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Prospects in the Search for Peptides for Specific Regulation of Aging

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Abstract—The interspecies differences in the mean lifespan and the composition of transposon sequences, the tissue- and stage-specific activation of which plays a role in the management of the cell differentiation process, allows the assumption that the regular processes that underlie aging are determined by the dysfunction of species-specific mobile elements. The presented literature data confirm this assumption and the key role of transposons in the regulation of gene expression during ontogenesis. The silencing mechanisms of mobile elements (which are depleted) are activated in terminally differentiated cells. This leads to dysfunction of the gene regulatory networks controlled by transposons, aging, and the development of age-associated pathologies. Transposons are capable of translocating into strictly defined loci of the genome, where they are transcribed into functional RNAs that are translated into peptides. It is assumed that the identification of activity changes associated with the aging of specific mobile elements via analysis of the noncoding RNA of transposon origin may be the basis for the development of ways to increase life expectancy and for targeted therapy of age-associated pathologies, including malignant neoplasms. In this regard, the study of peptides that affect the expression of specific transposons and noncoding RNAs may be a promising direction.

Keywords: heterochromatin, differentiation, peptides, lifespan, aging, stem cells, transposons
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INTRODUCTION

Aging is a multifactorial biological process that increases the susceptibility to cancer and metabolic, cardiovascular, and neurodegenerative diseases. Replicative aging [40] reflects the ability of the cell and its line to support a limited number of continuous division rounds [48]. Y. Kim et al. and T. Smeal et al. in 1996 and B.K. Kennedy et al. in 1997 showed in yeast that replicative aging correlates with a loss of heterochromatin in telomeric regions, *MAT* (*mating type*) loci, and DNA repeats. M. Kaeberlein et al. revealed in 1999 that overexpression of the histone deacetylase *Sir2*, which is responsible for the formation of heterochromatin and gene silencing, stimulates an increase in the yeast lifespan [11]. In studies on yeast, worms, flies, mice, and human cell cultures, a decrease in the content of repressed heterochromatin, the maintenance of which increases lifespan, was found with age. It is assumed that the cause of aging due to the loss of heterochromatin repression may be the activation of the mobile elements (MEs) located in it, which contributes to genomic instability [38]. However, ME expression and the activation of regulatory nucleotide sequences (NSs) of transposon origin begin with the first zygote division, which is a condition for successive stages of embryonic cell differentiation [20]. This need is associated with the structural and functional interrelations of MEs with epigenetic and transcription factors. In evolution, transposons turned out to be sources of many protein-coding genes, noncoding RNA, and a significant part of regulatory NSs characterized by activation features that depend on the tissue and developmental stage [6].

Different mechanisms inhibiting ME activity, including catalytic proteins *APOBEC3A*, *APOBEC3B, APOBEC1, ERCC, TREX1, RB1, HELLS, MEGP2* and the histone deacetylase *SIR*, developed in the body [44]. Proteins of the *SIR* family deacetylate not only histones but also transcription factors, such as *p53* and *FOXO*, which activate the expression of stress response genes, inhibit apoptosis, and promote cell survival and an increased lifespan [4]. In addition, miRNA that have a regulatory effect on both MEs and protein-coding genes (PCGs), which are complementary to these miRNA NSs, are processed from ME transcripts [5]. In addition, MEs are the basis of the functional domains of long noncoding RNA (ncRNA) [27, 28], which also affects self- and interregulation with PCGs.

The ME repression is incomplete, so most of the genomes are transcribed at different levels [14]. Studies in model organisms showed that MEs become activated with age as a result of heterochromatin deregulation due to *SIR* depletion [11]. In addition, the sup-

porting ME methylation in the genomes has an accuracy of about 99%; therefore, repressed chromatin markers can be lost with age, which causes ME derepression and an avalanche-like increase in transpositions [2]. The causes for the loss of repressed heterochromatin are also explained by the disturbance of the redox balance and genotoxic stress [38], i.e., it is believed that the causes of aging are random processes. However, it is impossible from this position to explain the average lifespan specific to each species or the significant differences in it among different, even closely related species. For example, a naked mole rat lives an order of magnitude longer than other rodents (up to 30 years old), and humans live much longer than chimpanzees and lemurs. In individuals of the same species, differences in lifespan can also differ significantly depending on external and social conditions, which indicates the important role of epigenetic factors in the regulation of aging. For example, in ants, the queen can live up to 30 years under the influence of the care of worker ants due to specific environmental conditions [4].

Differences between species are more strongly related to MEs than PCGs. For example, only 13% of mouse MEs are found in humans and 48% of human MEs are found in the mouse, whereas 99% of human and mouse PCGs are homologous [42]. Since MEs are involved in the regulation of gene expression during cell differentiation, starting with the first division of the zygote [56], it can be assumed that MEs are the main cause of the regular inherited processes underlying mechanisms of aging, although the influence of random factors, such as environmental stressors, is also of a great importance as a modulator of the most optimal lifespan for the species under present conditions. In this regard, the depletion of stress-sensitive ME repressors (for example, *SIRT6*) is a convenient system for lifespan regulation within the species. The stabilizing *SIRT6* protein induces a potent silencing of the *L1* activity. It interacts with the 5'*UTR* L1 element and packs it into transcriptionally repressed heterochromatin [53]. Since natural selection contributes to reproductive adaptiveness, the lifespan is a selective feature if it contributes to reproductive success. MEs are sensitive to stress [15, 57], which reduces the lifespan and contributes to earlier reproduction [4]. Stress is caused by a change in hormonal regulation, with which MEs are also closely related [3, 13, 32]. However, in addition to random processes, the regular aging of organisms for a particular species is predetermined by specific mechanisms underlying the control of the entire program of development. The identification of key links of these mechanisms can form the basis for lifespan regulation. The most likely candidates for the search are MEs, which serve as the basis for epigenetic regulation of ontogenesis [5] and participate in the construction of regulatory gene networks during the formation of species in evolution [16].

TISSUE-SPECIFIC AND STAGE-SPECIFIC TRANSPOSON ACTIVATION

ME (*L*1) transcription in vivo was detected as early as 1993 in the mouse embryo at the blastocyst stage [39]. In 1995, *L*1 transcription regulated by the determined developmental program was revealed by the method of immunohistochemistry in mouse embryos after implantation [52]. The active expression of ME was later described in many works on the experimental study of mammalian embryonic development. In 2007, J.L. Garcia-Perez et al. proved that ME activation in stem cells causes repression of certain genes. This mechanism was proposed as a universal system of the regulation of gene expression under the action of MEs, which is necessary for cell differentiation in ontogenesis [19, 50]. In subsequent studies, a large amount of evidence in support of this hypothesis was obtained by various authors.

