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REVIEW

Activity of DNA Repair Systems in the Cells of Long-Lived Rodents and Bats

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Abstract—Damages of various origin accumulated in the genomic DNA can lead to the breach of genome stability, and are considered to be one of the main factors involved in cellular senescence. DNA repair systems in mammalian cells ensure effective damage removal and repair of the genome structure, therefore, activity of these systems is expected to be correlated with high maximum lifespan observed in the long-lived mammals. This review discusses current results of the studies focused on determination of the DNA repair system activity and investigation of the properties of its key regulatory proteins in the cells of long-lived rodents and bats. Based on the works discussed in the review, it could be concluded that the long-lived rodents and bats in general demonstrate high efficiency in functioning and regulation of DNA repair systems. Nevertheless, a number of questions around the study of DNA repair in the cells of long-lived rodents and bats remain poorly understood, answers to which could open up new avenues for further research.

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INTRODUCTION

Aging is an age-related deterioration of body physiological functions, which may result in developing cardiovascular diseases, cancer, and neurodegeneration. Aging manifests itself at the cellular level as a consequence of pathological changes in cellular homeostasis, accompanied by irreversible cell cycle arrest and acquisition of a corresponding phenotype by the cell, development of a chronic inflammatory reaction at the tissue level, and many other symptoms [1]. Age-related accumulation of “aging” cells in the body, being dependent on the decreased efficiency of their removal from tissues, contributes to the body senescence and development of the aging-associated diseases [2]. One of the main causes of the cellular senescence is disruption of the genome structure. It could occur both spontaneously (replication errors, deamination of nitrogenous bases and depurination) and due to exogenous (UV radiation, drugs, etc.) and endogenous (reactive oxygen species) factors [3-6]. Various cellular mechanisms are involved in maintaining the mammalian genome stability [7-9] and DNA repair systems play an essential role among them. Many studies have been devoted to correlation between the DNA repair and aging [5, 10, 11]; decreased activity of DNA repair systems is known today to lead to the increased genome damage and damage accumulation rate, which, in turn, results in the significantly increased risk of the development of pathologies associated with aging [9, 12, 13]. At the same time, the results of comparative studies of the DNA repair system activity, as well as its function and regulation in the long-lived mammals have been investigated only to a small extent. Relevant information on the functional

Abbreviations: BER, base excision repair; HR, homologous recombination; NER, nucleotide excision repair; NHEJ, non-homologous DNA end junction; PARP1, poly(ADP-ribose)-polymerase 1; SIRT6, sirtuin 6 histone deacetylase.

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status of DNA repair systems and peculiarities of the corresponding proteins in the cells of long-lived mammals could provide a more detailed understanding of the links between the DNA repair and aging.

Various representatives of the Rodentia order are the most popular models for comparative studies of aging in mammals [14-16]. There are animals among them that demonstrate high maximum lifespan (over 30 years), as well as resistance to prolonged exposure to oxidative stress and cancer [17-19]. Much attention is also paid to bats (Chiroptera) as a potential model for studying aging in mammals. On the one hand, it is due to the high maximum lifespan (about 30-40 years) observed for many representatives of this order. On the other hand, it results from a huge lack of knowledge about the peculiarities of the DNA repair system functioning within bat cells [20]. Hence, search for and investigation of these peculiarities that promote genome stability and longevity in the long-lived rodents and bats could be of great research interest.

Objective of this review is to analyze relevant data on the activity of DNA repair systems in the cells of long-lived rodents and bats. In the first part of the review the described results of the studies devoted to activity of the DNA repair systems in the cells of these mammals are presented. In the second part of the review the results of studying activity of the NAD^+-dependent poly(ADP-ribose)polymerase 1 (PARP1) and histone deacetylase sirtuin 6 (SIRT6) in the context of investigation of the considered phylogenetic animal groups are discussed, since PARP1 and SIRT6 are among the main regulatory proteins of DNA repair processes. The review overlaps partially with the research of Yamamura et al. [19], Gorbunova et al. [20] and Boughey et al. [21], published recently. Information on the results obtained from the study of DNA repair processes within the cells of long-lived rodents and bats presented in the review may be relevant and useful to the researchers focused not only on the studying molecular basis of longevity in mammals, including humans, but also on the developing effective strategy for extension of lifespan and treatment of aging-associated diseases.

