a barrier function against malignant transformation of premalignant lesions ³⁻⁵. As DNA damage gradually accumulates during lifetime, both the likelihood of oncogenic transformation as well as tissue dysfunction and degeneration increases with age. Cellular responses to DNA damage are mediated through highly conserved DNA damage checkpoint mechanisms that are important for tumor suppression by arresting cell cycle progression, or evoking cellular senescence and apoptosis ⁶. p53 is a key player in the tumor suppressive DNA damage response (DDR) and is mutationally inactivated in approximately

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50% of human cancers⁷. Recent evidence suggests that p53 not only antagonizes oncogenic transformation, but also orchestrates non-cell autonomous responses to DNA damage by mediating clearance of damaged cells through the innate immune system⁸⁻¹⁰. On an organismal level, p53 activity has been implicated in driving tissue degeneration and aging^{11, 12}. In contrast to its role in contributing to the functional decline of tissues in aging, p53 also regulates genes that are associated with lifespan extension¹³. To understand the outcome of p53 activity in cancer and aging it is crucial to understand how p53 mediates distinct outcomes of DNA damage signaling in the context of cells and tissues. Here, we draw a picture integrating cell autonomous and non-cell autonomous p53-mediated DNA damage responses to cancer prevention and lifespan regulation.

DNA repair defects lead to cancer susceptibility, developmental abnormalities and premature aging

The genome of every cell is constantly threatened by intrinsic and extrinsic genotoxic insults, such as metabolic byproducts and radiation, respectively^{1, 14}. Genotoxic agents can lead to a plethora of different modifications in the physicochemical structure of DNA. This large variety of DNA lesions is recognized by highly specialized DNA repair systems¹⁵. Congenital defects in DNA repair systems underlie a variety of complex genetic disorders that are characterized by cancer susceptibility, developmental abnormalities, and accelerated tissue degeneration^{16, 17}. While the causal links between DNA repair defects and cancer susceptibility are rather well-established, how genome instability leads to complex pathologies during development and aging remains less well-understood. DNA repair defects can lead to enhanced mutation rates, which when occurring in tumor suppressors or oncogenes can lead to cancer development as for instance in mismatch repair defects¹⁸. Likewise defects in DNA damage checkpoints can fuel tumorigenesis by abrogating cellular senescence and apoptosis programs as seen for instance in highly cancer prone Li Fraumeni or ataxia telangiectasia patients^{19, 20}. However, when DNA damage persists and interferes with replication or transcription as observed in transcription-coupled repair (TCR)-deficient Cockayne syndrome patients, ensuing high levels of apoptosis and cellular senescence can accelerate tissue dysfunction and degeneration²¹.

The DDR effector p53 - tipping the balance between cancer and aging

Chronic DNA damage, as that observed in TCR defects, appears to be associated with constitutive DDR signaling and premature aging. On the other hand loss of downstream DDR effectors appears to be primarily linked to a tumor-prone phenotype. Indeed, mice lacking the critical DDR gene *TP53*, encoding for the p53 protein, are highly tumor-prone and regularly succumb to neoplastic disease²². Patients suffering from Li-Fraumeni syndrome, caused by germline mutations in the *TP53* gene, are characterized by the development of multiple tumors early in life¹⁹. The consequences of defective DDR activity in causing cancer and accelerating aging are particularly well-illustrated in mice carrying activated and impaired *TP53* alleles. p53 is a transcription factor that exerts tumor suppressive functions by inducing the expression of effector genes (Figure 1). Mutational inactivation of p53 allows the uncontrolled proliferation of damaged cells²³. In contrast, the expression of dominant active forms of p53 leading to constitutive expression of

downstream genes, results in degenerative phenotypes and premature aging^{12, 24}. It is likely that constitutive activation of p53 annihilates stem cell compartments thus impairing tissue regeneration. Interestingly, keeping a fine balance between p53 activation sufficient for tumor surveillance but insufficient to trigger stem cell depletion, seems to result in beneficial effects both for cancer protection and longevity as demonstrated by the expression of extraneous wt alleles of *TP53* in mice²⁵ (see below).

