Published in final edited form as:

Trends Genet. 2014 March ; 30(3): 95–102. doi:10.1016/j.tig.2013.12.001.

Systemic DNA damage responses: Organismal adaptations to genome instability

Maria A. Ermolaeva^{1,2} and Björn Schumacher^{1,2,3,*}

¹Institute for Genome Stability in Ageing and Disease, Medical Faculty, University of Cologne, 50931 Cologne, Germany

²Cologne Excellence Cluster for Cellular Stress Responses in Aging-Associated Diseases (CECAD), Institute for Genetics, University of Cologne, Zulpicher Str. 47a, 50674 Cologne, Germany

³Systems Biology of Ageing Cologne, University of Cologne, 50937 Cologne, Germany

Abstract

DNA damage checkpoints are important tumor suppressor mechanisms that halt cell cycle progression to allow time for DNA repair, or induce senescence and apoptosis to permanently remove damaged cells. Non-cell-autonomous DNA damage responses activate the innate immune system in multiple metazoan species. These responses enable clearance of damaged cells and contribute to tissue remodeling and regeneration but can also result in chronic inflammation and tissue damage. “Germline DNA damage-induced systemic stress resistance” (GDISR) is mediated by an ancestral innate immune response and results in organismal adjustments to the presence of damaged cells. We discuss GDISR as an organismal DNA damage checkpoint mechanism through which elevated somatic endurance can extend reproductive lifespan when germ cells require extended time for restoring genome stability.

The inevitability of DNA damage

Nuclear DNA is constantly exposed to a variety of genotoxic insults. DNA damage can be inflicted by endogenous sources such as metabolic byproducts, and by exogenous sources such as the ultraviolet spectrum of sunlight [1]. Accurate DNA repair is important for maintaining gene functions, while faulty repair results in mutations, which are the prerequisite of genome evolution. With the advent of specialized germ cells genome evolution was restricted to germline mutagenesis. Meiotic recombination became the main route for intraspecies genome diversity. Even in somatic cells the accuracy of DNA repair must be balanced between maintenance of genome integrity and the processes of DNA metabolism, namely replication and transcription. Particularly during the rapid mitotic cell divisions in embryos DNA repair processes must not compromise speedy DNA replication. Damage to the DNA is indeed not a rare event. It was estimated that each individual cell experiences tens of thousands of genotoxic events on a daily basis [2]. The types of damage range from frequent single strand breaks (SSBs) and oxidative base modifications to

*Correspondence: bjoern.schumacher@uni-koeln.de.

relatively rare, albeit highly cytotoxic lesions, such as double strand breaks (DSBs) and interstrand crosslinks (ICLs).

Cellular DNA damage checkpoints in tumor suppression

To cope with the variety of DNA lesions, cells have evolved highly sophisticated DNA repair machineries that are geared for recognizing and removing specific types of DNA alterations. The repair process, however, is embedded in a DNA damage response that affects the entire cell. The first programmed response to DNA damage was uncovered by yeast genetics. *Saccharomyces cerevisiae* that were mutant for the radiation sensitivity genes *rad9* or *Schizosaccharomyces pombe* defective in the *wee1* protein kinase failed to halt the cell cycle upon DNA damage [3,4]. These studies suggested that cell cycle arrest was important for allowing time to repair DNA damage and the response mechanisms were thus coined DNA damage checkpoints. After the initial identification of DNA damage checkpoints the number of genes implicated in linking the recognition of DNA lesions to halting of cell cycle progression steadily increased [5]. It became clear that checkpoint mechanisms were highly conserved from yeast to man. In metazoans, however, additional DNA damage checkpoint outputs complement the transient cell cycle arrest. Importantly, the metazoan DNA damage response (DDR) can also result in programmed cell death and cellular senescence [6]. Both of these “altruistic” behaviors of damaged cells could allow the organism to eliminate or at least inactivate potentially harmful cells.

Indeed, the most frequently mutated genes in human cancers were found to be part of the cellular DDR. The tumor suppressor gene p53 earned the title “guardian of the genome” as inactivating mutations in the gene, frequently found in human cancer cells, abolish large parts of the DNA damage checkpoint response [7,8]. The p53 molecule plays a central role in halting the cell cycle when DNA damage can be repaired, and also in promoting apoptosis or permanently withdrawing the cell from proliferation by inducing the cellular senescence program. p53 deficiency allows damaged cells to continuously proliferate and accumulate mutations -typical hallmarks of cancer cells [9]. Whereas inactivation of p53 can be sufficient for murine cells to continuously proliferate, human cells require additional mutations, for example activation of telomerase, an enzyme that maintains the ends of chromosomes, or constitutive activation of a growth signal producing oncogene to yield tumors [10]. As we will see below, tumors actively interact with other cell types and tissues. The development of tumors has, therefore, to be seen in the context of the entire organism [11]. In addition, the complexity of genome instability syndromes has provided important insights into the physiology of the DDR.

