

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



The Role of DNA Repair in Cellular Aging Process

*Francisco Alejandro Lagunas-Rangel
and Rosa María Bermúdez-Cruz*

Abstract

Aging is defined as the time-dependent decline of functional properties. One common denominator of aging is mitochondrial dysfunction and accumulation of genetic damage throughout life. In fact, the imperfect maintenance of nuclear and mitochondrial DNA likely represents a critical contributor of aging. Each day, the integrity and stability of DNA are challenged by exogenous physical, chemical, or biological agents, as well as by endogenous processes, including DNA replication mistakes, spontaneous hydrolytic reactions, and reactive oxygen species. In this way, DNA repair systems have evolved a complex network that is collectively able of dealing with most of the damages inflicted. However, their efficiency may decrease with age and, therefore, influence the rate of aging. Thus, the purpose of this work is to summarize the recent knowledge in cellular aging process and its link with DNA repair systems, with a particular emphasis on the molecular mechanisms associated.

Keywords: DNA damage, DNA repair, BER, NER, MMR, HR, NHEJ

1. Introduction

Aging is a complex biological process that results in a progressive loss of physiological integrity. Overall, aging is a consequence of accumulation of cellular damage and is characterized by nine hallmarks: genomic instability, telomere attrition, epigenetic alterations, cellular senescence, mitochondrial dysfunction, loss of proteostasis, deregulated nutrient sensing, stem cell exhaustion, and altered intercellular communication (**Figure 1**) [1]. Although aging may involve damage to various cellular constituents, there is evidence suggesting that DNA constitutes the key target in this process [2]; consequently, genomic instability is the main factor of aging [3–5]. Genome instability has been implicated as a cause of aging since unrepaired DNA damage, DNA mutations, and epimutations accumulate in an age-related manner [3]. In the same way, the notion that multi-system premature aging syndromes are mainly caused by defects in genome maintenance or affect genome function highlights the role of genome integrity in aging [6]. Meanwhile, normal aging is accompanied by telomere shortening with cell division due to the “end-replication problem” and telomere end processing. Currently, there is a wide body of evidence associating reduction in the length of telomeres with failure of cell division and senescence of normal cells, and oxidative stress and inflammation can contribute to the rate of attrition of telomere length [7]. Age-related changes involve

alterations in DNA methylation patterns and posttranslational modification of histones such as increased histone H4K16 acetylation [8], H4K20 trimethylation [9], or H3K4 trimethylation [10], as well as decreased H3K9 methylation [11] or H3K27 trimethylation [12]. At the same time, with aging there is also a global heterochromatin loss and redistribution [13], thus affecting the expression of several genes, mainly those involved in DNA repair, cellular proliferation, differentiation, and cell-cycle regulation, and therefore triggering the emergence of other hallmarks of aging [14, 15]. Cellular senescence is a process that has become an important contributor in aging since it imposes a permanent proliferative arrest of cells in response to various stressors such as DNA damage and telomere loss [16]. Furthermore, as cells and organisms age, mitochondria suffer a decline in their integrity and function, tending to diminish the efficacy of the respiratory chain and thus reducing ATP generation, increasing electron leakage and ROS production that can damage DNA, proteins, and lipids, among other important biomolecules [17]. Proteostasis involves mechanisms for correct folding proteins and mechanisms for the degradation of proteins, which act in a coordinated fashion to prevent the accumulation of damaged components and assuring the continuous renewal of intracellular proteins. There is evidence that aging is associated with perturbed proteostasis, thus favoring the development of several diseases [18]. Recent data have shown that anabolic signaling accelerates aging; in agreement with this, caloric-restricted diet decreases nutrient signaling and as a result, a long life span is promoted since DNA repair systems are improved; on the other hand, protein homeostasis decreases ROS production and delays cellular senescence [19]. Decline in the regenerative potential of tissues is one of the most obvious characteristics of aging, where stem cell exhaustion is also important and explained by a decreased cell-cycle activity. Interestingly, this correlates with the accumulation of DNA damage, telomere shortening, and overexpression of cell-cycle inhibitory proteins such as p16INK4a, increasing the relevancy of DNA repair systems [20]. Finally, aging also involves changes at the level of intercellular communication, where neurohormonal signaling tends to be deregulated together with composition of the peri- and extracellular environment