p53 activity has been linked to the regulation of a complex cellular DDR network (Figure 1) and more recently also to non-cell autonomous interactions between damaged cells and the innate immune system (see below). The cellular DDR has initially been characterized in single cell yeast, where it functions to arrest the cell cycle allowing time for DNA repair²⁶. DNA damage checkpoint mechanisms in yeast are highly conserved in mammals where they became part of a complex network that balances the DNA damage outcomes between transient cell cycle arrest, senescence and apoptosis. While yeast is devoid of a *TP53* homolog, the nematode *Caenorhabditis elegans* harbors a functional *TP53* homolog that mediates apoptosis in response to double strand breaks during meiosis through transcriptional induction of pro-apoptotic Bcl-2 homology (BH)3-only proteins²⁷⁻³⁰. While this mechanism of p53-mediated checkpoint responses is highly conserved, mammalian p53 is involved in a more complex signaling network³¹ and a variety of target genes that are transcriptionally controlled by p53 have been identified (Figure 1). The induction of p21 and BH3-only proteins is probably the physiologically best understood p53-mediated checkpoint response^{31, 32}. The cell cycle inhibitor p21 binds and inhibits cyclin dependent kinases (CDKs), thus preventing progression through the cell cycle. In contrast, BH3-only proteins such as p53 upregulated modulator of apoptosis (PUMA) as well as the BH domain proteins Bcl-2-associated protein X (Bax) and Bcl-2 antagonist/killer (Bak), are potent activators of apoptosis. Both, senescence and apoptosis are potent tumor suppressive mechanisms that ultimately prevent the (neoplastic) proliferation of damaged cells. On the other hand, both pathways have the potential to deplete proliferation-competent stem and progenitor cell pools, thus leading to impaired tissue renewal ultimately impairing organ homeostasis – a hallmark of aging. How these two outcomes of p53 activation are balanced is still poorly understood. One important factor is certainly a cell type specificity of the p53 response. For example, such a cell type-specific DDR is apparent in thymocytes that typically undergo apoptosis in response to genotoxic stress³³. In contrast, fibroblasts rather initiate cellular senescence, when exposed to DNA damage³⁴. This might relate to their physiological function where thymocytes are rapidly replenished while fibroblasts function in connective tissues, which require physical integrity.

While it is widely accepted that impaired p53 activity reduces organismal lifespan through uncontrolled proliferation of cancerous cells, loss of p53 activity should also lead to repression of catastrophic cell fate decisions, such as senescence and apoptosis, which result in aging phenotypes as tissue and organ degeneration (Figure 2). In fact, there is recent evidence from mouse models suggesting that p53 is indeed involved in regulating the aging process³⁵. The first hint that p53 activity might drive organismal aging came from experiments with mice in which a spontaneous recombination event deleted a stretch of DNA containing the 5' sequence of the *TP53* gene. This mutant allele, which was termed

TP53^m, contained exons 7-11 and transcription was driven from a promoter of an upstream gene. Experiments performed in mouse embryonic fibroblasts (MEFs) derived from *TP53^{m/+}* animals revealed that the *TP53^m* gene product augmented stability and transactivation capacity of wildtype p53. In keeping with the idea that increased p53 activity protects from cancer development, *TP53^{m/+}* animals displayed robust cancer resistance. However, this cancer resistance came at the cost of a statistically significant lifespan reduction of the *TP53^{m/+}* animals, which was accompanied by signs of premature aging. Some of the aging phenotypes observed in the *TP53^{m/+}* mutant animals might be the result of reduced stem cell proliferation in these animals compared to wildtype controls ³⁶. Additional support for a role of p53 function in organismal aging came from transgenic (tg) mice overexpressing a naturally occurring p53 isoform termed p44 ²⁴. Translation of the short isoform initiates at codon 41 in exon 4 producing a 44kD protein, lacking large parts of the transactivation domain ³⁷. *p44^{tg/tg}* animals, like *TP53^{m/+}* mutant mice, were cancer resistant and displayed signs of premature aging. These p44-mediated effects were dependent on p53, suggesting that p44 overexpression increased wildtype p53 activity.