Genome instability syndromes: systemic consequences of DNA damage

Congenital defects in DNA repair systems give rise to highly complex and diverse human disorders. Three main physiological components characterize DNA repair syndromes: developmental abnormalities, tissue specific cancer susceptibility, and segmental progeria. The latter refers to premature-ageing-like –or progeroid- symptoms that affect some tissues but never resemble all features of normative ageing. Intriguingly, all disease symptoms affect specific but never all tissues equally. Each DNA repair defect has distinct pathological

outcomes. For example, Fanconi anemia (FA) cells are defective in ICL repair [12]. FA patients suffer from a reduced ability to reconstitute the hematopoietic system; eventually genomically compromised cells, however, can give rise to leukemia [13]. Also ataxia-telangiectasia (AT) patients, who are impaired in their ability to repair DSBs, suffer from cancer susceptibility in addition to dilated blood vessels, microcephaly, and growth defects [14]. Even different mutations in the same gene can give rise to distinct disease outcomes. An intriguing example for this dimension of complexity is the xeroderma pigmentosum complementation group D (*XPD*) gene [15]. Some *XPD* mutations lead to XP that is characterized by pigmentation abnormalities specifically in sun exposed skin areas, skin atrophy, and highly elevated skin cancer predisposition. Other mutations in *XPD* result in trichothiodystrophy (TTD). TTD patients are severely impaired in postnatal growth and show characteristic brittle hair and nails. The latter phenotypes are explained by an inherent transcription defect that leads to failure to build the stabilizing sulfate bridges in keratin [16]. Indeed, the XPD protein is not only essential for repair of UV-induced helix-distorting lesions but is also an integral part of the transcription-factor (TF)-IIH complex [17]. Yet other mutations in *XPD* cause XP combined with Cockayne syndrome (CS) [18]. The very rare XPCS patients show the characteristic XP skin phenotypes in addition to the CS-associated postnatal growth failure, loss of subcutaneous fat tissue, and degenerative phenotypes including retinal degeneration. CS is typically caused by mutations in the *CSA* and *CSB* genes that initiate repair of helix-distorting lesions when RNA polymerase II stalls at damage sites. Intriguingly, different mutations in the *CSA* and *CSB* genes give rise to a wide range of disease severity ranging from cerebro-oculo-facio-syndrome (COFS) with a life expectancy of several months, classical forms of CS with an average lifespan of twelve years, to the mild UV-hypersensitivity syndrome [19].

The complexity of the symptoms of human disorders caused by congenital DNA repair deficiencies cannot be easily explained by cell-autonomous consequences of DNA damage alone; instead disease-associated developmental failure and premature ageing might result from organismal consequences of impaired maintenance of genome stability. The systemic consequences of DNA repair deficiencies have been revealed in several mouse models. For instance, Sirtuin6 (*Sirt6*) deficiency results in elevated genome instability and *Sirt6* knockout mice show severe growth impairments, several progeroid features, and bone marrow defects. Despite the leukopenia, i.e. reduction of the number of white blood cells, of *Sirt6* knockout animals, *Sirt6* deficient hematopoietic stem cells (HSCs) could reconstitute the hematopoietic system in wild-type recipient mice [20]. Similarly, HSCs from late generation telomerase knockout mice could contribute to lymphopoiesis in wild-type recipients, whereas wild-type HSCs were unable to rescue the bone marrow defects in telomerase deficient recipient mice [21]. Both examples suggest that systemic adjustments to genome instability can determine regenerative capacities of stem cells. Mouse models for CS and the related XPF-ERCC1 (XFE) progeria recapitulate the severe growth defects and degenerative features of their human counterparts [22,23]. Strikingly, the so-called somatotrophic axis, which comprises an endocrine signaling circuit connecting the pituitary and the peripheral tissues that regulates body growth in mammals, was systemically reduced in these mice. In mouse and human cells, transcription-blocking DNA lesions, representing the genotoxic culprit of CS and XFE, could indeed result in downregulation of the Insulin-

like growth factor I receptor (IGF-1R) and growth hormone receptor (GHR), which comprise the key mediators of somatic growth in mammals [24]. Indeed, supplementation with IGF-1 in Hutchinson-Gilford-progeria-syndrome (HGPS) mice was sufficient to overcome their severe growth defects and to extend maximal lifespan, indicating that the early impairment of growth could to some extent limit life expectancy [25]. In further indication of the systemic consequences of tissue specific genome instability, brain specific inactivation of *Sirt6* was sufficient to compromise early postnatal growth. However, instead of succumbing to hypoglycemia, as do whole-body knockout mice, neural *Sirt6* mutant mice caught up in growth with their wild-type littermates but then showed reduced expression of hypothalamic neural hormones and became severely obese [26].

Non-cell autonomous DNA damage responses: inflammation and degeneration versus repair and regeneration

In addition to the reduction of the hormonal growth axis, DNA repair deficient progeroid as well as aged wild-type mice show elevated expression of immune and inflammatory genes [27]. Inflammatory responses to ablation of the XFE progeria gene *ERCC1* in fat tissues can trigger lipodystrophy [28]. Moreover, two distinct mouse models of HGPS exhibit elevated secretion of inflammatory cytokines through activation of the DNA damage checkpoint kinase AT-mutated (ATM) and the nuclear factor kappaB (NF- κ B) signaling component NF- κ B essential modulator (Nemo). Inactivation of proinflammatory NF- κ B signaling could alleviate progeroid features and extend lifespan indicating a causal contribution of inflammatory responses to ageing-associated pathology [29]. Likewise, some of the disease symptoms of XFE mice could be delayed by inhibiting NF- κ B signaling [30].

