Editorial

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The Epigenetic Trends in Telomere Research

Yajun Wang*

Laboratory of Molecular Gerontology, National Institute on Aging/National Institute of Health, 251 Bayview Blvd, Baltimore, MD 21224, USA

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***Corresponding author:** Yajun Wang

yajunwang696@gmail.com

Laboratory of Molecular Gerontology, National Institute on Aging/National Institute of Health, 251 Bayview Blvd, Baltimore, MD 21224, USA.

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Editorial

The aging of organisms starts from a single cell at the molecular level. It includes changes related to telomere shortening, cell senescence and epigenetic modifications variation. These processes can accumulate over the lifespan. Research studies show that epigenetic signaling contributes to aging, human disease, and tumorigenesis. Epigenetic DNA modifications involve changes in the gene activity but not in the DNA sequence. An epigenome consists of modifications to the DNA and histone proteins without the changes in the DNA sequence itself. On the other hand, mounting evidence describes the great impact of telomeres on dynamics of aging, longevity, human health, and the development of many genetic diseases [1].

Telomeres are the protective heterochromatic nucleoprotein structures capping the physical ends of linear eukaryotic chromosomes and play a key role in preserving genomic stability. They consist of telomeric repeat DNA, lots of specialized proteins, and RNA. Telomeric DNA is composed of dsRNA repeats followed by a single-stranded overhang and has been suggested to form nonnucleosomal structures. The basic function of telomeres is to separate natural chromosome ends from unrepaired double-stranded DNA breaks and to protect the coding parts of the genome from the loss due to the incomplete replication of the distal region of the lagging DNA strand.

Telomere chromatin and the adjacent subtelomeric regions in mammals are organized in nucleosomes similar to the rest of chromosomal DNA, but with a shorter nucleosomal spacing. Telomeric chromatin shares some characteristics with pericentromeric heterochromatin in terms of sequence organization and epigenetic marks. Human telomeres are exclusively repetitive sequences whereas subtelomeres contain less organized degenerative repeats and various other sequences and include a low density of genes [2]. Depending on their length, telomeres have the ability to silence the transcription of nearby genes, through a variegation based phenomenon known as 'telomere position effect' (TPE) [3,4]. Mammalian telomeres and subtelomeres carry features of heterochromatin in that they contain HP1 proteins and heterochromatin-typical histone marks including H4K20me3 and H3K9me3. The repeat elements at subtelomere can initiate heterochromatin through an RNAi-mediated pathway. In addition, the telomere-binding protein complex shelterin also initiates heterochromatin at telomeres. The shelterin complex can recruit the histone H3K9 methyltransferase complex CLRC to establish subtelomeric heterochromatin. And the proper connection of shelterin components, which allows CLRC to skip telomeric repeats to internal regions, is also required for the subtelomeric heterochromatin assembly [5].

Another characteristic of telomeric chromatin is lower acetylation of histones H3 and H4 at both telomeric and subtelomeric regions [6]. In addition, unlike the telomere TTAGGG sequence, subtelomeric DNA contains CpG dinucleotides heavily methylated by DNA methyltransferases DNMT1, DNMT3a and DNMT3b. Disruption of either telomere histone modifications or subtelomere DNA methylation causes telomere length deregulation [7] which results in extremely elongated telomeres. It is proposed that these marks serve as negative regulators of telomere length in a manner that represses homologous recombination on telomeres. Telomere shortening affects epigenetic status in telomeric and subtelomeric chromatin which is accompanied by the loss of trimethylated H3K9 and H4K20, reduced subtelomeric DNA methylation and increased H3 and H4 acetylation on telomeres and subtelomeres. It is believed that these changes in the epigenetic status of short telomeres lead to the more open chromatin configuration so that they can interact with telomerase or take part in telomere recombination. Thus telomere has a higher order structure which is epigenetically regulated and therefore important for telomere length control.

Telomere length exhibits a balance between processes the ones shorten telomeres during cell divisions with incomplete DNA replication and those lengthen telomeres by the action

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of telomerase, an RNA–protein complex showing reverse transcriptase activity which adds telomeric repeats to DNA molecule ends. Telomerase activity and telomere length have a crucial role in cellular ageing and in the pathobiology of several human diseases attracting intense research. Emerging data have revealed that telomere length can be modified by genetic and epigenetic factors, sex hormones, reactive oxygen species and inflammatory reactions. And the telomere/telomerase assembly is also under the control of multiple epigenetic influences.

The telomerase complex consists of a telomerase RNA component (TERC), a catalytic reverse transcriptase protein subunit (hTERT) that adds telomere sequence repeats *de novo* after each cell division, correcting the incomplete end-replication events. Epigenetic mechanisms such as DNA methylation and histone modifications of the hTERT gene promoter can affect the expression of the hTERT gene. It has been reported that the epigenetic silencing of hTERT can repress telomerase activity contributing to telomere shortening. So far, the function of telomeric heterochromatin is not very clear. The more complete understanding of telomeric heterochromatin will induce the more definitive dissection of its function.

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