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Interrelation of Telomeres with Transposable Elements in Aging

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Abstract—The nature of telomere functioning, which affects the aging of the body, reflects global processes in the genome conditioned by the regulatory influence of transposable elements that are sequentially activated during ontogenesis. This is determined by the fact that centromeres and centromere proteins, telomeres and telomerases, introns and spliceosome components, transcription factors and their binding sites, noncoding RNAs and their targets in protein-coding gene sequences evolutionarily originated from transposable elements. The interrelation of these structural and functional elements of the genome is dynamically changing in individual development and depends on the nature of activations and transpositions of transposable elements. Each species is characterized by a specific set of transposable elements and associated tandem repeats, which reflect the epigenetic tuning of ontogenesis, mainly as a part of centromeres and telomeres; the impact on them is promising for the development of mechanisms of lifespan regulation. This is due to the ability of ribozymes and peptides to interact with specific sequences of DNA nucleotides, especially in tandem repeats. An important approach to the study of the relationship of transposons with telomeres, centromeres, and subtelomeric regions for the regulation of aging may be the study of the role of the peptides and microRNAs that unite them, the complex application of which has high potential for geroprotective effectiveness.

Keywords: noncoding RNA, reverse transcriptase, tandem repeats, self-regulation, telomeres

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INTRODUCTION

The effect of telomere shortening during successive cell divisions on the Hayflick limit and life expectancy remains a theory of aging that is recognized by modern researchers [31]. Experiments provided evidence that telomerase deficiency, which results in telomere shortening, leads to a decrease in the life expectancy of descendants [23]. Indeed, telomerase is a source of immortality and is expressed in cells capable of overcoming the Hayflick limit and proliferating infinitely. The telomerase composition includes reverse transcriptase (RT), an enzyme of retroelements [29], the activity of which varies in various tissues of an adult organism depends on the need for cellular proliferative activity. In many of them, RT is not expressed, which leads to a limitation in the number of divisions. This is due to the action of mechanisms that control telomerase activity; transposable elements (TEs), genome elements involved in the regulation of eukaryotic ontogenesis, play a key role in these mechanisms [2, 3]. TEs are subdivided into DNA-TEs (class II, transposed via cutting and insertion) and retroelements (REs, class I, transposed via copying and insertion). Telomerase [29], telomeres [9], centromeres [22, 36, 44, 61, 68] and other tandem repeats [44, 51] evolved from REs. At the same time, the role of REs in the direct regulation of telomeres was revealed [42].

It is traditionally believed that the length of leukocyte telomeres serves as a passive biomarker of human aging. However, there may be contradictions regarding aging-related diseases. For example, telomere shortening increases the risk of pathology associated with limited cell proliferation and tissue degeneration, including cardiovascular diseases. At the same time, long telomeres increase the risk of diseases associated with proliferative growth, such as malignant neoplasms [12]. Contradictions also arise in the comparison of the telomere length with the lifespan of species. For example, mouse telomeres on average consist of 30000–150000 bp [24], while human telomeres consist of only 15000 bp [4], although the average human lifespan is 50 times longer than that of the mouse. That is, there is an imbalance in the regulation of the telomere length with aging, which is a reflection of more complex regulatory processes in the genome. The key structural and functional units involved in the regulation of these mechanisms may be TEs, which serve not only as the material basis of the epigenetic heredity [2] but also as sources for gene regulatory networks, while human ontogenesis depends on the functioning of these networks.

In addition to the role in the emergence of tandem repeats [44, 51], centromeres [22, 36, 44, 61, 68], and telomeres [9], TEs evolutionarily became sources of telomerase [29] and centromere protein CENP-B [67]. A similar pattern, in which TEs in evolution turn out to be sources of targets and the elements interacting with them and this relationship is coopted by the host genomes, is found in all possible ways of genome functioning. For example, TEs became sources of the origin and evolution of protein-coding genes due to the formation of retrocopies [43, 64] and the domestication of the TEs themselves [8, 40, 67], which contain sequences homologous to noncoding RNAs (ncRNAs), the most important sources of which turned out to be TEs [32, 39]. TEs are sources of the emergence of transcription factors and their binding sites [28], spliceosome introns, and components of the spliceosome itself [56]. This suggests that the study of the composition and nature of the TE distribution in the human genome will allow us to determine their influence on the regulation of telomere length and aging of the body. The key role of TEs in controlling telomere length is indicated by data from evolutionary genetics (in drosophila, the role of the telomerase is played by the Telomere Associated and HeT-A Related (TAHRE), Telomere Associated Retrotransposon (TART), and Healing Transposon (HeT-A) retroelements [19]) and data from studies of human neoplasms (the immortality of clones is provided by an alternative elongation of telomeres with LINE-1 RE [1]). At the same time, the role of piRNA (piwi-interacting RNA, RNA interacting with proteins of the Piwi family) in drosophila and the role of LINE-1 in humans [42, 54] in controlling telomere length was revealed.