In 2011, data were presented on the presence of *Alu* and *L1s* expression in human embryonic stem cells [35]. In 2012, pronounced expression of *P1-LINE* in different tissues with the tissue-specific formation of heterogeneous RNA was shown in experiments on rats [50]. In 2015, a published paper indicated that *LTR* exerts tissue-specific regulation on neighboring genes in mouse ontogenesis. The cleavage of gene expression into 62 LTR classes in 18 tissue types was detected [41]. In the same year, the redistribution of ME arrays depending on the tissue and developmental stage was investigated in mouse experiments, and specific changes in the genomes of the skin and brain (at 6 weeks) and liver and heart (at 29 weeks) were revealed [29]. In 2016, reactivation of the transcription of specific MEs in the early embryonic development of animals in stem cell lines was proven. The profiles of certain MEs indicated cell identity; this proved the role of MEs in the control of gene expression, which is necessary to maintain pluripotency and cell differentiation [20]. At the same time, long ncRNA form in order to maintain pluripotency during the transcription of some MEs (*HERV*). They have a regulatory effect on genome functioning [43]. Based on the accumulated data, it can be assumed that the species-specific composition and ME location in the genomes formed in the course of evolution is the basis for the epigenetic regulation of ontogenesis of multicellular animals and their aging. A cause explaining the ME activation pattern in successive cell divisions during the development of a multicellular organism is ME sensitivity to stress [15, 57] and hormonal [3, 13, 32] effects. Therefore, starting from the first zygote division, the molecular composition of the internal environment of the cells, which changes as a result of division, serves as the basis for evolutionarily programmed ME activation (Fig. 1).

In addition to activation of the MEs themselves, regulatory NSs derived from MEs actively participate in the genetic regulation of ontogenesis. For example, a comparison of the genomes of 29 mammals revealed

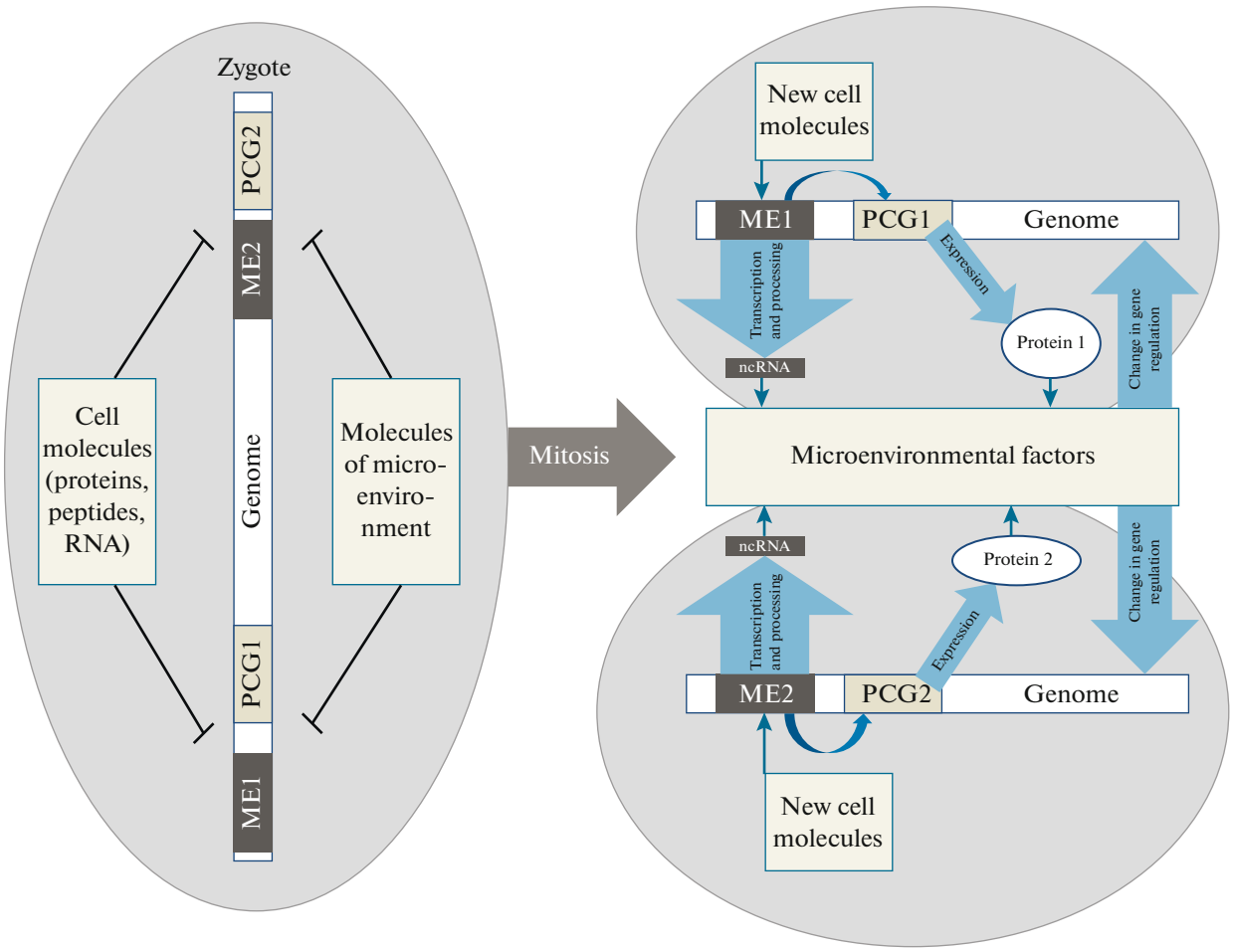

Fig. 1. Interdetermination of the activation of MEs with a change in the expression of PCGs, ncRNA, and the microenvironment during cell differentiation in embryogenesis.

280000 regulatory NSs derived from MEs [13]. Many promoters and enhancers of ME origin are characterized by activation in certain tissues and developmental stages. In humans and mice, up to 30% of all transcription start sites are located within MEs exhibiting tissue-specific activity [20]. In humans, *LTR* functions as a promoter for specific cell types [49]. This is determined by the ability of MEs to redistribute gene regulation depending on the tissue and phylogenetic context [41], which allows them to control gene expression in successive cell divisions and implement the ontogenetic development program encoded in the genome. For example, in early embryonic development, up to 20% of the human transcriptome is initiated from ME sequences [36]. It was found that many transcripts of mouse embryos are initiated as early as at the two-cell stage from *LTR* derived from *ERV*. This indicated the key role of *LTR* in the regulation of cell differentiation [34] and was confirmed in 2016 in experiments on the *LincGET* depletion associated with *LTR* in mouse embryos [56]. In the human genome, 794972 binding sites with transcription factors derived from ERV were detected. These regulatory NSs are activated according to the patterns of binding to specific transcription factors in different stem cell lines [24].

Thus, MEs play a key role in the evolutionary and ontogenetic transformations of animal genomes. This role is most fully displayed in the consideration of the possibility of ncRNA translation into functional peptides that are involved in tissue-specific regulation of cell functioning (for more details, see the review in [6]). Since MEs are the most important sources of miRNA and long ncRNA, which can be translated into active peptides, MEs serve in evolution as the source of the "double-search" mechanism of molecular pathways for the interaction of new biomolecules (Fig. 2). These mechanisms are important sources of the emergence of new genes encoding proteins and peptides in evolution. This process is common in eukaryotes, which was proven in the study of human, arabidopsis, drosophila, zebrafish, yeast, and house mice; the majority of their long ncRNA turned out to be associated with ribosomes and showed coding potential similar to evolutionary young PCGs [45].