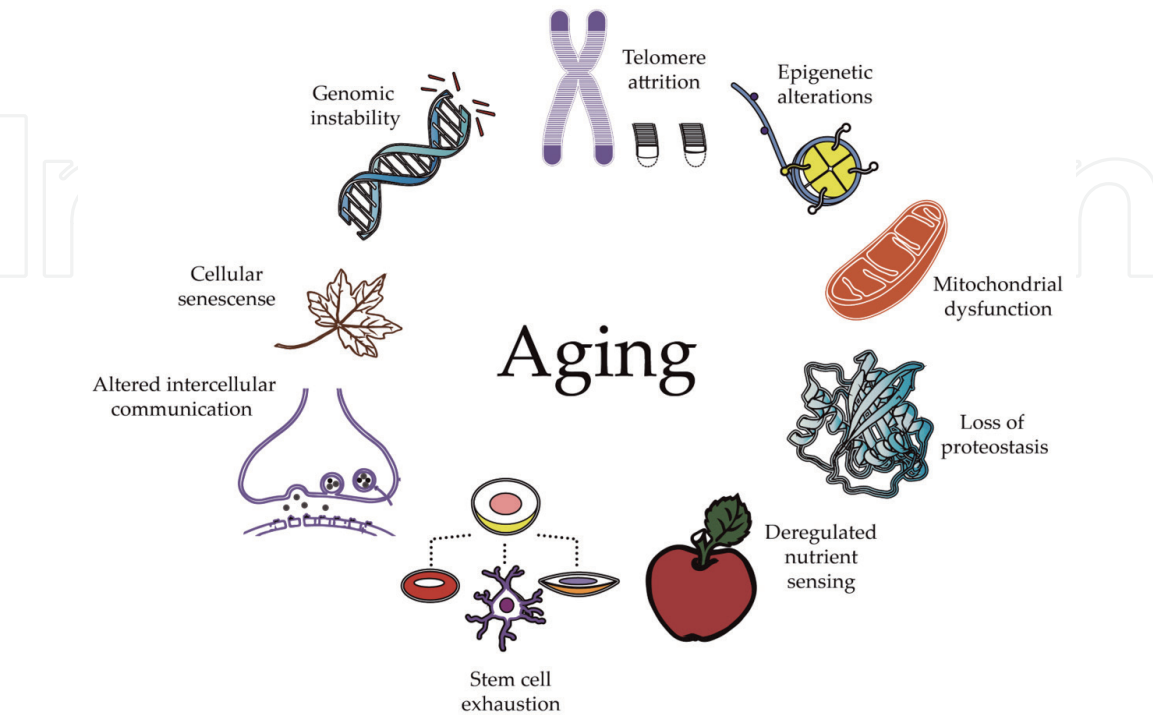


Figure 1. The hallmarks of aging. The figure illustrates nine hallmarks previously described [1] and where age-related changes in DNA repair systems have important roles to promote the development of this phenotype.

and immune system, specially increasing inflammatory reactions and declining immunosurveillance against pathogens and premalignant cells [21]. In this way, our work focuses on describing the molecular bases that associate DNA damage and the cell aging process, with a special emphasis in DNA repair systems.

2. Age-related changes in DNA repair

Each day, the integrity and stability of DNA are challenged by exogenous physical, chemical, or biological agents, as well as by endogenous processes, including DNA replication mistakes, spontaneous hydrolytic reactions, and reactive oxygen species (ROS). Thus, depending on the source of damage, DNA can be affected in different ways, including nucleotide alterations, bulky adducts, single-strand breaks (SSB), and double-strand breaks (DSB). To combat threats posed by DNA damage, cells have evolved complex and finely regulated mechanisms collectively referred to as DNA damage response (DDR) which detects DNA lesions, signals their presence, and promotes their repair [22–24]. However, according with the genome maintenance hypothesis of aging, DNA repair can itself be subject to age-related changes and deterioration, allowing accumulation of damages (**Figure 2**). The wide diversity of DNA-lesion types requires multiple, largely distinct DNA repair mechanisms that differ in their components, whereas some lesions are subject to direct protein-mediated reversal, most are repaired by a sequence of catalytic events mediated by multiple proteins [22]. Thus, cells with defects in key proteins involved in DDR have been shown an accelerated aging phenotype caused by the accumulation of mutations and epimutations that eventually cause malfunction of the cells, senescence, or apoptosis [25].

2.1 Response to DNA single-strand breaks (SSBs)

2.1.1 Base excision repair (BER)

BER pathway corrects DNA damage from oxidation, deamination, alkylation, and other small DNA alterations that do not distort the overall structure of double helix. In general, BER is initiated by a DNA glycosylase that recognizes and

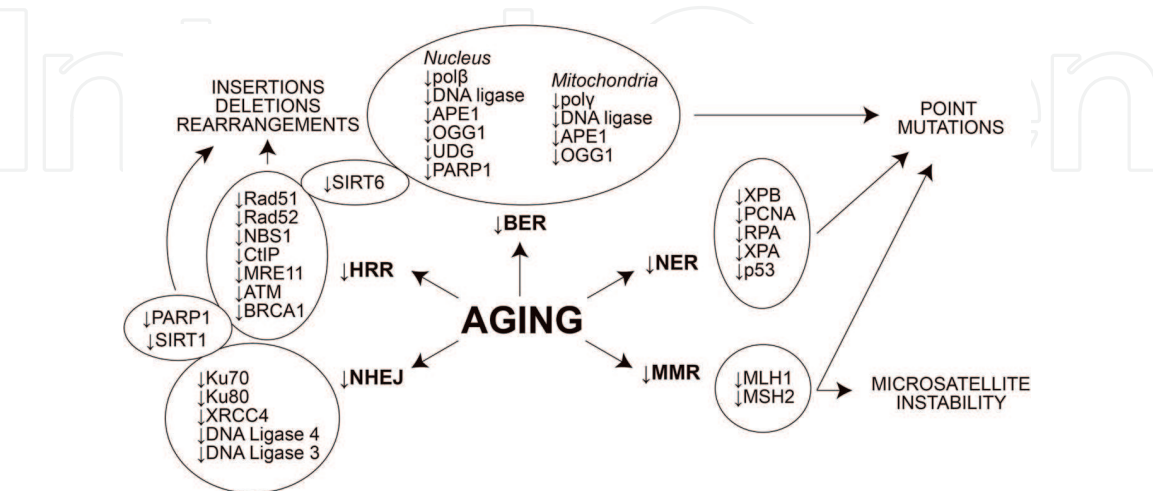


Figure 2. Age-related changes in DNA repair and their consequences. Aging involves deterioration of DNA repair systems allowing the damages to accumulate and eventually cause a malfunction of the cells. In general, all age-related changes in DNA repair pathways promote genomic instability in different ways. Decline in efficiency and fidelity of BER and NER leads to point mutations, whereas inefficient MMR leads to microsatellite instability and point mutations. Meanwhile, deficiencies in NHEJ and HRR result in deletions and genomic rearrangements.