DNA REPAIR SYSTEM ACTIVITY

Specialized DNA repair systems become activated in the cell in response to DNA damage, and their functions are associated with the cell cycle regulation and cell death [22]. Spontaneously formed apurine/apyrimidine (AP) sites, single- and double-strand breaks, DNA–DNA cross-linking, as well as DNA–protein crosslinks and various bulky DNA damages are serious disruptions of the genome structure, their persistence could lead to the cells death or their transformation into the state of cellular senescence. Cells maintain genome structure, which enables their normal functioning with the help of such efficient DNA repair systems as base excision repair (BER) and nucleotide excision repair (NER), as well as homologous recombination (HR) and non-homologous end joining (NHEJ) ensuring removal of the wide range of damages. All this gives grounds to focus on DNA repair as one of the main factors promoting longevity [5]. In the search for interrelations between the maximum lifespan and efficiency of these DNA repair systems, a number of experimental works were carried out comparing status of the repair systems in the mammalian cells from organisms with different maximum lifespan: humans, rodents, and bats.

RNA sequencing (RNA-seq) and subsequent analysis of expression of the 130 protein genes involved in DNA repair revealed that expression levels of more than 30 genes, including genes encoding proteins involved in the BER and NHEJ processes in the liver cells of naked mole-rat (*Heterocephalus glaber*, ~28 years) and humans were considerably higher compared to the mouse cells (*Mus musculus*, ~4 years) [23, 24]. The results of qPCR quantitative analysis of the mRNA content, carried out later, showed that within 24 h after UV irradiation expression level of many BER and NER protein genes in the mouse fibroblasts increased significantly, while no pronounced response at the expression level of these genes was shown in the naked mole-rat cells. At the same time, comparative assessment of activity of these repair systems showed that the DNA repair proteins activity in the naked mole-rat is 1.5-3 times higher than in a mouse [25].

Tian et al. [26] showed using the host cell reactivation method (HCR) that there is a significant variability of the repair efficiency of a plasmid, containing multiple UV lesions by the NER proteins *in vivo* among 18 rodent species; and there is no correlation between the plasmid repair efficiency and lifespan. At the same time, using HCR and another model plasmid, direct correlation was first established between the efficiency of double-stranded breaks repair by the proteins of NHEJ systems and HR in the pulmonary ($r^2 = 0.31$; $p < 0.05$) and dermal ($r^2 = 0.57$; $p < 0.01$) fibroblasts and lifespan within the studied group of rodents [26]. Despite some disadvantages associated with the difficulty in obtaining model plasmids, advantages of the HCR method make its further application to be especially in demand for measuring activity of the DNA repair systems at the cell level [27].

RNA-seq demonstrated that the cells of the long-lived Middle East blind mole-rat (*Spalax ehrenbergi*, ~20 years) also revealed higher gene expression levels of the BER and HR proteins compared to the cells of the short-lived brown rat (*Rattus norvegicus*, ~5 years) [28] and mouse [29]. Similar expression levels of the DNA repair genes in the blind mole-rat and

the naked mole-rat are believed to be a consequence of adaptation to hypoxic conditions of their habitat. Increase in expression of the genes of DNA repair proteins under hypoxic conditions has been also observed in some other rodents [30, 31].

High resistance of the naked mole-rat cells to the effects of DNA damaging agents (methyl methanesulfonate, 5-fluorouracil, and etoposide) [32] and gamma-radiation [33, 34] revealed in the subsequent studies could be the result of effective functioning of the DNA repair systems. Dermal fibroblasts of the long-lived blind mole-rat also show higher resistance to etoposide compared to the human and mouse cells, which allows blind mole-rat cells to avoid the stress-induced aging [35].

Whole genome sequencing (WGS) of the intestinal and skin cells of 18 mammalian representatives and subsequent statistical analysis of the results showed that the mutation accumulation rate in the somatic cell genome is inversely correlated with the mammalian lifespan [36]. It is notable that the mutation accumulation rate in the naked mole-rat somatic cells was almost 8-fold lower than that in the mouse cells. In the work of Robinson et al. [12] the level and rate of the spontaneously generated cyclopurine DNA damage accumulation in the wild-type mouse cells and the cells of mice with reduced ERCC1 expression (NER) were observed. Using mass spectrometry, it was shown that the content of cyclopurine in the $ERCC1^{-/\Delta}$ cells of 5-month-old mice was higher than that in the cells of wild-type mice of similar age and comparable to the level in the cells of the older wild-type mice (3 years old). Thus, in the absence of functionally active NER, accumulation rate of the spontaneous DNA damage in the cells increases, and the level of spontaneous damage is approaching to the values, typical for the aging cells. The results of β-galactosidase activity analysis in combination with the data obtained by the FISH method showed that these damages, if not eliminated, could contribute to cell senescence in mammalian tissues [12]. These assumptions were experimentally confirmed in the further study of mutant mice with ERCC1 gene knockout, which demonstrated chronic inflammatory reaction and characteristic aging phenotype [37].