Inflammatory responses to DNA damage are most evident in UV irradiated skin. UV-induced DNA lesions trigger mitogen activated protein kinase (MAPK) and NF- κ B dependent secretion of inflammatory cytokines in keratinocytes, thus leading to programmed death of skin cells and attracting immune cells to the skin (Figure 1). The systemic immune response to skin-restricted DNA damage is highly complex and, as of yet, incompletely understood. It is thought that during initial triggering of the inflammatory reaction RANK ligand produced by keratinocytes binds to the respective receptor on the surface of immune cells of the skin, the Langerhans cells [31]. Conditioned Langerhans cells migrate into lymph nodes where they induce peripheral expansion of regulatory T-lymphocytes thereby conferring systemic immunosuppression [32]. Also direct links between damaged DNA and the activation of an innate immune response have become evident. ATM signaling upon DNA damage can indeed induce expression of the ligand for the natural killer group 2 member D (NKG2D) receptor that is present on natural killer cells [33]. Moreover, the cellular inflammasome can detect not only microbial but also host DNA in the cytoplasm and trigger an innate immune response [34].

Cells that were driven into senescence as a result of high irradiation doses that cause persistent DSBs are –despite being permanently mitotically arrested- highly metabolically active and secrete a host of cytokines [35]. It is thought that the “senescence associated secretory phenotype” (SASP) could support the growth of surrounding cells. Indeed, senescent cells secrete matrix metalloproteases that can remodel the tissues and thus support

the growth of xenograft tumors [36]. In contrast, the senescence program can also suppress tumorigenesis; for instance pre-malignant senescent cells activate adaptive immune responses to ignite tumor surveillance [37]. Also inflammatory responses can have tumor suppressive functions. Activation of p53 in murine liver carcinomas led to secretion of inflammatory cytokines that resulted in an innate immune response leading to tumor cell clearance [38]. Moreover, p53 driven senescence in chronically damaged livers could activate macrophages that contributed to non-cell autonomous tumor suppression [39].

The activation of innate immune responses to DNA damage might in fact have highly complex and context-dependent outcomes. Cellular senescence for example could be a driving factor for the ageing process. This has recently been observed in progeroid mice that carried defects in the spindle checkpoint factor budding uninhibited by benzimidazoles-related 1 (*BubR1*), resulting in massive occurrence of senescent cells [40]. Ablation of senescent cells, by linking the expression of the p16Ink4a senescence gene promoter with caspase expression, alleviated the degenerative phenotypes of the *BubR1* mice [41]. It will be highly interesting to determine the consequences of senescent cell ablation during normal ageing and with regard to tumor suppression and inflammation.

Consistent with the importance of inflammatory signaling in the pathology of progeroid mice, it is widely believed that chronic inflammation drives tissue damage and impairs tissue homeostasis and repair during ageing. The chronic inflammation is likely to result –at least to some extent- from gradual accumulation of DNA damage with ageing. However, the consequences of the activation of the innate immune system are far more complex. Recent evidence has implicated several components of the innate immune system in promoting tissue repair. For example the remodeling of tissue that is orchestrated by recruitment of immune cells is prerequisite for wound repair [42]. In contrast to the pathological senescence in the *BubR1* spindle checkpoint mutants, senescence of fibroblasts could prevent fibrosis and promote wound healing in the skin [43]. Even apoptotic cell death can promote wound healing and liver regeneration potentially through releasing growth signals [44]. Also intestinal cells require toll-like receptors and cytokine production for repair and regeneration (Figure 1) [45-47]. It is tempting to speculate that a balanced innate immune response might support tissue maintenance and regeneration whereas chronic inflammation damages tissues. The complexity of both mechanisms and outcomes of the immune response in mammals makes it worthwhile to consider more ancestral model systems to understand how distinct tissues interact in the presence of genome instability.

From flies and worms: Physiology of tissue interactions in the DNA damage response

Systemic responses to tissue specific genome instability have been observed in the *Drosophila melanogaster* larvae [48]. UV-induced DNA damage in the larval epidermis evoked an innate immune response and proliferation of hemocytes, the fly's immune cells. The immune response to UV damage was dependent on c-Jun-N-terminal kinase (JNK) and Janus kinase (JAK)/Signal Transducer and Activator of Transcription (STAT) signaling – conserved signal transducers also implicated in the mammalian innate immune activation (Figure 2). Interestingly, DNA damage-induced cytokine production caused systemic

inhibition of insulin signaling and growth arrest via limiting the secretion of insulin-like peptides by the central nervous system. The non-cell autonomous response to DNA damage in flies thus appears highly reminiscent of the systemic attenuation of the GH/IGF-mediated somatic growth axis in mice carrying inborn defects in DNA repair pathways (see above), suggesting that systemic responses to DNA damage are conserved from invertebrates to mammals. Furthermore, the activation of the Forkhead-box-protein O (FOXO) transcription factor, due to reduced insulin signaling in the fat body of the larvae, led to the induction of the secondary nondestructive immune response via NF- κ B/Relish, once again bearing similarities to the immune responses upon UV irradiation of the mammalian skin. Moreover, upon damage of the *Drosophila* intestine, by infection or tissue stress, the production of cytokines and JAK/STAT signaling in intestinal stem cells are essential for the regeneration of the tissue [49] similar to the involvement of innate immune system components upon intestinal injury in mammals [50]. Taken together, the systemic responses to localized DNA damage as well as the central role of the innate immune system in tissue remodeling and regeneration appear highly conserved between fruit flies and mammals.