FEATURES OF TELOMERES AND TELOMERASES

Telomeres are nucleoprotein complexes that are necessary for chromosome stability. They protect the ends of linear chromosomes from recognition by the DNA damage system and provide a solution for the problem of end replication with telomerase, which is observed in unicellular and proliferating cells of multicellular eukaryotes. The protection of telomere ends and telomerase activity are under tight control, and their dysregulation is associated with various human diseases [46]. Tandem repeats at the ends of extrachromosomal linear molecules of ribosomal DNA in the ciliate *Tetrahymena thermophila* were found back in 1978 by E.H. Blackburn and J.G. Gall [16]. Further, telomeres and the telomerase enzyme were described in 1982 by J.W. Szostak, together with E.H. Blackburn [63], and in 1985 by C.W. Greider, together with E.H. Blackburn [34]. In human cells, telomeres are hexamer DNA repeats 5'-TTAGGG-3' that terminate in a single stranded protrusion [54] at the 3'-end. This region, the G chain, forms a *t* loop by weaving with the double-stranded region of DNA. Each telomere contains 250–1500 TTAGGG repeats related to the shelterin proteins TRF1, TRF2, TIN2, RAP1, TPP1, POT1. They serve as a molecular signal that hinders the mechanism of cell DNA recovery from erroneous telomeres for double-stranded DNA breaks [18].

The length of TTAGGG tandem repeats of telomeres is shortened by 50–200 bp in each cell division in the absence of a mechanism against the problem of end replication. In the end, telomeres reach the critical threshold at which cellular aging begins. Thus, telomeres function as clocks of the replicative lifespan [14]. When telomeres are too short, they signal the arrest of cell proliferation, aging, and apoptosis. This process explains the interruption of proliferation in human cell cultures. If protective mechanisms such as the *TP*53 tumor suppression gene are inactivated, proliferation continues, and the telomeres become extremely short and dysfunctional: the fusion of the ends ultimately causes chromosome instability [18].

There are three known mechanisms for the maintenance of telomere length: one that is telomerase-mediated mechanism, one that uses REs, and one that involves alternative telomere elongation based on homologous recombination. The most common of these is the telomerase-mediated mechanism. Less common is the alternative telomere elongation, which functions normally in yeast and insects [62], as well as with pathology in humans (in cells of malignant neoplasms [20]). The mechanism of telomere maintenance with REs is found much more rarely, mainly in insects that lost telomerase in evolution [19].

Telomerase is an enzyme consisting of subunits encoded in different chromosomes in humans: the *TERT* (telomerase reverse transcriptase) gene is located at 5q15.33, the *TER* (telomerase RNA) gene is located at 3q26.3 [4]. Telomerase RT (TERT) uses the RNA component of telomerase (TERC) as a template for DNA synthesis. The catalytic unit of telomerase contains two copies of TERT, TERC, and DKC1 and the proteins stabilizing this complex [18]. In addition to telomere elongation, telomerases have other properties. For example, an experiment on mice showed that TERT can stimulate the proliferation of resting stem cells through noncanonical pathways [60]. Telomerase overexpression mobilizes stem cells in adult mice and induces their proliferation without telomere elongation via modulation of the signaling pathways of (Wnt)-β-catenin in drosophila [25]. It is interesting that, unlike protein subunits, the telomerase RNA product is constitutively expressed in most somatic tissues in which RT is absent. It was shown that the transcript of human telomerase encodes the protein of 121 amino acids (hTERP), which protects cells from apoptosis caused by drugs and is involved in the processing of autophagosomes. The hTERP protein is involved in cell adaptation to stress via regulation of the relationships between autophagy and apoptosis [59].