A relatively small number of researches focused on DNA repair study in bat cells has been conducted; there have been no studies aimed at determination of activity of various DNA repair systems. Comparative transcriptome analysis of the cells from various tissues of the greater mouse-eared bat (*Myotis myotis*, ~37 years) and other mammals with different lifespan, such as mice, brown rats, human, and naked mole-rats, showed that in the greater mouse-eared bat cells expression level of many genes of the proteins participating in DNA repair and cell cycle regulation (for example, ATM, PARP1, RAD50, RFC3, RPA1, MLH3, XRCC5) is increased [38]. The later transcriptome analysis of blood samples of the long-lived greater mouse-eared bat revealed increased expression level of 32 protein genes of various DNA repair systems, among which 13 genes encode proteins of the NER system [39]. Notably, gene expression levels of the DNA repair proteins in the greater mouse-eared bat cells increase with age, while there is a decrease in the expression level of these genes in human cells. Using the same methods and samples, the authors of this work later conducted comparative transcriptome analysis of the cells obtained from the long-lived greater mouse-eared bat and the short-lived velvety free-tailed bat (*Molossus molossus*, ~5.6 years) and showed that expression levels of the DNA repair protein genes and macroautophagy protein genes are significantly increased in the cells of the long-lived greater mouse-eared bat [40].

Based on the presented data, it can be concluded that the long-lived rodents, unlike the short-lived ones, do demonstrate high activity of the DNA repair systems, which contributes to the timely removal of DNA damages and, as a result, decreased level and rate of their accumulation in the genome. Taken together, these data confirm modern ideas about the role of DNA repair in mammalian aging [5]. However, some contradictions that are observed when comparing the results of transcriptome analysis and assessing the DNA repair system activity in rodents [23-25] indicate the need to conduct experiments aimed at further identification and study of the proteins participating in this process by proteomic methods. These experiments should also be focused on the assessment of activity of the involved protein, since gene expression levels do not always correlate with the expression levels of the corresponding proteins, their content in the cell, and especially with their activity. For the long-lived bats, only increase in the expression level of the genes encoding DNA repair proteins has been shown and there is no information on the functional status of the DNA repair systems in the cells. Thus, further studies are needed using methods for determining activity of the DNA repair systems and quantifying the levels of DNA damage.

PARP1 AND SIRT6, KEY DNA REPAIR REGULATORS

Effective search for the DNA damages, as well as assembly of the repair complexes and functioning of the repair proteins are essentially affected by the chromatin compaction. In this regard, special attention is paid to two NAD^+-dependent proteins, PARP1 and SIRT6, which play a key role in many cellular processes, including regulation of repair proteins, as well as access of those two proteins to chromatin regions [41, 42].