Also in the nematode worm *Caenorhabditis elegans* systemic responses to tissue specific genome instability were recently uncovered [51]. The adult tissues of nematode worms are postmitotic, while germ cells undergo mitotic and meiotic cell divisions. Somatic tissues are highly resistant to ionizing radiation [52]; in contrast, germ cells are sensitive to DNA damage and respond through highly conserved DNA damage checkpoints that arrest mitotic cells and drive meiotic pachytene cells into *C. elegans* p53-like 1 (CEP-1) mediated apoptosis [53-55]. Strikingly, somatic tissues respond to the presence of DNA damage in germ cells by elevated resistance to oxidative and heat stress. The systemic stress resistance is mediated by the extracellular signal-regulated kinases 1/2 (ERK1/2) MAPK homolog MPK-1 in germ cells that triggers an innate immune response in the germline, which then becomes systemically established and confers resistance to pathogen infection [51]. This phenomenon, named “germline DNA damage-induced systemic stress resistance” (GDISR), depends on the activation of the ubiquitin proteasome system (UPS) in the soma (Figure 3). While the innate immune response upon germline DNA damage is triggered by MPK-1, the p38 homolog PMK-1 evokes a similar response upon intestinal infection by pathogens [56] also leading to systemic heat stress resistance [51] (See Box 1 for an overview of the *C. elegans* innate immune system). UPS activation as output of an innate immune response is intriguing, as elevated UPS activity can extend lifespan in worms [57]. In the context of immune induction, enhanced UPS activity might contribute to alleviating the folding stress during the production and secretion of large amounts of innate immune factors, similar to the function of the nematode’s unfolded protein response (UPR) during pathogen defense [58]. Moreover, it is conceivable that the enhanced stress resistance increases the endurance of somatic tissues to allow extension of the reproductive lifespan until the germ cell DNA has been repaired. Indeed, although DNA damage checkpoint activity transiently reduces offspring generation upon genotoxic stress in germ cells, progeny production resumes and continues at an age past the peak of reproduction under unperturbed conditions [51]. Conceptually, the innate immune system might thus mediate a “systemic” DNA damage checkpoint that “arrests” somatic lifespan until germline activity can resume [59]. By adapting somatic preservation to genome repair in the germline, GDISR might represent an

important mechanism of the disposable soma theory of ageing, which postulates that somatic maintenance needs to be adjusted to offspring generation in order to maximize fitness before the soma can be disposed off after successful passage of the genetic material to the successive generation [60]. It is tempting to speculate that a similar type of “somatic arrest” might be conferred by the temporary growth attenuation in UV irradiated flies, and during the systemic attenuation of the somatotrophic axis in DNA-repair deficient progeroid mouse models.

Concluding remarks

Systemic DNA damage responses have become apparent in metazoan species ranging from worms to mammals (Figure 4). In mammals, systemic DNA damage responses via activation of the immune system or reduced somatic growth signaling may play a major role in the physiological adjustments during the ageing process. Systemic responses may also play a role during acute genotoxic stress, for instance upon sun exposure or during chemotherapy. Exploring the emerging interactions between cell-autonomous and systemic responses as well as the interactions between different components of the immune response to DNA damage in mammals will likely yield new insights into cancer biology and the physiology of ageing. Further studies should aim to integrate tumor and progeroid models with tissue specific mutations in innate immunity components. Given the complexity of the innate immune responses in mammals, there is great value in studying ancestral immune responses to genome instability in flies and worms. Each model system has distinct advantages. *Drosophila* will be of particular importance for establishing systemic impingement on tissue homeostasis and regeneration in response to genotoxic stress. It will be particularly important to employ the fly model to further investigate the local and systemic interactions between growth and immune signaling and the consequences they have on regeneration and tissue maintenance with ageing. *C. elegans* allows the assessment of adjustments in terminally differentiated tissues, whose responses to genome instability are only poorly understood despite their significance for instance in the neurodegeneration that comprises a typical hallmark of progeroid syndromes and of the pathobiology of the ageing process in humans. The nematode system provides an opportunity to identify genes and uncover molecular mechanisms that orchestrate systemic DNA damage responses in a simple ancestral metazoan. Genetic approaches will be instrumental in understanding how the conserved components of the innate immune response, such as MAPK signaling, are linked to the recognition of DNA damage. Moreover, the nematode provides an interesting model for exploring how stress responses are linked to the innate immune system and how they allow withstanding pathogenic or genotoxic stress. The emerging field of systemic DNA damage responses should eventually lead to a more comprehensive understanding of the organismal adaptations to genome instability with ramifications to cancer, immunity, the biology of ageing, and mechanisms of age-related diseases.