Table 1. Diseases caused by mutations in genes of the telomerase complex (according to [10, 12, 18])

Diagnosis	Mutated gene and its function	Onset of disease, years
Sporadic pulmonary fibrosis	*hTR* (telomerase RNA)—encodes telomerase RNA component *hTERT* (telomerase reverse transcriptase)—encodes telomerase	5–77
Familial pulmonary fibrosis		
Sporadic and familial aplastic anemia		
Autosomal dominant DC syndrome		
Liver fibrosis Cryptogenic cirrhosis		
X-linked DC syndrome	*DKC*1 (dyskerin pseudouridine synthase 1)—encodes H/ACA RNP subunit-4 of telomerase complex	<30
Hoyeraal–Hreidarsson syndrome		<5
Sporadic DC syndrome	*TINF*2 (TERF interacting nuclear factor 2)—encodes one of the shelterin proteins of the complex that protects telomeres from DNA repair mechanisms and regulates telomerase activity *RTEL*1—encodes DNA helicase	<10
Autosomal dominant DC syndrome		–
Hoyeraal–Hreidarsson syndrome		<5
Autosomal recessive DC syndrome	*NOP*10—encodes a protein, a member of H/ACA RNP family of telomerase complex	–
	*NHP*2—encodes a protein, a member of H/ACA RNP family of telomerase complex	–
	PARN—encodes poly(A) ribonuclease	–
	CTC1—encodes a component of the telomere replication complex	–
	*WRAP*53—encodes a component of the telomerase holoenzyme complex	–
Autosomal dominant DC syndrome	*ACD*—encodes one of the shelterin proteins of complex	–

HUMAN DISEASES ASSOCIATED WITH TELOMERE DYSFUNCTION

Although aging is a physiological process, the study of diseases associated with telomere dysfunction can be one approach to the determination of the possible means of telomere dysregulation in normal ontogenesis. In addition, the regulatory pathways involved in the control of telomeres in aging can be used to develop effective treatments for diseases. Thus, the revealed correlation of TEs with telomeres in aging [42] reflects the principle of the use of REs for alternative telomere elongation in 10–15% of malignant neoplasms [20], which gives grounds for the possible use of RT inhibitors in the treatment of these types of tumors [11]. At the same time, drugs used to treat diseases associated with telomere dysfunction may be promising for the development of geroprotective therapy.

The importance of telomeres for human health is illustrated by the example of genetic diseases called telomereopathies (telomere biology disorders, TBD) or syndromes of telomere shortening. Collectively, TBDs encompass a spectrum of states of multisystemic disorders that are manifested from infancy to isolated diseases in adulthood. To date, 11 genes with mutations that cause TBD have been identified. Each of these genes is associated with certain aspects of telomere maintenance [14]. Telomere-mediated diseases were initially identified in the context of the rare Zinsser–Cole–Engman syndrome of premature aging (dyskeratosis congenita, DC). Mutations in the components of the telomerase complex were detected in patients with idiopathic pulmonary fibrosis, aplastic anemia, and Hoyeraal–Hreidarsson syndrome (Table 1) [10]. The telomerase gene is the locus of cancer susceptibility, and short telomeres are risk factors for cardiovascular diseases. Telomerase dysfunction is associated with the development of liver fibrosis [18]. In addition, the disruption of the functioning of the adaptive immune system observed during aging is also associated with a disruption in the regulation of telomeres and their shortening [31].

The development of TBDs is associated with mutations in the genes *ACD*, *CTC*1 [12], *DKC*1 [10, 12, 18], *NHP*2 [10, 18], *NOP*10 [18], *PARN*, *RTEL*1 [12], *TERT*, *TERC*, *TINF*2, and *WRAP*53 [7]. The *ACD* gene (adrenocortical dysplasia protein homolog) is localized on 16q22.1. It encodes one of six shelterin proteins TPP1 [18]. Mutations in the *ACD* gene cause autosomal dominant DC syndrome [12]. The *CTC*1