While both of the short isoforms of p53 promote cancer resistance, their expression was associated with decreased lifespan. In contrast to the short isoforms, where p53 mutants are expressed outside of the natural genomic context of the *TP53* gene, the so-called ‘super p53’ mouse was generated using BAC transgenics, allowing the expression of wildtype p53 from within its natural genomic surrounding ²⁵. As has been observed in the *p44^{tg/tg}* and *TP53^{m/+}* mice, the ‘super p53’ mouse, carrying one or two *TP53^{tg}* alleles in addition to the two endogenous copies is highly cancer resistant. However, in stark contrast to mice expressing the short isoforms of p53, the ‘super p53’ mouse did not display any signs of premature aging. While p53 expression and activity in ‘super p53’ cells were not elevated in the absence of stress, p53 activity was enhanced in response to genotoxic stress ²⁵. Despite enhanced p53-dependent apoptosis in response to genotoxic stress, ‘super p53’ mice had a normal lifespan and displayed no signs of premature aging. In an extension of this work, ‘super p53/ARF’ mice have been generated that not only carry an extra copy of p53, but also carry an extra allele of *p19 alternative reading frame protein (ARF)* ³⁸. Like the ‘super p53’ mice, the ‘super p53/ARF’ animals are cancer-resistant. In addition, the ‘super p53/ARF’ animals showed increased resistance to oxidative stress and a significantly increased lifespan. Thus, a picture is emerging where chronically elevated p53 expression is providing protection against cancer development at the cost of a reduced lifespan. However, a similar cancer resistance can be brought about when additional copies of wildtype p53 are available to increase the magnitude of p53 expression and activity only in response to appropriate stimuli (Figure 2).

p53 interacts with the immune system

While the different p53-dependent cellular outcomes are largely the result of cell-autonomous signaling cascades, p53 signaling also involves non-cell autonomous and systemic mechanisms (Figure 3). This is illustrated by observations made with mice, in which p53 could be re-activated in initially p53-deficient tumors. Reactivation of functional p53 in pre-existing p53-deficient tumors resulted in widespread apoptosis or senescence, where lymphomas appeared to be particularly prone to apoptosis, while senescence was the

primary response in sarcomas and liver carcinomas⁸⁻¹⁰. Of particular interest are experiments performed with mice carrying liver carcinomas¹⁰ that revealed an intimate relationship between p53 signaling and recruitment and activation of the innate immune system. Specifically, p53 reactivation-induced senescence in liver carcinomas was associated with upregulation of a number of pro-inflammatory cytokines including Colony-stimulating factor (Csf)1 and Monocyte chemotactic protein (Mcp)1, Chemokine CXC motif ligand (Cxcl)1, and Interleukin (IL)-15 that attract macrophages, neutrophils, and natural killer cells, respectively¹⁰. These mRNAs were also induced by p53 reactivation in cultured hepatoma cells, indicating that they are expressed specifically in tumor cells. Further experiments depleting macrophages, neutrophils or natural killer cells, suggested that innate immune cells were indeed required for tumor clearance¹⁰. Each antagonist efficiently depleted the targeted immune cell population, but did not impact on p53 reactivation-mediated cancer cell senescence, indicating that induction of p53-dependent tumor cell senescence and the evoked immune attack cooperate to promote tumor clearance.

In a different line of experimentation the impact of p53 signaling on ionizing radiation (IR)-mediated lymphomagenesis was directly investigated either in transgenic mice that expressed p53 fused to a tamoxifen-sensitive estrogen receptor allowing control of p53 activity through administration of 4-hydroxy-tamoxifen (4-OHT)³⁹ or in a conditional knockout model where p53 was deleted before, concurrent with, or after IR-induced DNA damage⁴⁰. When p53 was kept active at the time of irradiation, typical radiation toxicity could be observed, including widespread apoptosis in proliferative tissues, such as the gastro intestinal tract, bone marrow and lymphoid system. Following recovery from acute radiation toxicity, p53 was inactivated through 4-OHT withdrawal and lymphoma incidence was measured compared to animals in which p53 was kept inactive at the time of irradiation. Counterintuitively, the animals in which p53 was made available at the time of irradiation showed no detectable lymphoma protection. In contrast, p53 reactivation after IR prevented acute radio-toxicity and provided tumor protection. These findings suggest that rather than the intensity of acute p53-driven apoptosis in response to irradiation injury, a delayed function of p53 appears to have the determining impact on p53-mediated tumor suppression in this tumor model. Interestingly, the tumor suppressive effect of delayed p53 re-activation was dependent on *p19ARF*, which has been suggested as a critical mediator of oncogene-driven p53 activation leading to cellular senescence³⁹. However, these experiments did not directly test the acute role of proximal DDR components in preventing lymphomagenesis. This could be achieved through deletion of ATM or Chk2 in this system. Furthermore, it is very likely that there is a qualitative difference between acute radiation-induced DNA damage as a trigger for lymphomagenesis and sustained oncogene-induced replication stress. In fact, the observation that delayed p53 activation was protective in the above-mentioned experiments might argue that it is indeed oncogene-induced DNA damage that occurs after IR-induced mutational oncogene activation that is the relevant source of p53-activating DNA damage in this system. However this possibility has so far not been addressed. Lastly, whether such a delayed p53 effect on IR-induced tumorigenesis can also be observed in other models, specifically those mirroring solid tumors, remains to be elucidated. Together these data suggest that activation of the canonical DDR is critical to prevent the transformation of premalignant lesions facing oncogene-induced genotoxic stress.