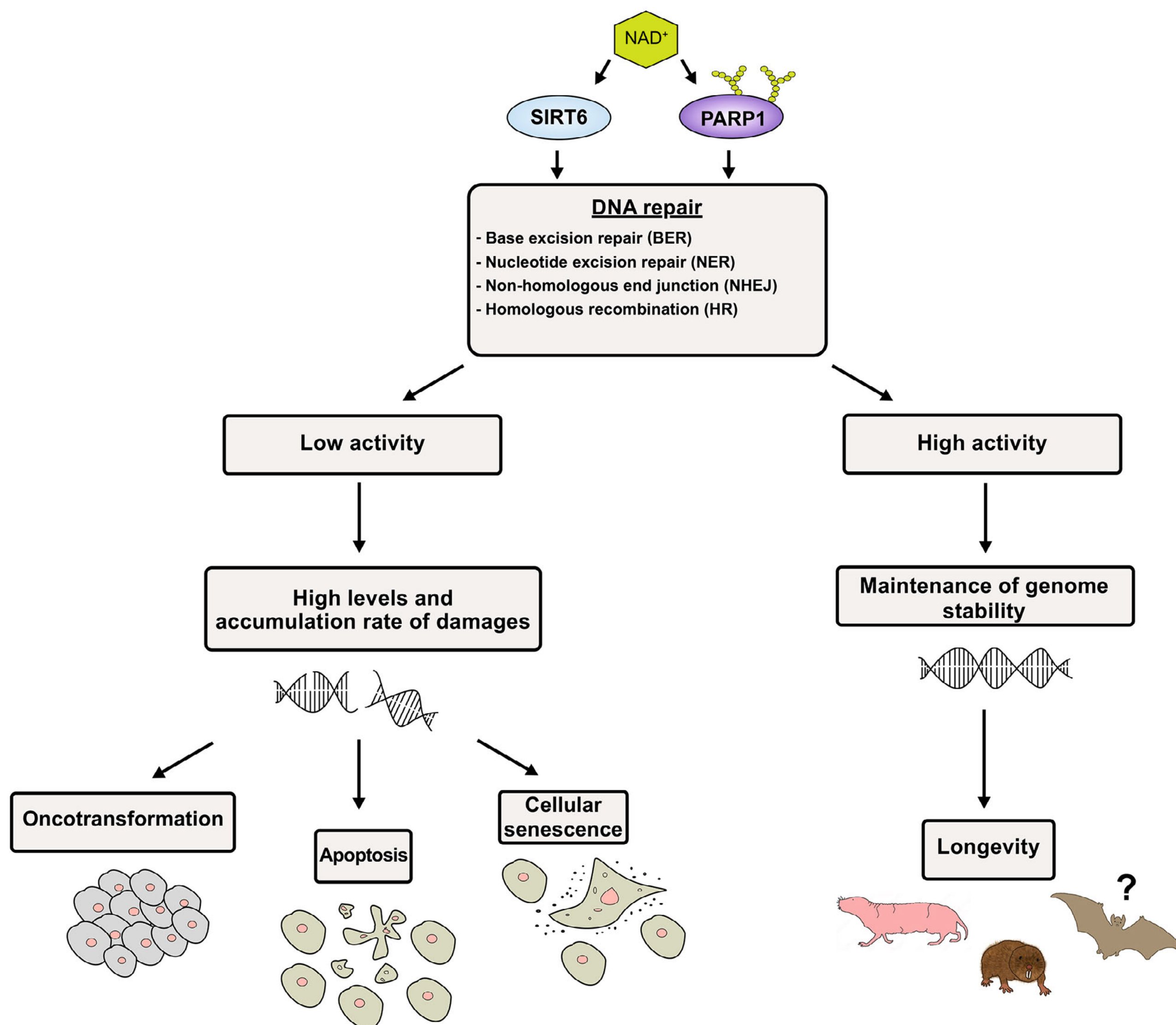
Along with enzymatic functions, PARP1 and SIRT6 act as sensors of DNA damage. PARP1 is able to attract chromatin remodeling factors and DNA repair proteins to the damage site, regulating them and its own activity [43-45] via carrying out poly(ADP-ribosyl)ation reaction with enzymatic activity activation caused by binding to the DNA damage. There are data revealing that the p53 protein [46], which plays an important role in the cell fate determination [47, 48], is involved in the DNA repair process through interaction with automodified PARP1. Products of the PARP1-mediated synthesis of branched poly(ADP-ribose) polymers (PAR) are involved in formation of non-membrane structures, so-called compartments, in which proteins of the repair complex are concentrated at the damaged DNA region for effective implementation of this process [49-51]. SIRT6 regulates activity of histones and other proteins via their deacetylation, which contributes to attraction of chromatin remodeling factors and binding of the repair proteins to the damaged DNA sites [52, 53]. A number of studies has shown that SIRT6 is one of the first to bind the double-stranded DNA breaks, thus facilitating attraction and mono(ADP-ribosyl)ation of PARP1 [54, 55]. At the same time, there is evidence that PARP1 is the first to bind the double-stranded DNA breaks, initiating NHEJ or HR processes [56, 57]. In addition to DNA repair, PARP1 and SIRT6 are actively involved in the telomere integrity maintenance and cell cycle regulation [41, 52].