removes the damaged base, leaving an abasic (apurinic/apyrimidinic; AP) site that is subsequently processed by an AP endonuclease (APE), an exonuclease, a DNA polymerase, a ligase, and many other ancillary factors in a short-patch repair or long-patch repair [26]. Notably, several pieces of evidence indicate that the efficacy of BER may negatively change with age, and it has a significant impact in longevity together with homologous recombination repair (HRR) [27]. Age-related changes in the BER mechanism have been studied mainly in neuronal extracts where it constitutes the main repair pathway. In this way, an overall deficiency in several factors has been observed [28], where DNA polymerase β (pol β) together with DNA ligase [29] and APE1 activities [30, 31] seem to be the most limiting factors. Interestingly, an age-dependent attenuation in the transcriptional activation of pol β and APE1 was observed in response to DNA damage [32] together with APE1 accumulation in the nucleus and mitochondria [33]. Aging has also been shown to have a significant effect on cleavage efficacy of tetrahydrofuran:A, U:G mispair, U:A base pair, thymine glycol:A, and 8-oxo-7,8-dihydroguanine:C [34]. Thus, senescent human fibroblasts as well as leukocytes from old donors showed higher basal level of AP sites than young donors. However, after a challenge with the oxidizing agent H_2O_2 or the alkylating agent methyl methanesulfonate (MMS), the number of AP sites increased quickly in young cells, whereas in senescent and older cells, they were observed to grow slowly with a concomitant loss of viability, suggesting a decrease in DNA glycosylase activity, mainly in OGG1 8-oxoguanine and 3-methyladenine DNA glycosylases [35], although other reports have also mentioned a decrease in the UDG uracil-DNA glycosylase [28]. Because polyADP-ribosylation (PARylation) levels are linked to downstream mechanisms in DNA repair together with other cellular deficiencies as cell-cycle arrest, cell survival, cell death, and/or cell transformation, a decline in PARP1 activity is important since it has been linked with the age in humans and rats [36]. Further, a decrease in the interaction between the endonuclease VIII-like NEIL1 and PARP1 was observed in old mice when compared to young mice [37], which also could be associated with the decrease in PARP1 activity. Meanwhile, a significant decrease in the expression of SIRT6 has been reported to have a relevant role in BER because it regulates repair activity through a PARP1-dependent pathway [38]. Since sirtuins can function as metabolic sensors, they could also be related with a significative increase in pol β [39] and APE activities [30] under caloric restricted diets. Consequently, BER pathway showed to be deficient when repairing age-downregulated genes in comparison with genes that are not affected by age [40].

On the other hand, the mitochondrial free radical theory of aging states that free radicals generated in mitochondria are strongly related with the intrinsic aging process, mainly due to the accumulation of oxidative damage and derived mutations in mitochondrial DNA (mtDNA) mainly in D-loop region. mtDNA is more susceptible to oxidative damage than the nuclear genome, presumably because of the physical proximity of the source of ROS and lack of histones [41]. BER is the predominant and best understood DNA repair pathway in mitochondria involving at least four components, a DNA glycosylase, an AP endonuclease (or other mechanism for processing abasic sites), DNA polymerase γ (pol γ), and DNA ligase [42]. Recently, pol β was also detected in mitochondrial protein extracts, where it is required to provide enhanced mtDNA BER activity [43]. In a similar way to nuclear BER, in rat brain mitochondria, there is a marked age-dependent decline in mitochondrial BER activity, as indicated by a pol β , pol γ , ligase, APE1 endonuclease, and OGG1 glycosylase activities [44]. Interestingly, activity of mitochondrial OGG1 AE8-oxoguanine DNA glycosylase increases in mouse liver mitochondria according with the age [45]. However, a significant fraction of the OGG1 remains in the outer membrane and intermembrane space in an immature form, presumably because

its import into the mitochondrial matrix is impaired as a consequence of aging. In addition, a nearly identical phenomenon was observed with the mitochondrial uracil-DNA glycosylase [46].

2.1.2 Nucleotide excision repair (NER)

NER is the primary pathway for repairing a wide range bulky DNA lesions, including UV-induced photoproducts (cyclopurimidine dimers [CPDs], 6–4 photoproducts [6-4PPs]), adducts formed by mutagens in the environment such as benzo[a]pyrene or some aromatic amines, some oxidative endogenous lesions such as cyclopurines, and adducts formed by cancer chemotherapeutic drugs such as cisplatin. NER can be initiated by two subpathways: global genome NER (GG-NER) where the participation of XPC-RAD23B is involved and the transcription-coupled NER (TC-NER) where RNA polymerase interacts with CSA, CSB, and XAB2. Both converge to complete the excision process requiring the core NER factors RPA, XPA, TFIIH, XPD, XPB, XPG, and ERCC1–XPF, among other auxiliary proteins [47]. NER activity decreases with aging possibly because there is a transcriptional downregulation of NER genes together with an altered protein function or processing and a decrease in energy production [48]. In this manner, it was previously observed that aged human skin [49] and fibroblasts [50] showed decreased levels of XPB, PCNA, RPA, XPA, and p53, and more importantly the UVB-induced pyrimidine dimers were removed in a slower manner than in younger counterparts [50]. Interestingly, the effect of age on the repair of UV-induced DNA damage varies for transcribed and nontranscribed DNA, decreasing considerably in unexpressed DNA [51, 52] but improving in both cases under calorie restricted diets [52]. Furthermore, UV-induced damage and repair in telomeres showed to be slower and less frequent than in other regions of the genome such as active genes [53]. Additionally, ERCC1 and XPF, which are considered as the rate-limiting members in NER, also showed an age-dependent decline in their relative expression levels [54]. Because XPC, XPB, and XPF appear to be dependent on the activation status of the IGF-1R, decreased levels of IGF-1R observed with aging also contributed with the decline of NER pathway [55]. Meanwhile, in an assay based in plasmid reactivation after UV damage, cells from older donors introduced an increased number of mutations in the transfected plasmid, which suggests that not only the repair is less efficient with age but also more mistakes are made [51].