Acknowledgments

ME received the EMBO long-term fellowship, BS acknowledges funding from the DFG (CECAD, SFB 829, and KFO 286), the ERC (Starting grant 260383), Marie Curie (FP7 ITN CodeAge 316354, aDdReSS 316390, MARRIAGE 316964, and ERG 239330), the German-Israeli Foundation (GIF, 2213-1935.13/2008 and 1104-68.11/2010), the Deutsche Krebshilfe (109453), and the BMBF (SyBaCol).

References

1. Loeb LA, Harris CC. Advances in chemical carcinogenesis: a historical review and prospective. *Cancer Res.* 2008; 68:6863–6872. [PubMed: 18757397]
2. De Bont R, van Larebeke N. Endogenous DNA damage in humans: a review of quantitative data. *Mutagenesis.* 2004; 19:169–185. [PubMed: 15123782]
3. Weinert T, Hartwell L. Control of G2 delay by the rad9 gene of *Saccharomyces cerevisiae*. *J Cell Sci Suppl.* 1989; 12:145–148. [PubMed: 2699734]
4. Rowley R, et al. The wee1 protein kinase is required for radiation-induced mitotic delay. *Nature.* 1992; 356:353–355. [PubMed: 1549179]
5. Harper JW, Elledge SJ. The DNA damage response: ten years after. *Molecular Cell.* 2007; 28:739–745. [PubMed: 18082599]
6. Jackson SP, Bartek J. The DNA-damage response in human biology and disease. *Nature.* 2009; 461:1071–1078. [PubMed: 19847258]
7. Lane DP. Cancer. p53, guardian of the genome. *Nature.* 1992; 358:15–16. [PubMed: 1614522]
8. Lane D, Levine A. p53 Research: The Past Thirty Years and the Next Thirty Years. *Cold Spring Harbor Perspectives in Biology.* 2010; 2:a000893–a000893. [PubMed: 20463001]
9. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell.* 2011; 144:646–674. [PubMed: 21376230]
10. Hahn WC, et al. Creation of human tumour cells with defined genetic elements. *Nature.* 1999; 400:464–468. [PubMed: 10440377]
11. Reinhardt HC, Schumacher B. The p53 network: cellular and systemic DNA damage responses in aging and cancer. *Trends Genet.* 2012; 28:128–136. [PubMed: 22265392]
12. Deans AJ, West SC. DNA interstrand crosslink repair and cancer. *Nat. Rev. Cancer.* 2011; 11:467–480. [PubMed: 21701511]
13. Andreassen PR, Ren K. Fanconi anemia proteins, DNA interstrand crosslink repair pathways, and cancer therapy. *Curr Cancer Drug Targets.* 2009; 9:101–117. [PubMed: 19200054]
14. Shiloh Y. ATM and related protein kinases: safeguarding genome integrity. *Nat. Rev. Cancer.* 2003; 3:155–168. [PubMed: 12612651]
15. Schumacher B, et al. Age to survive: DNA damage and aging. *Trends Genet.* 2008; 24:77–85. [PubMed: 18192065]
16. Vermeulen W, et al. A temperature-sensitive disorder in basal transcription and DNA repair in humans. *Nat. Genet.* 2001; 27:299–303. [PubMed: 11242112]
17. Schaeffer L, et al. DNA repair helicase: a component of BTF2 (TFIIH) basic transcription factor. *Science.* 1993; 260:58–63. [PubMed: 8465201]
18. Andressoo JO, et al. An Xpd mouse model for the combined xeroderma pigmentosum/Cockayne syndrome exhibiting both cancer predisposition and segmental progeria. *Cancer Cell.* 2006; 10:121–132. [PubMed: 16904611]
19. Laugel V, et al. Mutation update for the CSB/ERCC6 and CSA/ERCC8 genes involved in Cockayne syndrome. *Hum Mutat.* 2010; 31:113–126. [PubMed: 19894250]
20. Mostoslavsky R, et al. Genomic instability and aging-like phenotype in the absence of mammalian SIRT6. *Cell.* 2006; 124:315–329. [PubMed: 16439206]
21. Ju Z, et al. Telomere dysfunction induces environmental alterations limiting hematopoietic stem cell function and engraftment. *Nat. Med.* 2007; 13:742–747. [PubMed: 17486088]
22. Niedernhofer LJ, et al. A new progeroid syndrome reveals that genotoxic stress suppresses the somatotroph axis. *Nature.* 2006; 444:1038–1043. [PubMed: 17183314]
23. van der Pluijm I, et al. Impaired genome maintenance suppresses the growth hormone--insulin-like growth factor 1 axis in mice with Cockayne syndrome. *PLoS Biol.* 2007; 5:e2. [PubMed: 17326724]
24. Garinis GA, et al. Persistent transcription-blocking DNA lesions trigger somatic growth attenuation associated with longevity. *Nat. Cell Biol.* 2009; 11:604–615. [PubMed: 19363488]

