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Review

DNA double strand break repair, aging and the chromatin connection

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ABSTRACT

Are DNA damage and mutations possible causes or consequences of aging? This question has been hotly debated by biogerontologists for decades. The importance of DNA damage as a possible driver of the aging process went from being widely recognized to then forgotten, and is now slowly making a comeback. DNA double strand breaks (DSBs) are particularly relevant to aging because of their toxicity, increased frequency with age and the association of defects in their repair with premature aging. Recent studies expand the potential impact of DNA damage and mutations on aging by linking DNA DSB repair and age-related chromatin changes. There is overwhelming evidence that increased DNA damage and mutations accelerate aging. However, an ultimate proof of causality would be to show that enhanced genome and epigenome stability delays aging. This is not an easy task, as improving such complex biological processes is infinitely more difficult than disabling it. We will discuss the possibility that animal models with enhanced DNA repair and epigenome maintenance will be generated in the near future.

Contents

1. DNA damage and mutations accumulate during aging

DNA is distinct from all other cellular macromolecules in that it cannot be easily discarded and replaced. A cell with damaged DNA attempts to repair the damage, which is executed successfully most of the time. If the damage is too severe the cell will either become senescent or undergo cell death. The DNA repair machinery is highly efficient and in most cases the original DNA sequence is faithfully restored. However, occasionally repair is erroneous, leading to point mutations, small and large insertions or deletions, and large scale rearrangements. The nonhomologous end joining (NHEJ) pathway of DSB repair is particularly error prone, almost always resulting in a deletion or insertion. Once a mutation is introduced into the DNA it will remain there until the death of the cell. Over the lifetime of an organism somatic mutations accumulate leading to dysregulation of transcription patterns, tissue dysfunction, and possibly cancer.

2. DNA DSBs cause premature aging and senescence

Treatments that result in induction of DNA DSBs, such as gamma-irradiation and certain types of chemotherapy, lead to cellular senescence and accelerated aging in animal models and in human cancer survivors [1]. However, radiation also damages other cellular macromolecules, making it difficult to unequivocally link DSB induction to premature aging. Recently a mouse model was

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reported where DSBs were induced by controlled expression of a restriction enzyme [2]. These mice displayed multiple signs of aging indicating that DSBs alone can trigger aging pathology.

3. DNA DSB repair declines with age

Several classical studies revealed that mutations do not simply accumulate over time, but the rate of mutation accumulation increases with age [3–7]. Furthermore, aged tissues accumulated a unique type of mutation — genomic rearrangements, not seen in young tissues [3,8–12]. Genomic rearrangements, resulting from errors of DSB repair, affect multiple genes and have much broader consequences than point mutations. These findings suggest that multiple DNA repair pathways, and particularly DSB repair, become less efficient and more error-prone with age.

Several studies showed reduced levels of DSB repair enzymes in aged tissues [13,14] and senescent cells [15,16]. Direct measurements of DNA repair functions in cells of young and old individuals showed that DSB repair declines in peripheral lymphocytes of aged human donors [17–19]; DSB repair by nonhomologous end joining (NHEJ) declines in multiple tissues of aged mice [20], rats [21,22], and both NHEJ [23] and homologous recombination (HR) pathways decline in replicatively senescent cells [16].

4. Mutations in DSB repair genes lead to premature aging

Other strong evidence for the importance of DSB repair to aging comes from the fact that mutations in multiple genes involved in DSB repair lead to premature aging phenotypes. WRN protein, mutated in Werner syndrome, is involved in both HR and NHEJ (reviewed in Refs. [24–29]). Another human segmental progeroid syndrome, ataxia telangiectasia, is caused by defects in cellular responses to DSBs [30]. Mice with disruption in NHEJ genes Ku80 [31] and DNA-PKcs [32] show premature aging, as well as mice deficient in the ERCC1 gene involved in HR repair of DNA crosslinks [33,34]. The deficiency in Lamin A, which causes Hutchinson Gilford progeria syndrome (HGPS) also results in impaired homologous recombination [35]. Sirt6 knockout mice display severe premature aging and genomic instability [36]. SIRT6 is involved in DSB repair by HR through the activation of PARP1 [37] and the deacetylation of CtIp [38], and in NHEJ through activating PARP1 [37] and facilitating DNA-PKcs [39], and SNF2H recruitment to chromatin [40]. In summary, DSB repair is the top pathway according to the number of mutations leading to premature aging (Fig. 1).