gene (CST telomere replication complex component1) is involved in the regulation of telomere functioning. The localization of the gene is 17p13.1, and its mutations cause DC with the autosomal recessive type of inheritance [12]. The *DKC*1 gene is localized on Xq28 and encodes the dyskerin protein of the telomerase complex [10, 12]; its mutations cause a disturbance of the maturation and stability of the telomerase RNA component (hTR) [10]. The *NHP*2 and *NOP*10 genes encode proteins that, like dyskerin, are associated with the telomerase complex [18]. The product of the *PARN* gene (poly(A)-specific ribonuclease), which is localized on 16p13.12, stably binds to polysomes and ribosomal subunits. Hereditary biallelic mutations in this gene cause DC. The *RTEL*1 gene (the regulator of telomere elongation helicase 1), which is localized on 20q13.33, encodes DNA helicase, which is involved in telomere stabilization, protection, and elongation. Mutations in this gene are associated with the development of DC and the Hoyeraal–Hreidarsson syndrome. The *WRAP*53 gene (a WD repeat containing antisense to TP53) encodes the component of the telomerase holoenzyme complex, which interacts with dyskerin, TERT, and TERC, as well as small RNA of the Cajal bodies. In addition, mRNA of the *WRAP*53 gene functions as an antisense transcript that regulates endogenous p53 levels. Hereditary biallelic inactivation of the *WRAP*53 gene causes DC [12]. Despite the role of elongated telomeres [12] and telomerase reactivation in human carcinogenesis [13], shortened telomeres were found in colorectal cancer cells. That is, both the maintenance and a loss of telomeres can contribute to carcinogenesis and genetic instability in malignant tumors [37]. Thus, the likelihood of developing cancer is 11 times higher with the DC syndrome than in the general population [7]. This indicates the relationship of the genes of the telomerase complex with the global system for the control of genome functioning, the key regulators of which are transposable elements [2, 3]. This relationship is determined by the origin of telomerase [29] and telomeres [9] from TEs. Since centromeres could have evolved from telomeres [62, 66] and subtelomeric regions [29], highly dynamic chromosome structures that probably originate from REs [47, 65] and play an important role in the regulation of telomeres [42], the study of the relationship between telomeres and centromeres, subtelomeres, and TEs can become the basis to find ways to regulate aging. Moreover, new aspects of the biology of tandem repeats that originated from REs can be discovered in the determination of the relationship between TEs and centromeres.

INTERRELATION OF TELOMERES, CENTROMERES, AND TRANSPOSABLE ELEMENTS

Transposable elements are not only evolutionary sources of telomeres and telomerase; they also cause a regulatory effect on telomeres in ontogenesis. LINE-1 plays an important role in the regulation of telomere maintenance, which is considered a key point for survival of malignant cells, in which the global function of active LINE-1 in cell proliferation is supported. The inhibition of highly active LINE-1 was shown to cause telomere depletion in telomerase positive cells. In addition, a decrease in LINE-1 activity correlates with a decrease in the transcription and expression of KLF-4 and c-myc proteins, as well as the transcription factors for *TERT*. That is, the regulation of telomerase by LINE-1 can be indirect, via these two proteins. It was also shown that LINE-1 specifically induce shelterins [54]. The ability of Penelope-like elements (PLEs), Terminons, to attach to G-rich telomere repeats was discovered. It is believed that complementary repeats with a high cytosine content at the 3'-end of the RNA template directly adjacent to the hammerhead ribozyme motif contribute to this. Interestingly, PLE and RT telomerases evolved from a common ancestor [9]. In addition, the role of TEs in telomere regulation is manifested by alternative methods of telomere elongation with REs [20].

The principle of the use of tandem repeats, which are part of telomeres that arose from TE sequences, to control genome functioning is universal for eukaryotes. An example is centromeres, which also consist of tandem repeats, are associated with telomeres [29, 58, 62, 66], and also originated from TEs [22, 36, 44, 61, 68] due to site-specific transpositions of the latter [51]. There is a number of common properties and patterns of the functioning of telomeres and centromeres, which suggests that a thorough study of the mechanisms of the functioning and evolution of both structures may reveal the means of their relationships with specific TEs and their regulatory gene networks.

Centromeres are DNA regions of eukaryotic chromosomes that determine kinetochore formation and the attachment of sister chromatids. They interact with microtubules of the fission spindle to ensure chromatid segregation during mitosis and homologous chromosomes during meiosis [66]. In this case, both centromeres and telomeres have a common chromosome origin and are capable of functional exchange during evolution of the karyotype. In light of these data, the study of centromere features can become the basis for the determination of new ways to regulate telomere length [62], which is important for the development of methods to control the aging process of the body.