Senescent cells and their environment

Senescence of somatic cells has already been proposed in the late 19th century when August Weissmann realized that in contrast to the germ line, somatic cells have a finite lifespan⁴¹. This replicative senescence was experimentally observed in the 1960s by Leonard Hayflick when growing human primary fibroblasts in culture⁴². A plethora of senescence-promoting stimuli have since been identified, including telomere erosion, which causes a permanent DDR, non-telomeric genomic DNA damage and oncogenic stress, which also leads to an activation of a persistent DDR through misfired replication origins and replication fork collapse⁴³. As senescence is defined as an irreversible cell cycle arrest, it is obvious that senescence serves as a potent tumor-suppressive function through preventing the outgrowth of genomically damaged incipient cancer cells. Indeed, cellular senescence has recently been shown to act as a powerful barrier preventing malignant transformation of precancerous lesions^{4, 5, 44}. The importance of cellular senescence as a tumor-suppressive mechanism is underscored by the observation that most human tumors display inactivating mutations in the p53 and/or p16 inhibitor of cyclin-dependent kinase (INK)4A/ retinoblastoma (Rb) pathways, which are critical molecular constituents of the senescence response^{45, 46}. Studies on human tumor material have shown that senescent cells are enriched in premalignant lesions, while the malignant lesions ultimately arising from these precursors are essentially devoid of senescent cells, suggesting that senescence suppresses tumor development through an arrest at a benign state^{3, 47}. Interestingly, forced induction of senescence in malignant tumors through re-expression of p53 does not only halt tumor growth, but has been shown to result in tumor regression in mice. The senescent tumors were shown to be invaded by cells of the innate immune system, which ultimately cleared the senescent cells^{9, 10}. These observations suggest that senescence does not only act as a cell autonomous mechanism, but also involves a non-cell autonomous component, likely involving the induction of a local pro-inflammatory response (Figure 3). Thus, in addition to p53-dependent apoptosis, senescence has emerged as a powerful tumor suppressive mechanism downstream of p53. However, recent data are challenging this model of senescence as a simple failsafe mechanism redundant to p53-driven apoptosis. It has been shown that senescent cells do not just simply withdraw from the cell cycle, but that they induce the secretion of a variety of growth-promoting pro-inflammatory factors, including Il-6, Il-8, Cotton rat growth-regulated protein (GRO) α , Vascular endothelial growth factor (VEGF) and amphiregulin⁴⁸⁻⁵⁴. The secretion of these growth factors, which appears to be at least partially dependent on the activity of the DDR kinase ATM⁵⁴, is commonly referred to as senescence-associated secretory phenotype (SASP).

Cellular senescence in the aging organism

Intriguingly, the number of senescent cells increases with age in the majority of mitotically active mammalian tissues⁵⁵⁻⁶¹. The causal contribution of cellular senescence to aging has been recently demonstrated in a progeroid mouse model expressing hypomorphic (H/H) budding uninhibited by benzimidazoles (BubR)1, a key mediator of the mitotic checkpoint. *BubR1*^{H/H} mice display highly elevated levels of p16Ink4a-mediated cellular senescence. When senescent cells were eliminated by expressing an inducible Caspase-8 transgene under the control of the p16Ink4a promoter age-related pathology in the *BubR1*^{H/H} mice was