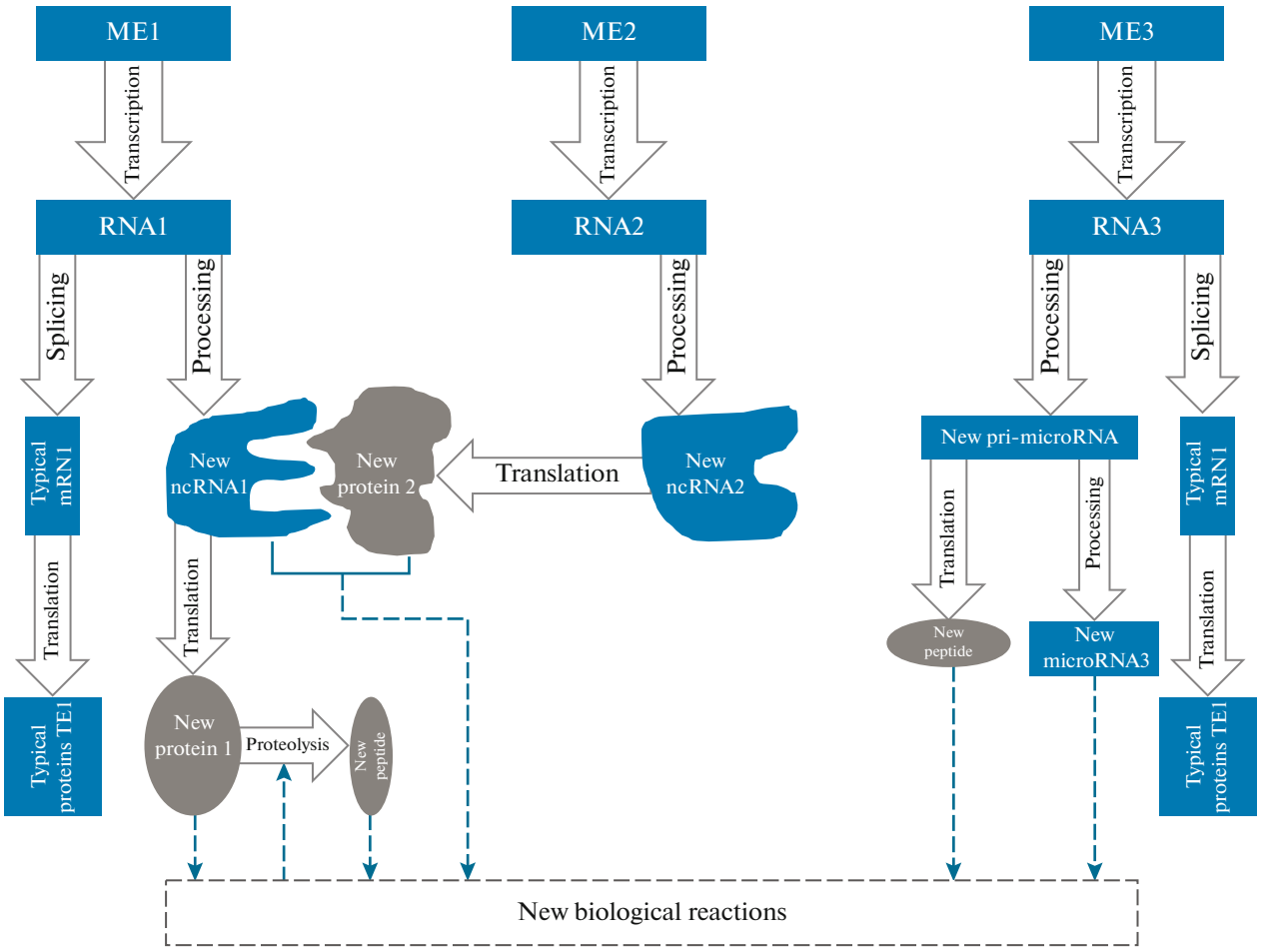

Fig. 2. "Transposons (MEs)–ncRNA–peptides" strategy in the "double-search" system for targets in evolution.

The presence of the double-search system indicates that MEs were the main sources of genome structures in evolution of eukaryotes. From this point of view, it can be assumed that the aging process, which is determined by mechanisms for the activation and repression of strictly defined MEs in the stem and terminally differentiated cells specific to each species, is of a reversible nature. The detection of changes in the expression of specific MEs in different organs and tissues will allow modeling of the exposure pathways to this process with ncRNA and peptides.

TRANSPOSON TRANSLOCATIONS TO SPECIFIC GENOME LOCI

Although ME activations potentially carry a threat to the genome due to the development of genomic instability, recent studies showed their importance in the control of cell differentiation. This is caused by the global role of MEs in the formation of regulatory structures of eukaryote genomes—binding sites of transcription factors [22, 24, 31], enhancers [13, 26], promoters [16], and insulators [55], the use of which is characterized by tissue-specific and stage-specific features [36]. In addition, MEs are important sources of ncRNA that cause epigenetic regulation of genome functioning via transcriptional and post-transcriptional effects (for more details, see the review in [5]). A possible condition in evolution for the selection of the most optimal variants of the composition and location of MEs in the genomes of one species, which serve as the basis for the regulation of ontogenesis, is the ability of MEs to translocate to strictly defined genome loci in successive cell divisions.

Data show that DNA transpositions catalyzed by *PGBD5* in human cells occur on the scale of the whole genome with precise removal and preferred insertion in the region *TTAA*. The apparent retention of the *PGBD5* transpositional activity suggests that genomic remodeling contributes to its biological function. The *PGBD5* proteins themselves are derived from MEs, since their genes are domesticated from DNA transposons [23]. That is, in evolution, MEs create mechanisms that facilitate their precise translocations to strictly defined genome loci containing specific NSs. Since the tissue- and stage-specific activation of cer-

tain MEs is observed in embryogenesis [19, 20, 29, 35, 41, 43], this indicates the existence of an important system for control of genome functioning in ontogenesis; it is formed by MEs and NSs derived from them. Some *non-LTR* MEs are introduced into specific NSs within target sites. Based on the structural and phylogenetic features of *non-LTR*, MEs are classified into two large groups: the first includes retroelements that encode endonucleases similar to restriction enzymes (*RLE*), and the second includes retroelements that encode apurin/apyrimidine endonucleases (*APE*). All representatives of the first group include site-specific elements (*SSE*). Among the 20 representatives of the second group, only *Tx*1 and *R*1 contain *SSE*. Targets of *SSE non-LTR* MEs are usually located within genes with multiple copies, such as rRNA cluster genes or repetitive genomic NSs. The specificity for sites and sequences varies even in closely related *non-LTR* MEs and changes during evolution. The specificity of *RLE* elements is influenced by motifs of DNA binding [17].