25. Marino G, et al. Insulin-like growth factor 1 treatment extends longevity in a mouse model of human premature aging by restoring somatotroph axis function. *Proc. Natl. Acad. Sci. U.S.A.* 2010; 107:16268–16273. [PubMed: 20805469]
26. Schwer B, et al. Neural sirtuin 6 (Sirt6) ablation attenuates somatic growth and causes obesity. *Proc. Natl. Acad. Sci. U.S.A.* 2010 DOI: 10.1073/pnas.1016306107.
27. Schumacher B, et al. Delayed and accelerated aging share common longevity assurance mechanisms. *PLoS Genet.* 2008; 4:e1000161. [PubMed: 18704162]
28. Karakasilioti I, et al. DNA Damage Triggers a Chronic Autoinflammatory Response, Leading to Fat Depletion in NER Progeria. *Cell Metabolism.* 2013; 18:403–415. [PubMed: 24011075]
29. Osorio FG, et al. Nuclear lamina defects cause ATM-dependent NF- κ B activation and link accelerated aging to a systemic inflammatory response. *Genes and development.* 2012; 26:2311–2324. [PubMed: 23019125]
30. Tilstra JS, et al. NF- κ B inhibition delays DNA damage-induced senescence and aging in mice. *J. Clin. Invest.* 2012; 122:2601–2612. [PubMed: 22706308]
31. Lee C-H, et al. Molecular Mechanisms of UV-Induced Apoptosis and Its Effects on Skin Residential Cells: The Implication in UV-Based Phototherapy. *Int J Mol Sci.* 2013; 14:6414–6435. [PubMed: 23519108]
32. Schwarz T. Mechanisms of UV-induced immunosuppression. *Keio J Med.* 2005; 54:165–171. [PubMed: 16452825]
33. Gasser S, et al. The DNA damage pathway regulates innate immune system ligands of the NKG2D receptor. *Nature.* 2005; 436:1186–1190. [PubMed: 15995699]
34. Muruve DA, et al. The inflammasome recognizes cytosolic microbial and host DNA and triggers an innate immune response. *Nature.* 2008; 452:103–107. [PubMed: 18288107]
35. Rodier F, et al. Persistent DNA damage signalling triggers senescence-associated inflammatory cytokine secretion. *Nat. Cell Biol.* 2009; 11:973–979. [PubMed: 19597488]
36. Liu D, Hornsby PJ. Senescent human fibroblasts increase the early growth of xenograft tumors via matrix metalloproteinase secretion. *Cancer Res.* 2007; 67:3117–3126. [PubMed: 17409418]
37. Kang TW, et al. Senescence surveillance of pre-malignant hepatocytes limits liver cancer development. *Nature.* 2011; 479:547–551. [PubMed: 22080947]
38. Xue W, et al. Senescence and tumour clearance is triggered by p53 restoration in murine liver carcinomas. *Nature.* 2007; 445:656–660. [PubMed: 17251933]
39. Lujambio A, et al. Non-cell-autonomous tumor suppression by p53. *Cell.* 2013; 153:449–460. [PubMed: 23562644]
40. Baker DJ, et al. BubR1 insufficiency causes early onset of aging-associated phenotypes and infertility in mice. *Nat. Genet.* 2004; 36:744–749. [PubMed: 15208629]
41. Baker DJ, et al. Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. *Nature.* 2011; 479:232–236. [PubMed: 22048312]
42. Gregorio J, et al. Plasmacytoid dendritic cells sense skin injury and promote wound healing through type I interferons. *J. Exp. Med.* 2010; 207:2921–2930. [PubMed: 21115688]
43. Jun J-I, Lau LF. The matricellular protein Ccn1 induces fibroblast senescence and restricts fibrosis in cutaneous wound healing. *Nat. Cell Biol.* 2010; 12:676–685. [PubMed: 20526329]
44. Li F, et al. Apoptotic Cells Activate the “Phoenix Rising” Pathway to Promote Wound Healing and Tissue Regeneration. *Science Signaling.* 2010; 3:ra13–ra13. [PubMed: 20179271]
45. Rakoff-Nahoum S, et al. Recognition of commensal microflora by toll-like receptors is required for intestinal homeostasis. *Cell.* 2004; 118:229–241. [PubMed: 15260992]
46. Fukata M, et al. Toll-like receptor-4 is required for intestinal response to epithelial injury and limiting bacterial translocation in a murine model of acute colitis. *Am. J. Physiol. Gastrointest. Liver Physiol.* 2005; 288:G1055–65. [PubMed: 15826931]
47. Rose WA 2nd, et al. TLR9 is important for protection against intestinal damage and for intestinal repair. *Sci Rep.* 2012; 2:574. [PubMed: 22893852]
48. Karpac J, et al. Dynamic coordination of innate immune signaling and insulin signaling regulates systemic responses to localized DNA damage. *Dev. Cell.* 2011; 20:841–854. [PubMed: 21664581]