5. Are naturally occurring mutations a driver of aging?

There is no direct evidence that naturally occurring somatic mutations are a cause of aging. Somatic mutation rates vary widely between tissues in mammals and are 13–75 times higher in the somatic cells than in the germline [41]. It was estimated that the body of a middle aged human might contain $>10^{16}$ point mutations [41]. This estimate does not include insertions, deletions and rearrangements. Modern high throughput sequencing methods make it feasible to screen the entire human genome for new mutations, which can be readily done to detect the frequency of de novo mutations in pedigrees and clonally expanded mutations in tumors. However, somatic mutations are often unique for an individual cell and their frequency cannot be easily determined in DNA from aggregate cells or bulk tissue from young and aged organisms. To better understand the impact of somatic mutations on tissue function, new methods involving single cell sequencing are being developed that would allow mapping out the landscape of somatic mutations in individual cells within a tissue (reviewed in Ref. [42]). We anticipate that these methods will provide accurate estimates of somatic mutation frequencies in humans and in model organisms. It would then be possible to answer whether somatic mutation frequency negatively correlates with species' longevity (reviewed in Ref. [43]).

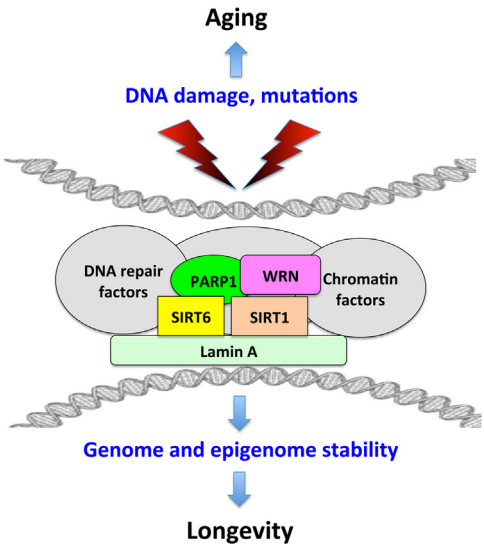

Fig. 1. DNA repair and chromatin maintenance factors cooperate to promote longevity. DNA damage and mutations compromise DNA sequences and chromatin organization leading to aging. Several proteins involved in longevity assurance have shared functions in DNA repair and chromatin maintenance. These proteins interact with each other and with other DNA repair and chromatin factors to maintain genome and epigenome stability and promote longevity.

6. Chromatin, mutations and aging

In addition to disrupting DNA sequence, mutations and genomic rearrangements affect chromatin structure. The higher order packaging of chromatin is now beginning to be understood [44–46]. Considering the complexity of chromatin organization, it is conceivable that an insertion or deletion can affect packaging and expression patterns of distant genes. Therefore, a mutation may have much broader consequences than could be envisioned by only considering the gene immediately affected. For example, transcription profiling and Hi-C analysis of the alteration of 16p11.2 genes implicated in autism spectrum disorders uncovered disrupted expression networks that involve multiple other genes and pathways [47]. To better understand the impact of mutations on age-related changes it would be important to measure the changes in chromatin organization after introduction of a deletion or insertion of different sizes in genomic DNA.

Chromatin organization undergoes dynamic changes during aging. Early work using HPLC measurements of 5-methyldeoxycytidine revealed a global reduction of CpG methylation with aging [48]. Recent studies applying genome-wide sequencing approaches found that CpG methylation decreases outside of CpG promoter islands [49]. In particular, repetitive sequences, tend to lose methylation with age [50]. In contrast, CpG methylation increases near promoters of genes involved in differentiation [49]. Older monozygotic twins show greater heterogeneity of methylation patterns as compared to young twins, suggesting an overall increase in genome somatic mosaicism with age [51]. Recently, a signature of 353 methylation sites was identified as a "methylation aging clock" that accurately predicts age across multiple human tissues [52].

At the level of chromatin, aging is associated with loss of heterochromatin and smoothening of patterns of transcriptionally active and repressed chromatin regions (for recent review, see Ref.