The highly specialized integration properties of these *SSE non-LTR* MEs make them the ideal alternative tools for the delivery of genes specific for NSs, especially for therapeutic purposes in human diseases [17]. A new group of DNA transposons *Spy* that do not create *TSD* (target site duplication) during insertion was identified. Instead, *Spy* transposes exactly between the host nucleotides 5'-*AAA* and *TTT*-3' without duplicating or modifying *AAATTT* target sites [21]. Organisms regulate ME expression, their transpositions, and the preference for the integration site, alleviating possible genomic instability. ME expression is sensitive to external environmental signals, and many MEs are activated by various cellular stresses. At the same time, MEs can cause local regulation of the gene, acting as enhancers, and can also provide global regulation of genes via their ncRNA, i.e., MEs can act as stress-sensitive regulators that control the expression of host genes in cis and in trans [57]. In the course of evolution, ME interaction with hosts led to the fact that MEs in ontogenesis have specific integration patterns, both in response to internal environmental factors and external environmental stressors. It promotes the expression of certain genes responsible for cell differentiation or stress response. For example, the *LTR*-containing *Tf1* retroelement in the *Schizosaccharomyces pombe* genome is preferably integrated into promoters of the stress response genes, enhancing gene expression by providing enhancer activity and manifesting synergy of the *Tf1* enhancer NSs with target promoters of the stress response elements. The *Tf1* promoter is activated during heat treatment and activates genes induced by heat exposure [15].

MEs constitute the majority of the genomes of animals and plants, serving as sources of new PCGs due to domestication, exonization, and duplication [16, 51]. Intergenic NSs and introns in evolution also originated from MEs, but many of them are significantly altered by mutations and are not recognized by standard methods for their identification [18]. Thus, ME sequences can be found in practically all functional structures of genomes, forming a convenient system for the control of ontogenesis. At the same time, MEs are most likely act as a primary link in regulation due to their capability of self-regulation with processed products of their own transcription in the form of ncRNA [5]. In a number of experimental studies, the necessity of the activation of specific MEs and long ncRNA, the domains of which are formed mainly by transposons [27, 28], was proved for consistent cell differentiation in embryogenesis [19, 20, 29, 35, 41, 43]. Based on this, it can be assumed that, when a species arises at the genome level, the optimal ME composition and location are formed, creating the basis for their sequential activations during each cell division due to mutual regulation with PCGs. During zygote formation, the epigenetic marks of each parent are erased, and global demethylation of the genome occurs. With each subsequent division, there is remodeling of the entire epigenome, depending on the tissue and developmental stage [1, 20].

In parallel, the expression of specific MEs, as well as the activation of regulatory sequences mainly derived from MEs, is observed. This suggests that an evolutionarily constructed pattern of ME activation in successive cell divisions is the basis for cell differentiation. Indeed, the experiment proved that ME activation is necessary, both for the maintenance of pluripotency and for specific regulation of gene expression in order to specialize the cells, which is necessary for performing certain functions [20, 24, 36, 41, 49]. The ability of MEs to translocate to strictly defined regions of the genome serves as a reason for the possibility of the selection of specific ME compositions. This contributes to their sequential movements, which are necessary to control cellular expression during their division and differentiation in evolution.

MEs are the most important sources of miRNA genes (for more details, see the review in [5]) and functional domains of long ncRNA [27, 28]. In addition, MEs form the regulatory structures of the genome characterized by activation with respect to the developmental stage and tissue type in evolution [20, 24, 36, 41, 49]. Many transcription factors are also derived from ME proteins containing DNA-binding domains [16, 51]. Thus, MEs form a complex regulatory network (Fig. 3) with the interregulation of proteins derived from them (including transcription factors), regulatory structures (promoters, enhancers, insulators) and ncRNA (which control expression not only posttranscriptionally but also due to the influence on methyltransferases and histone modifiers [5]). At the same time, the activation of strictly defined MEs and regulatory structures and epigenetic factors (miRNA, long ncRNA) derived from them in each type of cell and tissue is noted [19, 20, 29, 35, 41, 43]. This suggests that the composition and location of MEs of each species serves as a biological coding that

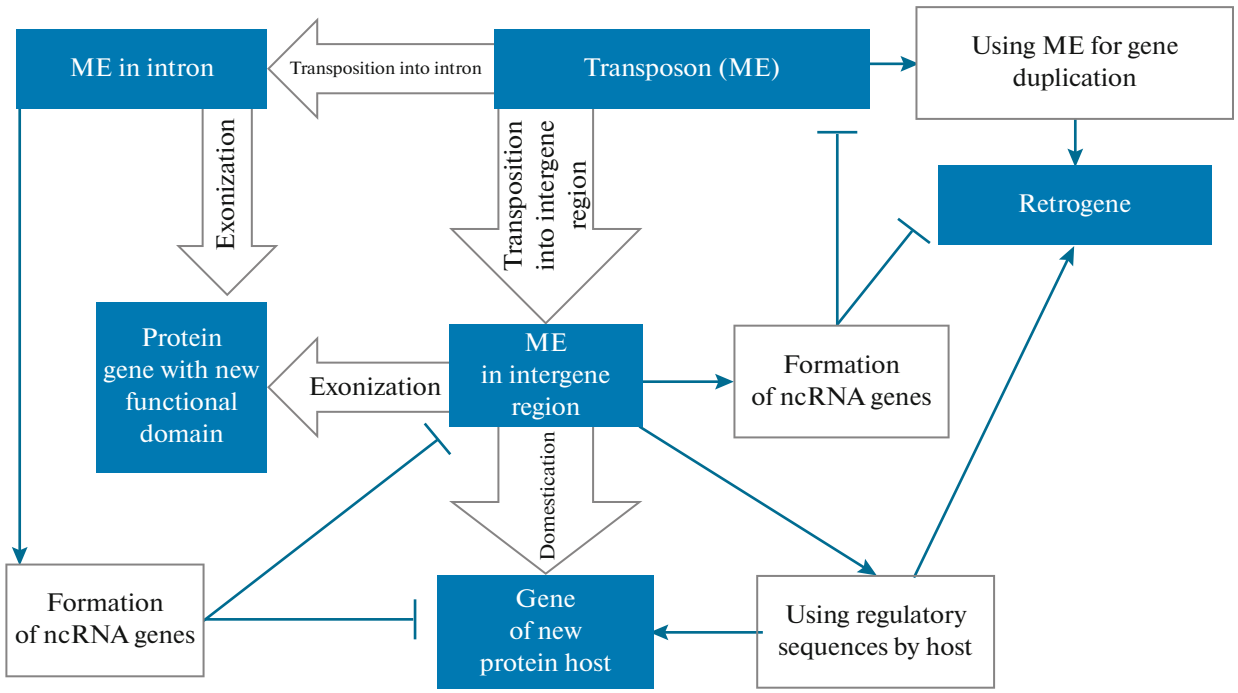

Fig. 3. Universal system for the formation of regulatory genomes network using transposons in evolution.

is disclosed in each subsequent division and causes aging of organisms. The identifying of specific MEs involved in the aging process could thus be the key to the search for ways to prolong life. A promising direction in this regard is the use of peptides that affect specific ncRNA genes based on the available data on the translation of miRNA and long ncRNA into functional molecules (for more details, see the review in [6]). An example of the specific activation of ME-derived genome structures depending on the cell type and developmental stage is *V*(*D*)*J* recombination (the origin of which is due to DNA transposons), which functions in specific cell types, T lymphocytes. Another example is the use of the syncytin gene, which is derived from the envelope gene of endogenous retroviruses *env* [51]. In addition, MEs were used in evolution for the most important, universal, structural transformations of genomes. For example, *Cenp-B* centromere-binding proteins originated from *pogo* transposases [54], and the linear structure of all eukaryotic chromosomes with telomeres at the ends owes its origin to retroelements, since telomerase is a domesticated reverse transcriptase of MEs [18].