In addition to their evolutionary origin, centromeres and telomeres are united by a close functional relationship in eukaryotic ontogenesis. For example, it was shown that telomeres are involved in the control of centromere activity during meiosis [41], and fragments with normal centromeric activity are generated by telomerase upon damage to holocentric chromosomes [38]. In some vertebrate species, units of (TTAGGG)*n* repeats, the so-called interstitial telo-

meric repeats, are detected in pericentromeric or centromeric regions [17].

Both centromeres and telomeres consist of satellite DNA characterized by species specific features of their structure and monomer length [15]. In the insect *Chironomus pallidivittatus*, it was found that tandem repeats that originated from TEs, which are typical for centromeres, are included in telomeres of their chromosome [58]. Both telomere and centromere transcription is performed by the RNA polymerase II enzyme [15]. Like centromeres, telomeres have multifunctionality; their role is not limited only to the protection of the terminal chromosome regions. This reflects the universal properties of TEs [3] from which they arose. Moreover, the transcription products of both structures, like TEs, are involved in the regulation of their own sequences in the DNA structure. For example, using RNA polymerase, functional long ncRNAs (telomeric repeat containing RNA, TERRA), which are an integral component of telomeric heterochromatin, are most actively formed from telomeres in the G1 phase [15].

The transcripts of centromeres and pericentromeric loci, which are involved in the regulation of the complex of kinetochore proteins and interaction with the histone variant CENH3 in plants [30] and CENP-A in animals [21], have similar properties. Like these structures, subtelomeric regions and their transcripts can also control the functioning of telomeres and their interactions with TEs. It was shown that centromeres in evolution could arise from telomeres [62, 66] or subtelomeric regions [29], which have an amazing complexity and plasticity due to the high variability of repeats in their composition, accelerated duplications, and the high degree of combinatorial variability in evolution [57]. This indicates both the origin of subtelomeric regions from TEs and their close relationship. In this regard, despite the plasticity, subtelomeric regions play an important role in telomere regulation. Thus, their effect on the replication time of telomeres associated with them in immortal cell lines was shown [55]. It is assumed that, when eukaryotes originated, the symbiosis of eubacteria and their archaea hosts was accompanied by an adaptive response with fragmentation of the circular genome into several linear fragments. Later, the free ends of DNA were stabilized by REs with the formation of prototelomeres, the subtelomeric regions of which were used as a new load for the tubulin-based cytoskeleton. These subtelomeric regions later turned into protocentromeres [62].

In rotifers of the Bdelloidea class, the gene-rich regions of the genomes practically do not contain TEs, and the subtelomeric regions are enriched with various TEs that retain their activity and capacity for horizontal transfer [33]. In humans, the p53 binding sites inhibit the accumulation of damage in telomeric repeats of DNA and have enhancer-like functions, which enhance the local acetylation of histones H3K9 and H3K27 and stimulate TERRA transcription; they are located in the subtelomeric regions [65]. These sites originated from REs, and their functional significance reflects the capacity of TEs for the global regulation of genome functioning [47]. Thus, subtelomeres may be regulatory regions that originated from TEs and are involved in the control of the telomere activity in ontogenesis, which is consistent with the property of REs to control telomere biology [42]. In addition, it was found that the functional state of the cardiovascular system is determined not only by telomere length but also by subtelomere methylation [52]. It was also proved that the formation of subtelomeres is not accidental, since most of them contain genes of the subclass of the Wiskott–Aldrich syndrome protein (WASP). Proteins of the WASP subclass, which is evolutionarily conserved in animals, are widely expressed in human tissues and colocalize with actin in filopodia and lamellopodia [48].