49. Jiang H, et al. Cytokine/Jak/Stat signaling mediates regeneration and homeostasis in the *Drosophila* midgut. *Cell*. 2009; 137:1343–1355. [PubMed: 19563763]
50. Iizuka M, Konno S. Wound healing of intestinal epithelial cells. *World J. Gastroenterol*. 2011; 17:2161–2171. [PubMed: 21633524]
51. Ermolaeva MA, et al. DNA damage in germ cells induces an innate immune response that triggers systemic stress resistance. *Nature*. 2013; 501:416–420. [PubMed: 23975097]
52. Johnson TE, Hartman PS. Radiation effects on life span in *Caenorhabditis elegans*. *J Gerontol*. 1988; 43:B137–41. [PubMed: 3418030]
53. Schumacher B, et al. The *C. elegans* homolog of the p53 tumor suppressor is required for DNA damage-induced apoptosis. *Curr. Biol*. 2001; 11:1722–1727. [PubMed: 11696333]
54. Derry WB, et al. *Caenorhabditis elegans* p53: role in apoptosis, meiosis, and stress resistance. *Science*. 2001; 294:591–595. [PubMed: 11557844]
55. Gartner A, et al. A conserved checkpoint pathway mediates DNA damage--induced apoptosis and cell cycle arrest in *C. elegans*. *Mol. Cell*. 2000; 5:435–443. [PubMed: 10882129]
56. Kim DH, et al. A conserved p38 MAP kinase pathway in *Caenorhabditis elegans* innate immunity. *Science*. 2002; 297:623–626. [PubMed: 12142542]
57. Vilchez D, et al. RPN-6 determines *C. elegans* longevity under proteotoxic stress conditions. *Nature*. 2012; 489:263–268. [PubMed: 22922647]
58. Richardson CE, et al. An essential role for XBP-1 in host protection against immune activation in *C. elegans*. *Nature*. 2010; 463:1092–1095. [PubMed: 20182512]
59. Ermolaeva MA, Schumacher B. The innate immune system as mediator of systemic DNA damage responses. *Communicative and Integrative Biology*. 2013 DOI: 10.4161/cib.26926.
60. Kirkwood TB. Understanding the odd science of aging. *Cell*. 2005; 120:437–447. [PubMed: 15734677]
61. Felix MA, et al. Natural and experimental infection of *Caenorhabditis* nematodes by novel viruses related to nodaviruses. *PLoS Biol*. 2011; 9:e1000586. [PubMed: 21283608]
62. Irazoqui JE, et al. Evolution of host innate defence: insights from *Caenorhabditis elegans* and primitive invertebrates. *Nat Rev Immunol*. 2010; 10:47–58. [PubMed: 20029447]
63. Troemel ER, et al. p38 MAPK regulates expression of immune response genes and contributes to longevity in *C. elegans*. *PLoS Genet*. 2006; 2:e183. [PubMed: 17096597]
64. Schulenburg H, et al. Specificity of the innate immune system and diversity of C-type lectin domain (CTLD) proteins in the nematode *Caenorhabditis elegans*. *Immunobiology*. 2008; 213:237–250. [PubMed: 18406370]
65. Bork P, Beckmann G. The CUB domain. A widespread module in developmentally regulated proteins. *J. Mol. Biol*. 1993; 231:539–545. [PubMed: 8510165]
66. Thomas JH. Concerted evolution of two novel protein families in *Caenorhabditis* species. *Genetics*. 2006; 172:2269–2281. [PubMed: 16415360]
67. Pujol N, et al. Distinct innate immune responses to infection and wounding in the *C. elegans* epidermis. *Curr. Biol*. 2008; 18:481–489. [PubMed: 18394898]
68. Hodgkin J, et al. A novel bacterial pathogen, *Microbacterium nematophilum*, induces morphological change in the nematode *C. elegans*. *Curr. Biol*. 2000; 10:1615–1618. [PubMed: 11137017]
69. Nicholas HR, Hodgkin J. The ERK MAP kinase cascade mediates tail swelling and a protective response to rectal infection in *C. elegans*. *Curr. Biol*. 2004; 14:1256–1261. [PubMed: 15268855]

Box 1**The *C. elegans* innate immune system**

In comparison to mammals and *Drosophila* the immune system of *C. elegans* is less complex. The nematode lacks both adaptive immunity and specialized immune cells leaving the additional function of pathogen surveillance to other tissues. Anti-viral protection is thought to be mediated by conserved RNA interference factors [61]. The intestine and the epidermis are the worm's primary lines of defense against bacterial and fungal infections.

Upon ingestion of pathogenic bacteria (for instance *Pseudomonas aeruginosa*, also a human pathogen) intestinal cells express a range of factors sharing structural and functional features with those involved in the mammalian innate immune response [62,63]. One large group of such factors is the C-type lectin domain containing proteins that bind specific carbohydrates on the bacterial surface [64]. Another group includes proteins containing a CUB domain, which is found in a diverse set of mostly extracellular proteins, including proteases. CUB denotes the presence of this domain in the C1s/C1r complement components, the embryonic sea urchin protein (Uegf), and bone morphogenetic protein 1 (Bmp1) [65]. Finally, a number of short, likely secreted, peptides are induced. They are thought to have antimicrobial function similar to mammalian AMPs, despite the lack of apparent direct structural homology [66]. Not only ingestion of bacteria but also mechanical wounding of the cuticle or infection with *Drechmeria coniospora*, a fungus that penetrates the epidermis of the worm, lead to induction of the worm's innate immune response [67]. Similarly, infectious *Microbacterium nematophilum* adheres to the cuticle of *C. elegans* and induces a local swelling response [68].