TRANSPOSONS AS REGULATORS OF AGING

MEs can serve as the basis for the regulatory program of the development of the entire organism, starting with zygotic division and ending with death from natural processes. At the same time, the composition, number, and distribution nature of MEs relative to each other, protein-coding genes, and telomeres is a peculiar biological encoding that forms in natural selection and is implemented in successive cell divisions. The influence of MEs on ontogenesis regulation is global, since MEs in evolution became sources of transcription factors and binding sites for them; miRNA and its mRNA targets (for more details, see the review in [6]); and centromeres [18] and genes, the products of which interact with centromeres in cell divisions [54]. In this respect, the origin of telomerase from reverse transcriptase in evolution plays an important role, since the linear chromosomal structure with end telomeres, which is universal for all eukaryotes, owes its origin to transposons. Centromeres also appeared due to MEs and telomeres [18], while centromere-binding proteins *Cenp-B*, which are conservative for all eukaryotes, evolutionarily originated from *pogo* transposases [54]. The origin of telomerase from *RT* indicates the presence of close relationships between the structure and maintenance of telomeres on ME composition and functioning in the genome. Since the majority of researchers recognized the role of telomeres in aging, the relationship of telomeres with MEs indicates the promise of the search for ways to influence the change in the activity of specific MEs to regulate lifespan.

In evolution, MEs serve as sources of proteins specifically expressed in certain tissues and developmental stages, as well as proteins universal for the entire ontogenesis (telomerase, *Cenp-B*). The proteins derived from MEs regulate genes (due to the use of their DNA-binding domains) and chromatin structure (*Cenp-B*, *BEAF*-32, *HIM*-17 proteins), participate in

apoptosis (*THAP*0, *THAP*1, *E93*), control the cellular cycle (protein family *THAP*, *LIN*-36, *LIN*-15*B*), and protect against invasions of other transposons (dynamic interregulation during ontogenesis) [51]. At the same time, new PCGs may occur via the domestication of transposase genes (*RAG* in vertebrates, *Daysleeper* in drosophila, *Tram*, *Buster*1–3, *Zbed*4, *P*52*rlPK* in mammals, *Cenp-B* in all eukaryotes, *Metnase* and *Pgbd* in humans), integrase genes (*Gin*-1, *Fob*1*p*), *Gag* genes (*Mart*, *Ma*, *Fv*1), and retroviral envelop genes (*Syncytin*) [54].

An example of the relationship of regulators with domesticated genes derived from MEs is the *env* gene, which participates in the formation of a unified cell layer on the surface of the uterus [54], since the ancient MEs transformed the regulatory landscape of the uterus and transcriptome during the evolution of mammalian pregnancy. The expression of the endometrium was developed by thousands of genes upon the existence of the placenta, including genes mediating the relationship of the mother with the fetus and immunotolerance. At the same time, thousands of cis-regulatory elements mediating the decidualization and identity of cell types in decidualized stromal cells (DSCs) were obtained from ancient mammalian MEs that were coopted into hormone-dependent regulatory elements distributed throughout the genome. A total of 194 different families of ancient MEs enriched with cis-elements, which are active in human DSCs, were identified. Many of these MEs are donors of binding sites for the transcription factors that establish the identity of the cell type and the response to progesterone in DSCs [33]. The relationship between MEs and telomeres, which owe their origin to evolutionary ME activity, could develop according to a similar pattern. In this regard, it can be said that the observed telomere dysfunction with aging [48] carries more complex genomic transformations, including changes in ME regulation and, as a result, in the entire regulatory network of the genome. The identification of key pathways in the processes deregulating the primary MEs and those most probable for each species may be the key to possible modeling of the lifespan with ncRNA and peptides.

IMBALANCE OF TRANSPOSON REGULATION IN STEM AND MATURE CELLS DURING AGING

Aging is accompanied by a change in DNA methylation and chromatin remodeling. The formation of a separate type of heterochromatin, known as senescence-associated heterochromatin foci (SAHF), is an important component of cellular aging. The chromatin of the main retroelement classes (*Alu*, *SVA*, *L*1) becomes relatively more open with age, which leads to an increase in their transcription and, ultimately, to transpositions. The areas of constitutive heterochromatin in the centromeric and pericentromeric regions also become more open [12]. If terminally differentiated cells require repression of TEs, which promote their continuous division when a predetermined size of an organ is reached, then it is necessary to maintain the activity of certain MEs in order to maintain stem cell proliferation [20, 43]. At the same time, for stem-cell differentiation into somatic cells, the activation of other MEs is required [19, 20, 41, 49]; ncRNA and the peptide products of their translation most likely act as a "switch." For example, the activation of specific MEs in vivo can form genetically different subpopulations of mammalian brain cells; it creates their phenotypic differences and affects the peculiarities of the formation of certain structures [14], i.e., in the activation of certain MEs (for differentiation), specific repression of other MEs (for pluripotency) is necessary.

ME derepression plays an important role in molecular aging and can potentially occur in most terminally differentiated cells. However, in stem cells that have a significant risk of chronological and replicative aging [48], a high ME activity is necessary to maintain the pluripotency and differentiation potential during successive divisions. It can be assumed that the most optimal functional relationships between the systems of ME activity control in mature and stem cells form for each species in the course of evolution. The average lifespan, as a species feature, can reflect the interconnection and confrontation of these systems for the survival of the species as a whole. At the same time, aging and death can be considered a necessary process for this, one that is determined by variability and adaptation. The basis for the design of these dynamic systems can be the ratio of specific MEs to PCGs and other genome structures. The depletion of mechanisms for control of ME activity with age leads to ME derepression, which, in turn, activates new protective systems from unplanned transpositions. These protective mechanisms can affect stem cells, causing in them an imbalance in ME regulation, which is necessary for pluripotency and differentiation potential. As a result, the depletion of stem-cell centers of various organs occurs. In the course of natural selection in evolution, individuals with the most convenient system ratio for the survival of the species, which are encoded in ME composition and location relative to other genome structures, are preserved, which is reflected in the average lifespan for the species. Interestingly, the epigenetic labels of telomeres and *LTR* are identical and consist of the trimethylation of lysine 9 (*H*3*K*9*me*3) and lysine 20 (*H*4*K*20*me*3) [37]. This suggests that ME dysregulation observed with age may affect the telomere state and serve as a trigger for aging.