The relationship between telomeres and centromeres in evolution [29, 58, 62, 66], as well as the origin of both structures from TEs [9, 22, 29, 36, 44, 61, 68], indicates the possible existence of common principles for their evolution and functioning, since they participate in common processes related to cell division. Like telomeres, the tandem repeats of the transcripts of which are an integral component of the heterochromatin packing them [15], the nucleotide sequences in the centromeres play a role in interactions with functionally significant molecules. Thus, both tandem repeats of centromeres and the REs in their composition can bind to the kinetochore protein [69]. The nucleotide sequences of centromeres are similar to those of TEs. Specific LTR-containing REs from the Ty3/gypsy group enrich centromeres in grassy grains and interact with the CENH3 protein [53], which evolved from REs [67]. Moreover, the REs in the composition of centromeres can take an active part in the dynamic rearrangements of centromeres and kinetochore formation [61]. Like subtelomeric regions [33], centromeres can contain not only LTR-containing REs but also other TEs. Thus, the enrichment of centromeres with LINE-1 elements in bats [27] and helitrons in plants [68] was revealed. In addition to the distribution as a part of centromeres, TEs participate in the generation of their tandem repeats. This is indicated by the similarity of the sequences of their satellites with specific REs. For example, the identity of tandem repeats of centromeres with Ty3/gypsy-like RE in *Aegilops speltoides* plant [22] was revealed with the use of Alu and ERVK9 elements in humans and chimpanzees [44] and with SVA, PVA, and LAVA in gibbons [36].

Thus, TEs form a unified species-specific structural and functional network involved in the control of gene expression in ontogenesis [2, 3]. The study of the role of individual links in this network is promising for the control of both the lifespan and the proliferation of individual cells. The presence of general properties

and evolutionary regularities suggests that the study of the functional significance of centromeres and the TEs that are a part of them can serve as the basis for an elucidation of the interrelation between TEs and telomeres. The similarity of the properties of telomeres and centromeres and their interrelations suggest that the structural organization and composition of telomere tandem repeats are also determined by the ability of their nucleotide sequences to interact with regulatory molecules such as ribozymes and peptides. This is associated with the ability of ribozymes [35] and peptides [5] to bind to specific nucleotides in the double helix of DNA and can serve as an explanation for the mechanism of the geroprotective action of peptides used in practice [6]. It can also become the basis of the search for the most effective biomolecules, specifically those interacting with telomeres during aging.

The most promising is the combined use of peptides and noncoding RNAs that have a high potential for the regulation of the differentiation of cells capable of reprogramming mature cells into stem cells [49]. Since TEs are important sources of the emergence of ncRNA genes [32, 39], the transcripts of which are not only able to processing into ribozymes but also to translate into functional peptides [45], specific miRNAs or translation products of their unprocessed precursors can be used to regulate telomeres [50]. Peptides translated from ncRNAs are capable of altering the expression of their own sources [26], which suggests that there is potential in the search for specific combinations of amino acids that can interact with TE sequences in the DNA structure and can regulate their functioning in ontogenesis, which may be reflected by the telomere length.

CONCLUSIONS

Telomeres and centromeres originated from TEs during evolution. This determines their common properties and multifunctionality, their interconversions during evolution, and their interdependence in ontogenesis. These universal structural units are transcribed with the formation of ribozymes, which are involved in the regulation of the functioning of their own DNA structures. The ability of tandem repeats of centromeres and centromere-specific retroelements to bind to the kinetochore protein reflects the ability of TE sequences in DNA to interact with their own transcripts and the peptide products of their translation. The molecular mechanisms of the formation of the bond between peptides and DNA molecules discovered by V.Kh. Khavinson can serve as the basis for these interactions. In this regard, it is assumed that an increase in the efficiency of the used geroprotective peptides may be associated with the combined use of specific noncoding RNAs, which can interact with subtelomeric, centromeric, and telomeric regions. The need to study these interactions is determined by the close evolutionary and functional relationship of these genome structures with each other and with transposable elements.

It is assumed that a detailed study of the most dynamic subtelomeric regions of the genome, the activity of which may reflect the functioning of specific transposons associated with telomere regulation in ontogenesis, can be a promising direction in the development of methods to prolong life. Subtelomeric regions, due to their plasticity, play an important role in genome functioning and in interrelations with molecules involved in the global regulation of the gene networks. Thus, the p53 binding sites that originated from REs are located in subtelomeric regions in humans. This suggests that the study of the relationships of conservative structural units of human chromosomes that originated from TEs and are regulated by them are promising for the development of geroprotective therapy.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest. The author declares that there is no conflict of interest.

Statement on animal welfare. This article does not contain any studies involving animals performed by any of the authors.

Statement of compliance with standards of research involving humans as subjects. This article does not contain any studies involving humans as subjects of research.

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