alleviated⁶². It will be highly interesting to determine whether ablation of senescent cells might also antagonize normal aging. While it remains unclear whether the accumulation of senescent cells in aging organisms is the result of increased generation, reduced clearance or both, senescent cells, by way of the SASP, might collectively contribute to the sterile inflammation that is frequently observed in aged tissues. Through the secretion of pro-inflammatory cytokines, senescent cells could create a local inflammatory reaction. In fact, there is a strong correlation between chronic organ inflammation and development of neoplasias within that particular organ⁶³. Intriguingly, several studies have shown that low-grade systemic inflammation is a characteristic feature of the aging organism and that molecular markers of inflammation, such as IL-6 and Tumor necrosis factor (TNF)- α , are significant predictors of mortality in aging humans^{63, 64}. Various molecular mechanisms mediate the link between an inflammatory microenvironment and tumor initiation and progression. Pro-inflammatory leukocytes, which might be recruited in response to factors secreted by resident senescent cells^{9, 10}, release genotoxic reactive oxygen and nitrogen species, which lead to genomic instability and growth-promoting alterations of the genome of the surrounding incipient cancer cells. In addition, activated leukocytes also secrete a number of growth-promoting cytokines, including IL-4, IL-6, IL-10, transforming growth factor (TGF)- β and TNF- α , further fueling the oncogenic process through various mechanisms, including direct stimulation of epithelial cancer cells, as well as activation of angiogenesis. Furthermore, established tumors have also been shown to maintain an inflammatory microenvironment further promoting malignant transformation and tumor maintenance⁶⁵. There is mounting evidence suggesting that senescent cells might indeed promote the transformation of premalignant epithelial cells. This is exemplified by the observation that co-injection of senescent fibroblasts with premalignant epithelial cells resulted in the successful formation of xenograft tumors⁶⁶. In addition, co-injection of senescent cells with malignant tumor cells increases the take rate in xenograft models^{49, 66-69}.

p53 impacts the IGF-1 system, a key regulator of Aging and Cancer

In contrast to its role in promoting cellular aging through mediating cellular senescence, p53 might also exert longevity assurance functions by impacting on the conserved insulin-like growth factor (IGF)-1 signaling network. p53 was shown to antagonize mitogenic signaling, energy metabolism, autophagy and cellular survival signaling through inhibiting IGF-1 and target of rapamycin (mTOR)-mediated signaling pathways at multiple levels (Figure 3)¹³. p53 transcriptionally induces a number of inhibitors of IGF-1 and mTOR signaling including the PIP3 phosphatase PTEN, the antagonistic IGF-binding protein IGF-BP3, AMP-activated protein kinase (AMPK)- β , Tuberous sclerosis (Tsc)2 and Sestrin1/2 and p53 expression was also found to lead to reduced transcription of the IGF-1 receptor (IGF-1R)⁷⁰⁻⁷⁴. IGF-1 receptor-mediated signaling is frequently hyperactivated in tumor cells providing proliferative and pro-survival signals⁷⁵. While activation of IGF-1 signaling promotes cellular growth and tumorigenesis, reduced IGF-1 signaling in various model systems including nematodes, fruit flies and mammals delays aging and extends lifespan⁷⁶. mTOR functions as a downstream effector of IGF-1 signaling and regulates translation, autophagy, metabolism, cell growth and stress resistance⁷⁷. Consistent with the conserved

longevity assurance effect of dampened IGF-1 signaling, inhibition of mTOR by administering rapamycin led to lifespan extension in mice ⁷⁸. By regulating genes that control IGF-1 signaling activity both cell intrinsically as well as systemically through induction of the antagonistic circulating IGF-1 carrier IGFBP3, p53 might thus play an important role in the physiological adjustments during the aging process. The concept that DNA damage signaling dampens the IGF-1 mediated somatic growth axis resulting in a shift from growth to cellular preservation as DNA damage accumulates with aging has been based on the observation of reduced IGF-1 levels in DNA repair defective progeroid mice (see box 1) ²¹. Likewise, aging humans display lower circulating levels of IGF-1 and growth hormone (GH) ⁷⁹ and an association between polymorphisms in the IGF-1 receptor and human longevity has been reported ⁸⁰. However, while p53 transcriptionally induces negative regulators of the IGF-1 signaling network, mice that express the hyperactive *p44^{tg/tg}* allele display elevated IGF-1 signaling activity and age prematurely ¹¹. It is conceivable that hyperactive p53 might lead to depletion of stem cell compartments by inducing extraneous levels of apoptosis and cellular senescence while IGF-1 mediated cellular growth factor signaling might function to compensate for the cell intrinsic growth arrest in this model. Taken together, these data suggest that p53 can exert both pro- and anti-aging functions. It will be highly important to determine how the physiological outcome of p53 activity is mediated through the differential transcriptional regulation of apoptotic, senescence and longevity target genes.