The hormonal trigger serves as one of the key points determining the onset of aging, switching in the body the activity of certain MEs that are sensitive to hormonal effects [3, 13, 32]. The selection of annual plants could be determined by the evolutionary selection of epigenetic regulation of stress-sensitive MEs, and the mass mortality of salmon after spawning could

be determined by avalanche-like ME transpositions under the influence of hormones. The female of the bumblebee two-spot octopus stops feeding and dies immediately after egg laying, which can be prevented by the removal of the optical glands from it [4]. This suggests the importance of the trigger mechanism. It initiates an imbalance between ME activity (stress or hormones) in stem and mature cells, leading to aging and death, as well as the possibility of its exposure to the lifespan.

PROSPECTS IN GERIATRICS FOR THE USE OF PEPTIDES THAT AFFECT TRANSPOSONS

The literature describes data showing that even a nonspecific effect to normalize the function of MEs, which changes with aging, can increase lifespan. For example, a restrictive diet regimen prolongs the life of flies by repressing MEs located in the heterochromatin. Enhanced expression of *Su*(*var*) 3–9 or *Dicer*-2 increases lifespan, and the lifespan of short-lived fruit flies with *Dicer*-2 mutations significantly increases upon exposure to the reverse transcriptase inhibitor 3*TC*, which suppresses ME transposition [58]. Experiments with diet changes in flies show that drosophila undergo rapid switching of gene-silencing levels. This demonstrates the epigenetic plasticity of chromatin [25].

Since MEs play a key role in the regulation of differentiation of embryonic cells and stem cells of adult organisms, ME activation, which leads to aging, cannot be a random process determined by the imbalance according to modern data [38]. On the contrary, regular processes that determine the average lifespan of individuals of the same species should underlie ME activation. The basis of these regularities is the composition, location, and number of ME copies in the genome, which affect the control of ontogenesis. Most likely, ME control systems in mature cells in evolution were selected and improved depending on the average lifespan required to preserve the species as a whole (for example, to control offspring development in mammals). The relationship of ME control systems with evolutionary necessity can be demonstrated in the mass death of pink salmon after spawning under the influence of hormones [4]. This is also evidence of the role of hormone levels in the switching of the activity of MEs sensitive to them [3, 13, 32], i.e., the change in ME activity with age, which leads to aging, is a regular process specific for each species. This regularity is determined by the activation of certain MEs that are the most sensitive to imperfection in their control systems, which leads to a cascade of epigenetic reactions. Determination of the primary activation of specific MEs typical of individuals of the same species may be the key to a targeted effect on this process with ncRNA and peptides.

The study of ME activation with aging led to certain results. A relationship was found between the mobilization of *gypsy* ME in the fat bodies of drosophila and age with the *gypsy TRAP* system, which was previously used to study brain aging in flies. It was shown that the activation of certain MEs may contribute to an age-dependent loss of neuronal function. In addition, mutations of the *Ago2* gene in drosophila lead to increased ME expression, progressive age-dependent memory impairment, and a reduced lifespan [30]. This indicates the importance of self-regulation systems of MEs by processed products of their own transcription (Fig. 4), since miRNA derived from MEs can participate in a wide range of regulatory effects, including changes in the chromatin state via specific effects on histone deacetylases [5]. The epigenetic plasticity of the lifespan and changes in it, even under the influence of the diet with a restriction of the energy value of food, suggests that complex regular processes are the basis of aging. The *Sir*2 depletion may be a secondary effect caused by the regulatory influence of ncRNA and MEs.

The detection of miRNA and long ncRNA translation into functional products (for more details, see review [6]) allows a new look at evolution and the ontogenetic role of peptides. It also indicates prospects to develop ways to combat aging with their use. MEs form functional domains of long ncRNA [27, 28]. Small ncRNA that have a regulatory epigenetic effect on gene expression are transcribed from ME sequences (described in the review in [5]). Thus, it can be assumed that all MEs have an inherent dualism of activity—functionality is manifested by the products of both their transcription and translation. This explains their active distribution and domestication in eukaryotic evolution as sources of regulatory structures and PCGs [6]. The ability to form global regulatory links controlling the entire developmental program, starting with zygotic division, suggests that many genes encoding biologically active peptides could originate in evolution from MEs or under their influence. Since the peptides that form during ncRNA translation can affect the expression of their own genes, they can be used to regulate the activity of the MEs from which ncRNA originated. At the same time, analysis of the level of miRNA and peptides in different age periods will allow the identification of specific means of changing ME activity during aging.

As with ncRNA that affect genome methylation [47], an increase in the site-specific binding of short peptides to DNA due to an age-associated decrease in the methylation degree of repetitive NSs in the genome was detected. The role of these interactions in the epigenetic regulation of aging processes is assumed [8]. It is not excluded that the identified changes show the mechanism of the action of *miPEP* translated from pri-miRNA, which exerts a regulatory effect on MEs, the products of which are these miRNA. In addition, since MEs are important sources of proteins in evolution [6], specific proteolysis of their protein products can be a programmed process for regulation of the epigenetic activity of the genome. Such complex reac-