Numerous studies have been conducted exploring PARP1 and SIRT6, but functioning of these proteins still needs detailed investigation due to their involvement in a wide variety of cellular processes. Functional relationship between PARP1 and SIRT6 with regard to DNA repair is of great interest, since both proteins use the same intranuclear NAD^+ pool to perform their catalytic functions and, apparently, compete for it [58]. The question of the joint participation of PARP1 and SIRT6 in the repair of single-strand and double-strand DNA breaks remains poorly understood; literature data on this issue are contradictory [54-57].

With regard to the study of aging, there are also conflicting experimental data on the role of PARP1 obtained using the PARP1 knockout mice. There is evidence suggesting that PARP1 could be counted among the factors contributing to aging [59-61] due to its involvement in activation of the transcription factor NF-κB, since NF-κB stimulates inflammatory response by expressing proinflammatory cytokines. At the same time, it was found in the work by Piskunova et al. [62] that the PARP1 knockout mice, on the contrary, show signs of accelerated aging. It is noteworthy that SIRT6 contributes to the decrease of NF-κB activation by deacetylating the H3 histone at the promoter site of the NF-κB protein gene [63]. Thus, the study of PARP1 and SIRT6 is a promising research area, the results of which could, on the one hand, significantly improve our understanding of the nature of the DNA repair system organization and regulation in mammalian cells, and, on the other hand, it could shed light on the role of both proteins in aging.

Currently, very little work has been done to compare the PARP1 functioning in the mammalian cells from the species with different lifespans. Grube and Bürkle [64] performed for the first time comparative analysis of PARP1 activity in the leukocytes of 13 mammalian species, which revealed direct correlation ($r^2 = 0.84$; $p < 0.001$) between the activity of this protein and longevity of the studied animals. Later, these data were supported by the results of comparing kinetic characteristics of the recombinant human and short-lived brown rat PARP1 [65, 66]. Recently, it was shown that the level of PAR production synthesized by PARP1 of the naked mole-rat cell extract was 1.5-2.5 times higher than in the extract of mouse cells [25, 67]. Photoaffinity modifications of the proteins in the cell extract produced using photoactive DNAs containing BER intermediate analogues demonstrated that the naked mole-rat PARP1 interacted 2-3 times more efficiently with the model DNAs than the mouse PARP1. Higher yields of the photoaffinity modification products of PARP1 in the cell extract of the naked mole-rat allowed to assume higher content of this protein [67]. Therefore, comparison of the PARP1 structure and its functioning specifically in the naked mole-rat with the similar enzyme in the mouse requires further investigation.

Recently potential role of PARP1 in demethylation of DNA from mouse embryonic stem cells was analyzed in the research by Schwarz et al. [68]. Demethylation and sequential oxidation of 5-methylcytosine to 5-carboxycytosine is carried out by the proteins of the TEN (ten-eleven translocation proteins) complex [69], after which 5-carboxycytosine is removed by thymine-DNA glycosylase (TDG) to form an AP site. TDG remains associated with the AP site and, thereby, restricts access to it of the BER proteins for some time. Using various biochemical approaches, PARP1 in the mouse embryonic stem cells has been shown to carry out TDG poly(ADP-ribosyl)ation, promoting its rapid dissociation from the DNA complex. PARP1 also facilitates both poly(ADP-ribosyl)ation of itself and of the BER proteins that is necessary for efficient repair of the AP site *in vitro* and *in vivo* [68]. Taken together, this ensures not only a faster TDG turnover and, consequently, a rapid removal of modified bases from DNA, but also contributes indirectly to the decrease in the DNA methylation level in the mouse cells. Since the DNA methylation rate in mammalian blood and skin cells inversely correlates with maximum lifespan ($r^2 = 0.81$ and 0.80, respectively; $p < 0.001$) [70], the results, obtained in the study by Schwarz et al. [68], support an important role of PARP1 in regulating BER process and ensuring



Activity of DNA repair systems and its importance for mammalian genome stability. PARP1 (poly(ADP-ribose)-polymerase 1) and SIRT6 (sirtuin 6), NAD^+-dependent DNA repair regulators.

mammalian longevity. It is worth noting that the level of available NAD^+ in the cell is a critically important factor for the effective PARP1-mediated regulation of BER in mammalian cells [71]. There is a decrease in the NAD^+ level and in the DNA repair efficiency in the cells with age [71, 72]. Further studies revealed another reason for association between the NAD^+ concentration and PARP1 activity in mammalian cells. The PARP1's partner is DBC1 (deleted breast cancer 1 protein), which blocks its functioning. Protein–protein interactions between DBC1 and PARP1 are regulated by the NAD^+ level. Along with the decrease in NAD^+ level with age, the DBC1-mediated inhibition of PARP1 activity occurs, as well as decrease in the DNA repair efficiency [73].