Concluding remarks: Targeting the p53 balance

p53-mediated apoptosis and cellular senescence in combination with the systemic dampening of the IGF-1 growth axis might be crucial to prevent tumor growth, an inevitable requirement given the accumulation of potentially harmful mutations resulting from DNA damage accrual during aging. One consequence of growth factor deprivation might be increased frailty as for instance reduced GH levels have also been linked to osteoporosis ⁸¹. In addition, the renewal capacity of tissues might be compromised by a combination of increasingly activated p53 in stem and progenitor cells and a less growth permissive environment in the aging organism. Parabiosis experiments demonstrating that a circulation of a young mouse can reactivate stem cells and consequently tissue repair in old animals ⁸² have raised the question under which circumstances hormone replacement therapy could be beneficial to avert age-related pathologies. Such stem cell niche-reactivating therapies might be beneficial at late stages of life when frailty becomes a major health concern. However, it is likely to come at the cost of enhanced tumor initiation and progression. Somatotrophic mutants, in contrast, have suggested that a long-term reduction of IGF-1 signaling can have beneficial effects on lifespan and tumor suppression. In addition, a moderately enhanced expression of p53 in combination with Ink4a/ARF using BAC transgenic mice resulted in tumor free life extension ²⁵. In order to develop “health span” promoting therapeutic strategies that avert cancer development while maintaining tissue function and renewal, it will be crucial to further understand how the intricately complex network of p53 target genes regulates the very fine balance between tissue physiology, maintenance, repair and renewal and tumor suppression in the aging organism.

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Box 1**Systemic DNA damage responses in tumor suppression and aging**

Recent evidence in progeroid (“premature aging-like”) mouse models have revealed links between DNA damage accumulation and the regulation of genetic longevity pathways. DNA damage responses were shown to dampen somatotrophic signaling in mice that prematurely aged as result of defects in Sirt6, a deacetylase linked to base excision repair (BER) and double strand break (DSB) repair, or impairment of nucleotide excision repair (NER) ⁸⁶⁻⁸⁹. Transcriptome analysis and endocrine measurements in *Csb^{m/m}/Xpa^{-/-}* mouse mutants that model Cockayne syndrome (CS) as well as in mice carrying defects in the downstream NER components *ERCC1* have suggested that IGF-1 secretion, circulation and signaling is reduced ^{87, 88}. Moreover, it was shown that DNA lesions leading to blockage of RNA Polymerase II induce a growth suppressive response ⁹⁰. In particular, IGF-1 receptor signaling is reduced in response to even low amounts of persistent transcription-blocking lesions. It is thus conceivable that part of the tumor suppressive phenotypes observed in CS patients might be due to the growth factor-deprived endocrine environment. In fact, a large number of tumors have been shown to critically depend on IGF-1 signaling ⁹¹.

As aging humans and mice, as well as progeroid mice with DNA repair defects dampen the IGF-1-mediated somatotrophic axis, it is conceivable that cellular responses to DNA damage accumulation in aging orchestrate the shift from a growth permissive endocrine environment to tissue maintenance and enhanced systemic tumor surveillance. There is evidence from various model systems to support this hypothesis. Experiments performed in the early 1970s have shown that aging of murine mammary tissue, measured by reduced ductal elongation capacity throughout serial transplantations, is not consistently influenced by the age of the donor animal. In fact, mammary grafts from young and old mice showed similar growth kinetics and overall lifespan when transplanted into a young recipient. In marked contrast, old host animals did not support the growth of either old or young transplants ⁹². Likewise, transplantation of muscle tissue from old rats into young recipients resulted in successful regeneration, while transplantation of young muscle grafts into old hosts did not ^{93, 94}. It has been shown that Notch signaling is critical for the proliferation and myogenic lineage progression of satellite cells, which are essential for muscle regeneration ⁹⁵. The age-associated reduced regenerative potential of muscle tissue is at least in part due to an inability of this pathway to be activated ⁹⁶. Intriguingly, exposure of old murine muscle tissue to a circulation of young mice in the context of parabiosis experiments, resulted in a restoration of Notch signaling, regenerative potential and proliferation of satellite cells within the aged parabiosed partner, suggesting that the age-related decline of tissue progenitor cell activity can be modulated and restored through exposure to circulating factors present in younger organisms ⁸². A similar correlation between host age and growth rate could be observed when mammary tumor growth rates were assessed in women ⁹⁷. In these studies, serial mammography was used to estimate the age-dependent tumor volume doubling time in primary breast cancer. The median volume doubling time in women between 50 and 70 years of age was almost twice that of breast cancers diagnosed in females younger than 50 years. These