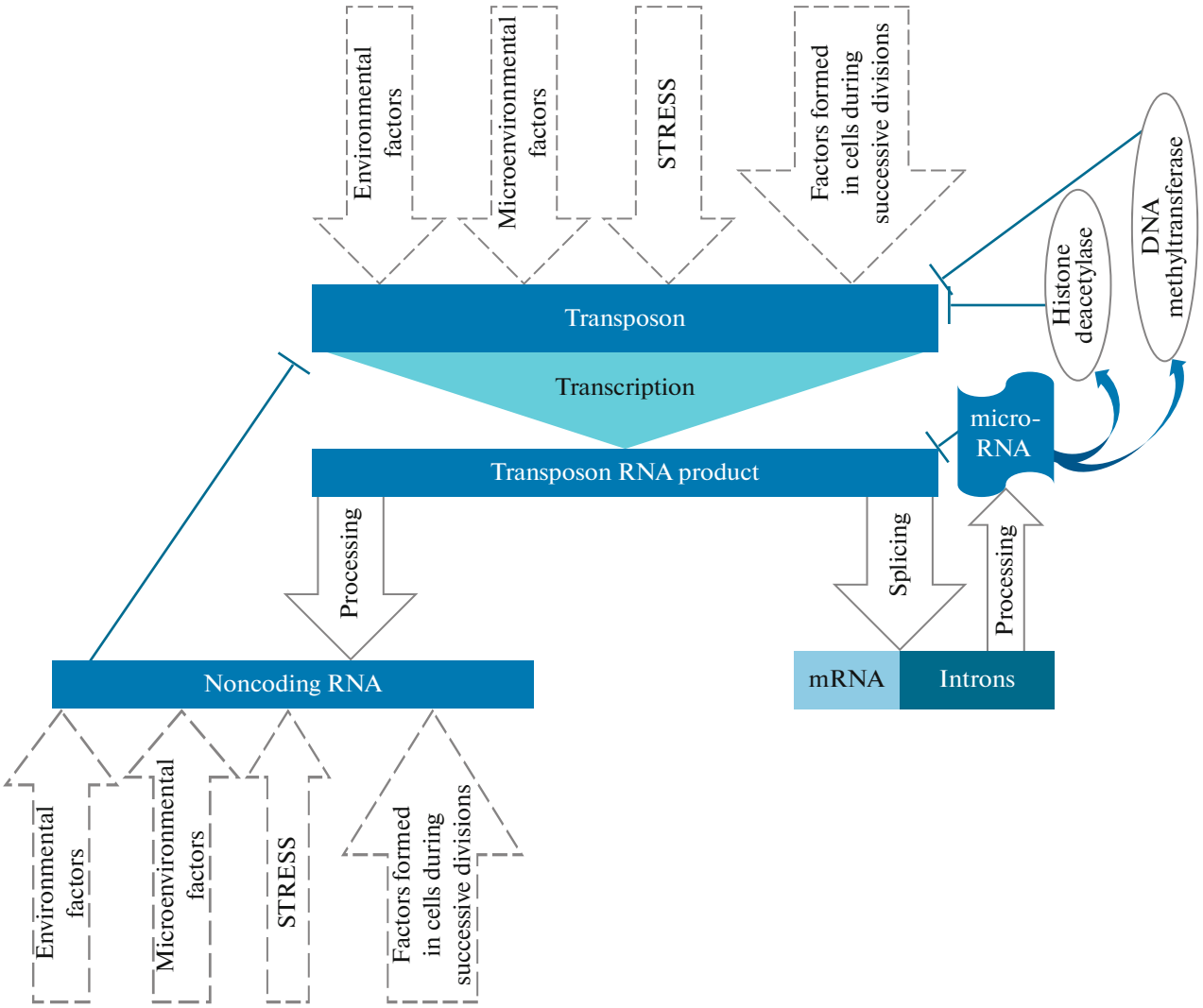

Fig. 4. Self-regulation of transposons in ontogenesis.

tions could form in natural selection due to the globalization of the role of MEs and their products in all possible regulatory processes, including self-regulation both by ncRNA translation products of the transposon origin and proteolysis products of proteins, the gene sources of which in evolution could be MEs (Fig. 5).

An example of the role of protein proteolysis in the formation of functional peptides is the formation of hormones from polypeptide precursors [46]. In this regard, the mechanism of the interaction of peptides with the DNA molecule is an important discovery [8, 9], since it shows the possibility of the self-regulation of genes by their peptide translation products. Like RNA processing, protein products also undergo processing—proteolysis. Like RNA molecules, which have dual functions, with processing into active ncRNA and translation, protein molecules also have this dualism. The dual functionality consists in the fact that, in addition to the activity of the protein with its spatial domains, peptides that also have the ability to regulate their own genes and ME genes form (which is manifested in their hormone sensitivity) when it undergoes programmed proteolysis. This capacity for self-regulation is most likely typical for protein products of genes derived from MEs, since their NSs contain specific repeats with which active peptides can bind.

The use of peptides is promising not only for increased lifespan [7] but also for the treatment of age-associated diseases. In this respect, a differentiated approach with the definition of the "double search for targets" of ncRNA and their translation products can serve as a key link for further research and mechanisms explaining the effectiveness of the used geroprotective peptides. For example, recent studies by V.H. Khavinson et al. showed the effectiveness of the *Lys-Glu-Asp-Trp* peptide, which affects the blood glucose level, plasma insulin concentration, and insulin resistance

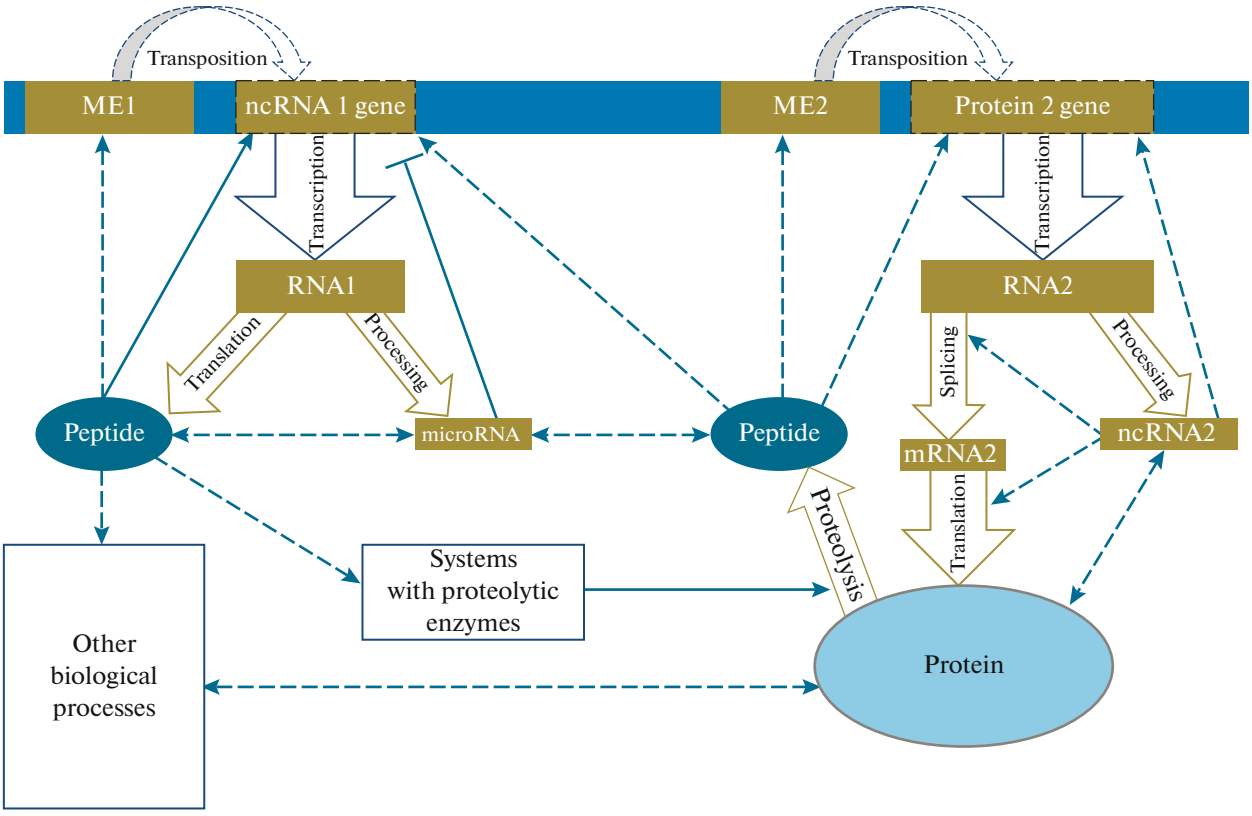

Fig. 5. System of mutual regulation of peptides that form in two ways: translation of ncRNA and proteolysis of proteins, the genes of which were derived from transposons (MEs) in evolution.