The role of SIRT6 in DNA repair regulation in the long-lived mammalian cells is being actively investigated, but still remains poorly understood. Western blot analysis of the SIRT6 expression in the cells of human donors with different ages showed an inverse correlation ($r^2 = 0.65867$; $p < 0.0001$) of the SIRT6 expression level with the age and direct correlation ($r^2 = 0.32568$; $p < 0.05$) with the BER efficacy [74]. Increased SIRT6 expression in the mouse embryonic fibroblasts resulted in the almost 2-fold increase of the BER efficacy. It is noteworthy that the PARP1 inhibition with PJ34 or knockdown of the corresponding gene in the immortalized HCA2-hTERT human adenocarcinoma cells led to disruption in BER activation regardless of the SIRT6 expression level. According to the authors, it indicates the need for the SIRT6-mediated PARP1 involvement to activate BER [74].

In the work carried out by Tian et al. [26] the SIRT6 activity was analyzed in rodents with different lifespan. Direct correlation between the stimulation

of NHEJ ($r^2 = 0.34$; $p < 0.05$) and HR ($r^2 = 0.40$; $p < 0.01$) by high SIRT6 activity and longevity of the studied rodents was established by the HCR method using a corresponding plasmid construct. Results of the additional experiments performed using recombinant SIRT6 of the long-lived North American beaver (*Castor canadensis*, ~24 years old) and the short-lived mouse, made it possible to establish that the SIRT6 of the North American beaver shows a slightly greater affinity for NAD^+ and higher rate of its transformation in the mono(ADP-ribosyl)ation reactions ($K_m = 138.6 \pm 10.6$ μM and $V_{max} = 10.4 \pm 0.25$ rfu/s, respectively), than the mouse SIRT6 ($K_m = 150.9 \pm 9.6$ μM and $V_{max} = 5.0 \pm 0.1$ rfu/s, respectively). It may significantly increase the SIRT6-mediated stimulation of PARP1 to participate in NHEJ and HR in the North American beaver cells [26]. The observed differences, according to the authors of this work, could be due to two unique substitutions, His249Gly and Thr263Cys, found when comparing the SIRT6 amino acid sequence of the North American beaver with the mouse protein [26]. Two rare single nucleotide polymorphisms identified later in the SIRT6 sequence of human centenarians, which led to the appearance of amino acid substitutions of Asn308Lys and Ala313Ser, were responsible for an almost twofold increase in the mono(ADP-ribosyl) transferase activity of SIRT6 in the human cells [75].

Despite the fact that there are only few studies of SIRT6 and PARP1 in the long-lived rodents, the available results suggest that the tendency to increase activity of these proteins in the cells of long-lived animals is caused by the necessity of more effective regulation of DNA repair processes. The issue of the SIRT6 and PARP1 functioning and their properties in the cells of long-lived bats remains completely unexplored. It is also worth noting that one of the main factors ensuring high efficiency of DNA repair also involves modulation of SIRT6 and PARP1 activity by other partner proteins [73, 76, 77]. Considering importance of SIRT6 and PARP1 for the senescence-associated cellular processes [61, 63], further study of these proteins is of great interest.

CONCLUSION

One of the factors ensuring longevity is stability of the genome structure and functioning. DNA repair processes play an important role in maintaining genome stability. The results of the studies considered in the review allow us to conclude that rodents with high maximum lifespan demonstrate effective and well-coordinated functioning of DNA repair systems (figure). Due to the small amount of available data and, as a result, insufficient knowledge, the issue of the functional status of DNA repair systems along with PARP1 and SIRT6 activity in bats, which demonstrate high maximum lifespan, is still open today. Overall, in order to understand high efficiency of the DNA repair systems in the cells of long-lived mammals, it is necessary to conduct further studies devoted to the properties of the proteins participating in DNA repair, as well as their possible contribution to other cellular processes that may be associated with senescence. Moreover, direct comparative assessments focused on the functional status of DNA repair systems in the cells of long-lived mammals (in addition to the transcriptome analysis of gene expression) using modern advanced methods should be conducted.

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