observations are supported by other reports that found significantly less tumors with short doubling times in patients over the age of 60 years than in those below the age of 60 ⁹⁸. One might argue that breast cancer growth, at least partially, depends on the endocrine status of the host organism and that passage through menopause might result in decreased hormonal growth support of both primary breast epithelium, as described in the experiments discussed above ^{92,97}. However, a recent study examining tumor volume doubling times in hereditary (*BRAC1/2* mutation carriers) and familial breast cancer patients using multivariate analysis showed that only age, but not risk group or menopausal status correlated significantly with tumor volume doubling times ⁹⁹. In addition, CT-guided tumor growth rate analysis in stage I lung cancer, as well as renal carcinoma, irrespective of the histologic subtype, revealed that age at diagnosis was negatively correlated with tumor volume doubling time of these hormone-independent cancers ^{100, 101}. Together, these observations from mouse models and different human tumor entities support the hypothesis that tumor growth is attenuated in an aged host environment and that responses to accumulating DNA damage with aging mediate this shift from cellular growth to tissue preservation.

Figure 1. p53 is activated downstream of the proximal DNA damage checkpoint signaling cascade in response to genotoxic damage or oncogene-induced replication stress. The depicted checkpoint kinase complexes DNA-PK, ATM, ATR, CHK1, CHK2 and MK2 mediate DNA damage signaling, which funnels into activation of p53. Upon activation, p53 transcriptionally induces a host of target genes, which promote cell cycle arrest, allowing time for DNA repair, senescence or apoptosis leading to cell loss and ultimately contributing to tissue degeneration in aging. The fine balance between these different p53-mediated cellular outcomes translates into physiological consequences between cancer protection and aging. DSB, DNA double strand break; SSB, DNA single strand break.

Figure 2. Activation modes of p53 determine the physiological outcome.

(a) In wildtype cells and tissues, p53 exhibits low baseline activity through tight regulation of p53 protein levels. Only upon the appropriate cellular stress signals, such as those evoked by genotoxic lesions, p53 is activated to prevent oncogenic transformation of cells. (b) Increased tonic p53 activity, such as that induced by the expression of short p53 isoforms, promotes cancer resistance. However, the increased baseline activity of p53 appears to prevent tissue regeneration and to accelerate the aging process. (c) Low baseline levels with strong p53 activity only in response to appropriate stress stimuli, such as DNA damage, lead

to extraordinary cancer protection with normal lifespan. Interestingly, recent data suggest that the physiological p53 response following exposure to ionizing radiation (IR) occurs in a non-linear oscillating fashion in repeating pulses with fixed amplitude and duration^{83, 84}. The observation of these oscillations became possible with recent advances in single-cell imaging techniques⁸⁵. This pulsatile behavior of p53 is induced by activation of p53 through ataxia telangiectasia mutated (ATM) subsequently resulting in transactivation of Mouse double minute (Mdm)2 and Wild-type p53 induced phosphatase (Wip)1, two negative regulators of p53⁸⁵. This induction of Mdm2 and Wip1 results in downregulation of p53 through a negative feedback loop. Such pulsatile waves of p53 activation occur in 4- to 7hr intervals at similar intensity until the DNA is fully repaired. In contrast to the IR response, UV irradiation causes a dose-dependent sustained induction of p53 that does not appear to result in oscillating waves⁸⁵. The role of IR-induced p53 pulses in determining cell fate remains to be elucidated.

p53 induces several negative regulators of the cell intrinsic Insulin-like growth factor (IGF)-1 receptor signaling pathway as well as systemically acting IGF-BP3, the major antagonistic IGF-1 carrier in the circulation. IGF-1 signaling induces cell proliferation, while reduced IGF-1 signaling is associated with extended lifespan in species ranging from nematode worms to mammals. p53-mediated cellular senescence, in contrast, promotes cellular aging, while senescent cells modify their tissue environment through the senescence associated secretory phenotype (SASP) resulting in cytokine secretion that activates the

innate immune system. The innate immune system in turn can act tumor suppressive (blue) by clearing cells that have become senescent as result of oncogene activation or chronic DNA damage. However, SASP might also have tumor promoting consequences on surrounding cells as cytokine signaling and chronic inflammation can promote proliferation of tumor cells. In addition, chronic inflammation is also associated with tissue aging.