2.1.3 Mismatch repair (MMR)

The mismatched nucleotides in the DNA can result from polymerase misincorporation errors, recombination between imperfectly matched sequences, chemical or physical damage to nucleotides, and deamination of 5-methylcytosine (5mC) mostly during replication. MMR pathway consists of four major heterodimeric complexes, MutL homolog (MutL) α , MutL β , MutS homolog (MutS) α , and MutS β . MutL α involves MLH1 and PMS2, whereas MutL β consist of MLH1 and PMS1. Meanwhile, MutS α consists of MSH2 and MSH6, and MutS β is constituted by MSH2 and MSH3. Thus, MutS α complex recognizes single mispaired bases, whereas MutS β detects mispaired runs of 3–6 bases. MutS α or MutS β recruits MutL α or MutL β and forms a tetrameric complex that serves as a base for the recruitment of excision and repair machinery [56]. MMR removes mispaired bases preventing mutations [57], and defects in this pathway are strongly associated with a substantial destabilization of microsatellites, which are tandemly repeated sequences (from 1 to 6 bp), highly polymorphic, interspersed in the genome, and susceptible to slippage during replication [58]. Previously, a decline in MMR function and efficiency correlation with age

was observed [59, 60], especially in microsatellite sequences [61] where age-related methylation of the MLH1 [62, 63] and MSH2 [64] promoters could be associated to microsatellite instability (MSI). Interestingly, MLH1 shores showed a decrease in methylation with increasing age [65]. Shores are regions of the genome around CpG islands with lower GC content and with the ability to control gene expression.

2.2 Response to DNA double-strand breaks (DSBs)

2.2.1 Homologous recombination repair (HRR)

With aging there is an increase in DNA double-strand breaks [66]. However, it is unknown whether this increase is a consequence of accumulation of unrepaired DSBs or progressively delayed repair events, possibly as a reflection of an inherently limited capacity to process DSBs [67]. To repair this kind of DNA damage, HRR, considered a highly reliable pathway, allows the cell to access and copy information from the intact DNA sequence into the sister chromatid. Notably, HRR is restricted to late S to G2 phases when chromosomes are aligned [68]. RAD51 and other members of the RAD52 epistasis group as RAD50, MRE11, and XRS2 are needed for HRR. The efficiency of HRR is enhanced by mediator proteins that promote the loading of RAD51 onto ssDNA, RAD52 among them [69]. HR-mediated repair efficiency declines precipitously during cellular aging together with a decline of RAD51, RAD51C, RAD52, NBS1, CTIP, and MRE11 levels [66, 70]. Furthermore, in human and mice oocytes, a decrease in expression of BRCA1 and ATM [71] and an impaired recruitment of RAD51 to DNA damage sites during aging [72] were observed, which could force cells to utilize the error-prone NHEJ pathway. At the same time, in older mice a lower activity of the ATM kinase that results in less p53 phosphorylation was reported, thus affecting apoptosis, cell-cycle arrest, and senescence [73]. In addition to the above, the decrease in the levels of PARP1 [36] and SIRT6 [38] not only affects BER pathway but also has a relevant role in HRR since supplementation of recombinant SIRT6 was able to partly restore HR activity [70]. This could be related to a higher binding of DBC1 to PARP1 inhibiting its enzymatic activity as well as the change in NAD⁺ levels [74]. Decreased NAD⁺ levels observed with age also reduce activity of other sirtuins as SIRT1 and SIRT7 together with PARP1, reducing NHEJ and HRR pathways [75]. Although HRR is essential, its activity must be carefully controlled in order to maintain genomic integrity [76]. Previously, it has been demonstrated that frequency of recombinant cells is highly variable among tissues, from very low levels in the brain and stomach to very frequent in the pancreas and spleen. Additionally, de novo recombination events indeed accumulate in mice colonic somatic stem cells with age [77].

2.2.2 Nonhomologous end joined (NHEJ)

In human cells, NHEJ is the major pathway for the repair of DSBs, where two ends of DNA with little or no sequence homology are brought together and repaired. NHEJ can act throughout most of the cell cycle but predominantly in G1 phase [68]. NHEJ is divided into two subpathways: the classical NHEJ pathway (c-NHEJ), in which DNA-PKcs, Ku70/Ku80 heterodimers, Artemis, XRCC4, XLF, and DNA Ligase 4 are involved, and the alternative NHEJ pathway (alt-NHEJ), comprised of the repair factors PARP1 and DNA ligase 3 [78]. Both NHEJ pathways are associated with changes in DNA sequence, where c-NHEJ causes deletions and insertions, whereas alt-NHEJ propitiates the loss of genetic information between microhomologies on chromosomes [79]. NHEJ becomes inefficient and more error-prone during cellular senescence, thus favoring genomic instability and higher

incidence of cancer in the elderly [80, 81]. Furthermore, NHEJ-mediated VDJ recombination in B lymphocytes is impaired, reducing class switch recombination efficiency and contributing to reduced humoral repertoire and impaired immunity with aging [82]. Frequency of microhomology-mediated end joining (MMEJ) increases as a compensatory mechanism; however, at the same time, it favors that more mistakes are generated [81]. Ku 70 and 80 proteins decreased their expression at least twofold in two lines of senescent human fibroblast; at the same time, their localization was changed concentrating them in the nucleus when compared with young cells where they are present in both the nucleus and cytoplasm [83]. Cytoplasmic Ku proteins could serve as a reserve (pool) that is recruited to the nucleus upon DNA damage; therefore in senescent cells these proteins are unavailable to repair new lesions [25]. Additionally, binding activity of the Ku 70/80 heterodimers to broken DNA ends also declines with aging [66]. Notably, mice and cells deleted for either Ku70 or Ku80 exhibited not solely NHEJ disruption but also altered BER [84]. On the other hand, decreased expression of XRCC4, DNA ligase 4, and DNA ligase 3 has been observed, and this implicates that during the aging process, NHEJ becomes more inefficient and inaccurate, leaving more damage sites repaired with a loss of additional genetic information [72]. Interestingly, aging increases DNA-PK activity phosphorylating HSP90 α and decreasing its chaperone function in AMPK, which is critical for mitochondrial biogenesis and energy metabolism [85]. Consistently, DNA ligase 4 and Ku80 gene promoters were frequently observed as hypermethylated in elderly people, which could be associated with the silencing expression of both genes [86]. However, as mentioned for other DNA repair mechanisms, caloric restriction diet improves NHEJ activity possibly through SIRT1 and FOXO activity [87].