The infection-dependent expression of immune factors in *C. elegans* is mediated by conserved signaling platforms involved in innate immunity across different species. The intestinal immune pathway and the response to *D. coniospora* are dependent on the activation of the p38 MAP kinase homolog PMK-1, while the response to *M. nematophilum* is regulated by another MAP kinase - MPK-1/ERK [56,67,69]. Curiously, the Toll-like receptor (TLR) pathway that links fungal and bacterial infections to MAP kinase activation in mammals and *Drosophila* is not functional in nematodes [62]. Also the IMD/TNFR-1 pathway is absent in *C. elegans*. Worms express a single TLR, TOL-1, which plays a role during development but not in the immune response. This might be explained by the fact that important TLR downstream immune mediators such as Myd88 and NF- κ B are not encoded in the *C. elegans* genome.

Figure 1. Systemic responses to injury and DNA damage in the mammalian intestine and skin – similar features, mediators and outcomes

Given the complexity of mammalian physiology our understanding of the consequences of tissue-specific DNA damage in mammals has been largely restricted to the affected tissues and their direct neighbors. The skin and intestine are arguably the most environmentally exposed organs and, therefore, are at greater risk of damage and injury. Although distinct in their physiology, the two organs share common response mechanisms to DNA damage or infection. In both cases, the first reaction to the insult is the induction of an innate immune response via the NF-κB family of transcription factors and the MAP kinases JNK, p38 and ERK1/2. In the course of this response similar cytokines are produced such as TNFα and IL-6 that both contribute to the inflammatory tissue damage and also activate tissue remodeling and subsequent regeneration. In parallel to the innate immune reaction -or rather as part of it- local and systemic immune suppressive mechanisms are induced that limit the inflammatory tissue damage. For instance RANK ligand produced upon UV treatment of the skin triggers an immune-modulator phenotype of resident Langerhans cells making them travel to the lymph nodes where they mediate peripheral expansion of regulatory T-lymphocytes thus contributing to systemic immune suppression. When functioning properly,

the depicted signaling system is fine-tuned for clearing the damaged material and facilitating repair, thus ensuring maintenance of tissue homeostasis.

Figure 2. Systemic responses to DNA damage and injury in the fruit fly

The physiology of the fruit fly *Drosophila melanogaster* is far less complex than that of mammals. Yet, like the mammalian skin depicted on Figure 1, the epidermis of *Drosophila* larvae also activates an innate immune response upon UV-induced DNA damage. Intriguingly, the immune response has traceable systemic consequences: the initial immune induction in the epidermis, mediated by JNK signaling is amplified by *Drosophila* immune cells, i.e. the hemocytes. The amplification process consists of hemocyte expansion and massive cytokine production. JAK/STAT signaling plays a key role in this event. The cytokines produced act on the central nervous system to downregulate expression of insulin-like peptides, thereby inhibiting insulin signaling in the whole organism. At the level of the fat body, this leads to the activation of the *FOXO* transcription factor, causing systemic growth arrest and expression of stress-related genes. Consequently, a second wave of immune responses is activated through transcriptional induction of NF-κB/Relish. Systemic attenuation of insulin signaling has an inhibitory effect on hemocyte expansion and production of cytokines by these cells. Infection or injury of the *Drosophila* intestine also leads to the activation of JNK signaling and expression of innate immune mediators similar to those produced in response to DNA damage in the epidermis. The cytokines induce proliferation and differentiation of intestinal stem cells by binding to the IL-6R homologue

dom and activating JAK/STAT signaling. This event is crucial for the repair of the gut upon injury and tissue stress.

Figure 3. Germline DNA damage-induced systemic stress resistance (GDISR) in the nematode *C. elegans*

The systemic response to tissue-specific DNA damage in *C. elegans* was recently described. Induction of genome instability in germ cells by exogenous or endogenous sources causes activation of the ERK1/2 MAP kinase MPK-1, leading to the transcriptional induction of putative secreted innate immune peptides in the germline. The innate immune response becomes systemically established, thus conferring pathogen resistance and systemic resistance to environmental factors such as heat and oxidative stress. The resistance to stress is mediated through activation of the ubiquitin proteasome system (UPS), which likely acts downstream of the innate immune response. When an innate immune response is triggered in the intestine via ingestion of immunogenic bacteria, similar pathogen and stress resistance are induced. However a different MAP kinase, namely the p38 homolog PMK-1, is the key mediator of pathogen induced innate immunity.

Figure 4. Comparison of systemic responses to DNA damage between *C. elegans*, *D. melanogaster*, and *M. musculus*

Despite differences in organismal complexity and the degree of mechanistic dissection of respective signaling cascades it has become increasingly apparent that similar pathways are induced by DNA damage in all three model organisms, leading to conceptually similar global consequences. For instance innate immune activation mediated by MAP kinase signaling is involved in systemic responses to DNA damage in all presented models. Therefore, the systemic responses to tissue specific DNA damage appear to be conserved throughout metazoan evolutionary.