3. Conclusions

Aging is a consequence of damage accumulation in different cellular constituents and where DNA damage is one of the most important. Every day there are thousands of insults that affect DNA, either due to endogenous factors (such as metabolism) or exogenous factor like contact with radiation sources or exposure to toxic substances; but only a minimal amount (less than 0.02%) accumulates as permanent damage, while the rest is totally repaired. However, if only one gene is not repaired and its function is important as that of a proto-oncogene, a tumor suppressor, or any DNA repair genes, this could lead to accumulation of mutations, and then DNA damage checkpoints can halt the cell cycle and induce cellular senescence or apoptosis, or well erroneous repair or replicative bypass of lesions can result in mutations and chromosomal aberrations leading the cells to transform into cancer cells.

Notably, DNA repair systems are able of dealing with most of the damages inflicted to DNA; however, their efficiency decrease with age, permitting that point mutations, insertions, deletions, and rearrangements, among others, occur more frequently and accumulate over time. This is due in part to the fact that critical proteins involved in DNA repair significantly decrease their expression in an age-related manner. In **Figure 2**, the main age-related changes reported over the different mechanisms of DNA repair together with their consequences that globally cause genomic instability and favor cellular senescence and cancer are summarized.

Overall, this area needs to be more exploited in order to improve our quality of life and prevent or delay the harmful effects of aging. Thus, the more knowledge we acquire about the natural cell aging process and its interrelation with the mechanisms of DNA repair, the closer we will be to develop drugs, therapies, or even vaccines that could help us to prolong our life.

Acknowledgements

FALR is recipient of a doctoral scholarship (application number 2018-000012-01NACF-07226) from the National Council of Science and Technology, CONACyT.

Conflict of interest

The authors declare no conflict of interest.

Author details

Francisco Alejandro Lagunas-Rangel and Rosa María Bermúdez-Cruz*
Department of Genetics and Molecular Biology, Center for Research and Advanced Studies of the National Polytechnic Institute (CINVESTAV), Mexico

*Address all correspondence to: roberm@cinvestav.mx

IntechOpen

© 2019 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell*. 2013 Jun;**153**(6, 6):1194-1217
- [2] Lenart P, Krejci L. DNA, the central molecule of aging. *Mutation Research: Fundamental and Molecular Mechanisms of Mutagenesis*. 2016 Apr;**786**:1-7
- [3] Vijg J, Suh Y. Genome instability and aging. *Annual Review of Physiology*. 2013 Feb;**75**(1):645-668
- [4] Vijg J, Dong X, Milholland B, Zhang L. Genome instability: A conserved mechanism of ageing? *Essays in Biochemistry*. 2017 Jul;**61**(3):305-315
- [5] Lombard DB, Chua KF, Mostoslavsky R, Franco S, Gostissa M, Alt FW. DNA repair, genome stability, and aging. *Cell*. 2005 Feb;**120**(4):497-512
- [6] Vermeij WP, Hoeijmakers JH, Pothof J. Aging: Not all DNA damage is equal. *Current Opinion in Genetics and Development*. 2014 Jun;**26**:124-130
- [7] Prasad KN, Wu M, Bondy SC. Telomere shortening during aging: Attenuation by antioxidants and anti-inflammatory agents. *Mechanisms of Ageing and Development*. 2017 Jun;**164**(April):61-66
- [8] Dang W, Steffen KK, Perry R, Dorsey JA, Johnson FB, Shilatifard A, et al. Histone H4 lysine 16 acetylation regulates cellular lifespan. *Nature*. 2009 Jun;**459**(7248):802-807
- [9] Nelson DM, Jaber-Hijazi F, Cole JJ, Robertson NA, Pawlikowski JS, Norris KT, et al. Mapping H4K20me3 onto the chromatin landscape of senescent cells indicates a function in control of cell senescence and tumor suppression through preservation of genetic and epigenetic stability. *Genome Biology*. 2016 Dec;**17**(1):158
- [10] Cruz C, Della Rosa M, Krueger C, Gao Q, Horkai D, King M, et al. Tri-methylation of histone H3 lysine 4 facilitates gene expression in ageing cells. *eLife*. 2018 Oct;**7**:1-24
- [11] Djeghloul D, Kuranda K, Kuzniak I, Barbieri D, Naguibneva I, Choisy C, et al. Age-associated decrease of the histone methyltransferase SUV39H1 in HSC perturbs heterochromatin and B lymphoid differentiation. *Stem Cell Reports*. 2016 Jun;**6**(6):970-984
- [12] Ma Z, Wang H, Cai Y, Wang H, Niu K, Wu X, et al. Epigenetic drift of H3K27me3 in aging links glycolysis to healthy longevity in *Drosophila*. *eLife*. 2018 May;**7**:1-33
- [13] Tsurumi A, Li W. Global heterochromatin loss. *Epigenetics*. 2012 Jul;**7**(7):680-688
- [14] Booth LN, Brunet A. The aging epigenome. *Molecular Cell*. 2016 Jun;**62**(5):728-744
- [15] Zane L, Sharma V, Misteli T. Common features of chromatin in aging and cancer: Cause or coincidence? *Trends in Cell Biology*. 2014 Nov;**24**(11):686-694
- [16] Childs BG, Durik M, Baker DJ, van Deursen JM. Cellular senescence in aging and age-related disease: From mechanisms to therapy. *Nature Medicine*. 2015 Dec;**21**(12):1424-1435
- [17] Chistiakov DA, Sobenin IA, Revin VV, Orekhov AN, Bobryshev YV. Mitochondrial aging and age-related dysfunction of mitochondria. *BioMed Research International*. 2014;**2014**:1-7
- [18] Klaips CL, Jayaraj GG, Hartl FU. Pathways of cellular proteostasis in aging and disease. *The Journal of Cell Biology*. 2018 Jan;**217**(1):51-63

- [19] López-Otín C, Galluzzi L, Freije JMP, Madeo F, Kroemer G. Metabolic control of longevity. *Cell*. 2016 Aug;**166**(4):802-821
- [20] Kosan C, Heide F, Godmann M, Bierhoff H. Epigenetic erosion in adult stem cells: Drivers and passengers of aging. *Cell*. 2018 Nov;**7**(12):237
- [21] Rebelo-Marques A, De Sousa Lages A, Andrade R, Ribeiro CF, Mota-Pinto A, Carrilho F, et al. Aging hallmarks: The benefits of physical exercise. *Front Endocrinol (Lausanne)*. 2018 May;**9**(May):1-15
- [22] Jackson SP, Bartek J. The DNA-damage response in human biology and disease. *Nature*. 2009 Oct;**461**(7267):1071-1078
- [23] Ciccia A, Elledge SJ. The DNA damage response: Making it safe to play with knives. *Molecular Cell*. 2010 Oct;**40**(2):179-204
- [24] Harper JW, Elledge SJ. The DNA damage response: Ten years after. *Molecular Cell*. 2007 Dec;**28**(5):739-745
- [25] Gorbunova V, Seluanov A, Mao Z, Hine C. Changes in DNA repair during aging. *Nucleic Acids Research*. 2007 Nov;**35**(22):7466-7474
- [26] Krokan HE, Bjoras M. Base excision repair. *Cold Spring Harbor Perspectives in Biology*. 2013 Apr;**5**(4):a012583-a012583
- [27] Debrabant B, Soerensen M, Flachsbar F, Dato S, Mengel-From J, Stevnsner T, et al. Human longevity and variation in DNA damage response and repair: Study of the contribution of sub-processes using competitive gene-set analysis. *European Journal of Human Genetics*. 2014 Sep;**22**(9):1131-1136
- [28] Swain U, Rao KS. Age-dependent decline of DNA base excision repair activity in rat cortical neurons. *Mechanisms of Ageing and Development*. 2012 Apr;**133**(4):186-194
- [29] Krishna TH, Mahipal S, Sudhakar A, Sugimoto H, Kalluri R, Rao KS. Reduced DNA gap repair in aging rat neuronal extracts and its restoration by DNA polymerase beta and DNA-ligase. *Journal of Neurochemistry*. 2005 Feb;**92**(4):818-823
- [30] Kisby GE, Kohama SG, Olivas A, Churchwell M, Doerge D, Spangler E, et al. Effect of caloric restriction on base-excision repair (BER) in the aging rat brain. *Experimental Gerontology*. 2010 Mar;**45**(3):208-216
- [31] Li M, Yang X, Lu X, Dai N, Zhang S, Cheng Y, et al. APE1 deficiency promotes cellular senescence and premature aging features. *Nucleic Acids Research*. 2018 Jun;**46**(11):5664-5677
- [32] Cabelof DC, Raffoul JJ, Ge Y, Van Remmen H, Matherly LH, Heydari AR. Age-related loss of the DNA repair response following exposure to oxidative stress. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*. 2006 May;**61**(5):427-434
- [33] Szczesny B, Mitra S. Effect of aging on intracellular distribution of abasic (AP) endonuclease 1 in the mouse liver. *Mechanisms of Ageing and Development*. 2005 Oct;**126**(10):1071-1078
- [34] Pons B, Belmont A-S, Masson-Genteuil G, Chapuis V, Oddos T, Sauvaigo S. Age-associated modifications of base excision repair activities in human skin fibroblast extracts. *Mechanisms of Ageing and Development*. 2010 Nov;**131**(11-12):661-665
- [35] Atamna H, Cheung I, Ames BN. A method for detecting abasic sites in living cells: Age-dependent changes in base excision repair. *Proceedings of the*

National Academy of Sciences. 2000
 Jan;**97**(2):686-691

[36] Grube K, Bürkle A. Poly(ADP-ribose) polymerase activity in mononuclear leukocytes of 13 mammalian species correlates with species-specific life span. *Proceedings of the National Academy of Sciences of the United States of America*. 1992 Dec;**89**(24):11759-11763

[37] Noren Hooten N, Fitzpatrick M, Kompaniez K, Jacob KD, Moore BR, Nagle J, et al. Coordination of DNA repair by NEIL1 and PARP-1: A possible link to aging. *Aging (Albany NY)*. 2012 Oct;**4**(10):674-685

[38] Xu Z, Zhang L, Zhang W, Meng D, Zhang H, Jiang Y, et al. SIRT6 rescues the age related decline in base excision repair in a PARP1-dependent manner. *Cell Cycle*. 2015 Jan;**14**(2):269-276

[39] Cabelof D. Caloric restriction promotes genomic stability by induction of base excision repair and reversal of its age-related decline. *DNA Repair (Amst)*. 2003 Mar;**2**(3):295-307

[40] Lu T, Pan Y, Kao S-Y, Li C, Kohane I, Chan J, et al. Gene regulation and DNA damage in the ageing human brain. *Nature*. 2004 Jun;**429**(6994):883-891

[41] Yakes FM, Van Houten B. Mitochondrial DNA damage is more extensive and persists longer than nuclear DNA damage in human cells following oxidative stress. *Proceedings of the National Academy of Sciences*. 1997 Jan;**94**(2):514-519

[42] Prakash A, Doublié S. Base excision repair in the mitochondria. *Journal of Cellular Biochemistry*. 2015 Aug;**116**(8):1490-1499

[43] Sykora P, Kanno S, Akbari M, Kulikowicz T, Baptiste BA, Leandro GS, et al. DNA polymerase beta participates in mitochondrial DNA repair.

Molecular and Cellular Biology. 2017 Aug;**37**(16):1-20

[44] Chen D, Cao G, Hastings T, Feng Y, Pei W, O'Horo C, et al. Age-dependent decline of DNA repair activity for oxidative lesions in rat brain mitochondria. *Journal of Neurochemistry*. 2002 Jun;**81**(6, 6):1273-1284

[45] de Souza-Pinto N, Hogue B, Bohr V. DNA repair and aging in mouse liver: 8-oxodG glycosylase activity increase in mitochondrial but not in nuclear extracts. *Free Radical Biology and Medicine*. 2001 Apr;**30**(8):916-923

[46] Szczesny B, Hazra TK, Papaconstantinou J, Mitra S, Boldogh I. Age-dependent deficiency in import of mitochondrial DNA glycosylases required for repair of oxidatively damaged bases. *Proceedings of the National Academy of Sciences*. 2003 Sep;**100**(19):10670-10675

[47] Schärer OD. Nucleotide excision repair in eukaryotes. *Cold Spring Harbor Perspectives in Biology*. 2013 Oct;**5**(10):a012609

[48] Meyer JN, Boyd WA, Azzam GA, Haugen AC, Freedman JH, Van Houten B. Decline of nucleotide excision repair capacity in aging *Caenorhabditis elegans*. *Genome Biology*. 2007;**8**(5):R70

[49] Yamada M, Udonon MU, Hori M, Hirose R, Sato S, Mori T, et al. Aged human skin removes UVB-induced pyrimidine dimers from the epidermis more slowly than younger adult skin in vivo. *Archives of Dermatological Research*. 2006 Jan;**297**(7):294-302

[50] Goukassian D, Gad F, Yaar M, Eller MS, Nehal US, Gilchrist BA. Mechanisms and implications of the age-associated decrease in DNA repair capacity. *The FASEB Journal*. 2000 Jul;**14**(10):1325-1334

- [51] Moriwaki S-I, Ray S, Tarone RE, Kraemer KH, Grossman L. The effect of donor age on the processing of UV-damaged DNA by cultured human cells: Reduced DNA repair capacity and increased DNA mutability. *Mutation Research/DNA Repair*. 1996 Oct;**364**(2):117-123
- [52] Guo ZM, Heydari A, Richardson A. Nucleotide excision repair of actively transcribed versus nontranscribed DNA in rat hepatocytes: Effect of age and dietary restriction. *Experimental Cell Research*. 1998;**245**(1):228-238
- [53] Kruk PA, Rampino NJ, Bohr VA. DNA damage and repair in telomeres: Relation to aging. *Proceedings of the National Academy of Sciences*. 1995 Jan;**92**(1):258-262
- [54] Deng XD, Gao Q, Zhang W, Zhang B, Ma Y, Zhang LX, et al. The age-related expression decline of ERCC1 and XPF for forensic age estimation: A preliminary study. *Journal of Forensic and Legal Medicine*. 2017 Jul;**49**:15-19
- [55] Loesch MM, Collier AE, Southern DH, Ward RE, Tholpady SS, Lewis DA, et al. Insulin-like growth factor-1 receptor regulates repair of ultraviolet B-induced DNA damage in human keratinocytes in vivo. *Molecular Oncology*. 2016 Oct;**10**(8):1245-1254
- [56] Liu D, Keijzers G, Rasmussen LJ. DNA mismatch repair and its many roles in eukaryotic cells. *Mutation Research/Reviews in Mutation*. 2017 Jul;**773**:174-187
- [57] Li GM. Mechanisms and functions of DNA mismatch repair. *Cell Research*. 2008 Jan;**18**(1):85-98
- [58] Coolbaugh-Murphy MI, Xu J, Ramagli LS, Brown BW, Siciliano MJ. Microsatellite instability (MSI) increases with age in normal somatic cells. *Mechanisms of Ageing and Development*. 2005 Oct;**126**(10):1051-1059
- [59] Annett K, Duggan O, Freeburn R, Hyland P, Pawelec G, Barnett Y. An investigation of DNA mismatch repair capacity under normal culture conditions and under conditions of supra-physiological challenge in human CD4+T cell clones from donors of different ages. *Experimental Gerontology*. 2005 Dec;**40**(12):976-981
- [60] Yehuda AB, Globerson A, Krichevsky S, Bar On H, Kidron M, Friedlander Y, et al. Ageing and the mismatch repair system. *Mechanisms of Ageing and Development*. 2001 Jan;**121**(1-3):173-179
- [61] Neri S, Gardini A, Facchini A, Olivieri F, Franceschi C, Ravaglia G, et al. Mismatch repair system and aging: Microsatellite instability in peripheral blood cells from differently aged participants. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*. 2005 Mar;**60**(3):285-292
- [62] Nakagawa H, Nuovo GJ, Zervos EE, Martin EW, Salovaara R, Aaltonen LA, et al. Age-related hypermethylation of the 5' region of MLH1 in normal colonic mucosa is associated with microsatellite-unstable colorectal cancer development. *Cancer Research*. 2001 Oct;**61**(19):6991-6995
- [63] Kenyon J, Fu P, Lingas K, Thomas E, Saurastri A, Santos Guasch G, et al. Humans accumulate microsatellite instability with acquired loss of MLH1 protein in hematopoietic stem and progenitor cells as a function of age. *Blood*. 2012 Oct;**120**(16):3229-3236
- [64] Conde-Pérezprina JC, Luna-López A, López-Díazguerrero NE, Damián-Matsumura P, Zentella A, Königsberg M. Msh2 promoter region hypermethylation as a marker of aging-related deterioration in old retired female breeder mice. *Biogerontology*. 2008 Oct;**9**(5):325-334

- [65] Savio AJ, Lemire M, Mrkonjic M, Gallinger S, Zanke BW, Hudson TJ, et al. MLH1 region polymorphisms show a significant association with CpG Island shore methylation in a large cohort of healthy individuals. *PLoS One*. 2012 Dec;7(12):e51531
- [66] Frasca D, Barattini P, Tirindelli D, Guidi L, Bartoloni C, Errani A, et al. Effect of age on DNA binding of the ku protein in irradiated human peripheral blood mononuclear cells (PBMC). *Experimental Gerontology*. 1999 Aug;34(5):645-658
- [67] White RR, Vijg J. Do DNA double-strand breaks drive aging? *Molecular Cell*. 2016 Sep;63(5):729-738
- [68] Zhao X, Wei C, Li J, Xing P, Li J, Zheng S, et al. Cell cycle-dependent control of homologous recombination. *Acta Biochimica et Biophysica Sinica (Shanghai)*. 2017 Aug;49(8):655-668
- [69] Sung P, Klein H. Mechanism of homologous recombination: Mediators and helicases take on regulatory functions. *Nature Reviews. Molecular Cell Biology*. 2006 Oct;7(10):739-750
- [70] Mao Z, Tian X, Van Meter M, Ke Z, Gorbunova V, Seluanov A. Sirtuin 6 (SIRT6) rescues the decline of homologous recombination repair during replicative senescence. *Proceedings of the National Academy of Sciences*. 2012 Jul;109(29):11800-11805
- [71] Titus S, Li F, Stobezki R, Akula K, Unsal E, Jeong K, et al. Impairment of BRCA1-related DNA double-strand break repair leads to ovarian aging in mice and humans. *Science Translational Medicine*. 2013 Feb;5(172):172ra21, 172ra21
- [72] Li Z, Zhang W, Chen Y, Guo W, Zhang J, Tang H, et al. Impaired DNA double-strand break repair contributes to the age-associated rise of genomic instability in humans. *Cell Death and Differentiation*. 2016 Nov;23(11):1765-1777
- [73] Feng Z, Hu W, Teresky AK, Hernando E, Cordon-Cardo C, Levine AJ. Declining p53 function in the aging process: A possible mechanism for the increased tumor incidence in older populations. *Proceedings of the National Academy of Sciences*. 2007 Oct;104(42):16633-16638
- [74] Li J, Bonkowski MS, Moniot S, Zhang D, Hubbard BP, Ling AJY, et al. A conserved NAD + binding pocket that regulates protein-protein interactions during aging. *Science*. 2017 Mar;355(6331):1312-1317
- [75] Mendelsohn AR, Larrick JW. The NAD+/PARP1/SIRT1 axis in aging. *Rejuvenation Research*. 2017 Jun;20(3):244-247
- [76] Guirouilh-Barbat J, Lambert S, Bertrand P, Lopez BS. Is homologous recombination really an error-free process? *Frontiers in Genetics*. 2014 Jun;5(Jun):1-15
- [77] Sukup-Jackson MR, Kiraly O, Kay JE, Na L, Rowland EA, Winther KE, et al. Rosa26-GFP direct repeat (RaDR-GFP) mice reveal tissue- and age-dependence of homologous recombination in mammals in vivo. *PLoS Genetics*. 2014 Jun;10(6):e1004299
- [78] Rulten SL, Grundy GJ. Non-homologous end joining: Common interaction sites and exchange of multiple factors in the DNA repair process. *BioEssays*. 2017 Mar;39(3):1600209
- [79] Rodgers K, McVey M. Error-prone repair of DNA double-strand breaks. *Journal of Cellular Physiology*. 2016 Jan;231(1):15-24
- [80] Seluanov A, Mittelman D, Pereira-Smith OM, Wilson JH, Gorbunova V. DNA end joining becomes less efficient

and more error-prone during cellular senescence. Proceedings of the National Academy of Sciences. 2004 May;**101**(20):7624-7629

[81] Vaidya A, Mao Z, Tian X, Spencer B, Seluanov A, Gorbunova V. Knock-in reporter mice demonstrate that DNA repair by non-homologous end joining declines with age. PLoS Genetics. 2014 Jul;**10**(7):e1004511

[82] Puthiyaveetil AG, Caudell DL. Non homologous end joining-mediated DNA break repair is impaired in B lymphocytes of aging mice. Molecular Immunology. 2013 Jan;**53**(1-2):79-87

[83] Seluanov A, Danek J, Hause N, Gorbunova V. Changes in the level and distribution of Ku proteins during cellular senescence. DNA Repair (Amst). 2007 Dec;**6**(12):1740-1748

[84] Choi YJ, Li H, Son MY, Wang X, Fornsglio JL, Sobol RW, et al. Deletion of individual Ku subunits in mice causes an NHEJ-independent phenotype potentially by altering apurinic/apyrimidinic site repair. PLoS One. 2014 Jan;**9**(1):e86358

[85] Park S, Gavrilova O, Brown AL, Soto JE, Bremner S, Kim J, et al. DNA-PK promotes the mitochondrial, metabolic, and physical decline that occurs during aging. Cell Metabolism. 2017 May;**25**(5):1135-1146.e7

[86] Martín-Guerrero I, de Prado E, Lopez-Lopez E, Ardanaz M, Vitoria JC, Parada LA, et al. Methylation of the nonhomologous end joining repair pathway genes does not explain the increase of translocations with aging. Age (Omaha). 2014 Dec;**36**(6):9730

[87] Lee JE, Heo JI, Park SH, Kim JH, Kho YJ, Kang HJ, et al. Calorie restriction (CR) reduces age-dependent decline of non-homologous end joining (NHEJ) activity in rat tissues. Experimental Gerontology. 2011 Nov;**46**(11):891-896