index. The authors rightly proposed a hypothesis of the epigenetic effect of this peptide on the expression of irisin and betatrophin genes [10]. It is not excluded that, in addition to the direct effect, the mechanism for the realization of the epigenetic effect is the similarity of the peptide with the products of translation of specific miRNA that affects the expression of irisin and betatrophin genes. In addition, from the point of view of a double search for targets, in the strategy of "MEs–ncRNA—peptides," the influence of genetic *SNP* on the development of age-associated multifactorial diseases can be explained: although *SNP* in the gene evolutionarily derived from ME does not cause significant changes in the structure of the translation product, *SNP* can significantly affect the spatial structure of the processed RNA of a given gene. Since in the double search for targets ncRNA and the protein (peptide) derived from a single gene can participate in common biological reactions, disruption of the ncRNA structure can lead to decompensation of the regulation of these pathways during aging of the organism and can result in age-associated pathologies (Fig. 6).

CONCLUSIONS

Since lifespan is a species-specific feature, regular genetic processes associated with the activation of certain MEs typical for each species, though not random ones, can serve as the cause of aging. This is supported by the following facts.

(1) The required activation patterns of MEs necessary to maintain the pluripotent state of the cells, as well as their differentiation, with stage and tissue-specific features were identified.

(2) MEs are the most important sources for the transcription of miRNA and long ncRNA, which are factors of the mutual regulation of MEs and PCGs in ontogenesis.

(3) In evolution, MEs serve as sources of both regulatory structures of the genome (possessing specific activation properties at certain stages of embryonic development in specific cells) and PCGs, the products of which interact with these regulators.

(4) The effect of MEs on the change in the chromatin structure interconnected with methylation was proven, i.e., the stochastic drift of genome methylation observed with age may reflect complex processes of successive changes in the activation of certain MEs, the order of which was selected during evolution.

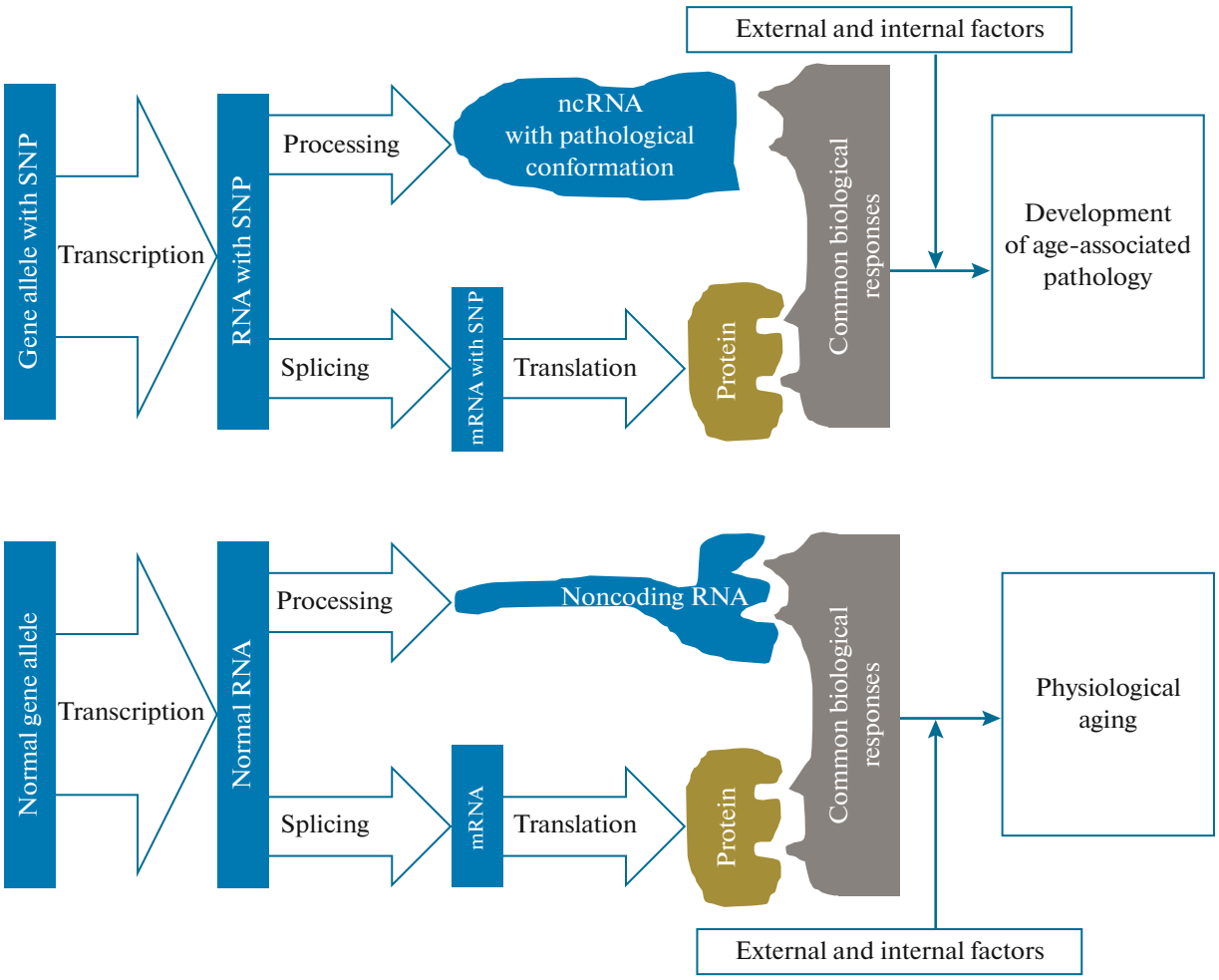

Fig. 6. Proposed role of SNP in the development of age-associated pathology due to imbalance in the strategy of "transposons–ncRNA–peptides" in the regulation of ontogenesis.

(5) Telomeres owe their origin to transposons; therefore, the telomere dysfunction observed with age is a particular reflection of the general process of the dysregulation of MEs.

(6) MEs are able to translocate to strictly defined loci of the genome, which indicates the possibility of the selection in the evolution of the pattern of ME transpositions in successive cell divisions, which have a regulatory effect on cell differentiation.

The ability of ncRNA to be translated allows a fresh look at the epigenetic regulation of genome functioning during ontogenesis, in which peptides are an important link. It creates a clear picture of the system of regulation by individual development, in which all parts are associated with each other and with MEs. This system serves as a basis for the effectiveness of peptides used in gerontology [7] and indicates the prospects for the development of new products in light of their possible origin from ncRNA in the strategy of "ME–ncRNA–peptides." In particular, *miPEP*, in addition to lifespan regulation, can be effectively used to treat oncopathology associated with age.

COMPLIANCE WITH ETHICAL STANDARDS

The authors declare that they have no conflict of interest. This article does not contain any studies involving animals or human participants performed by any of the authors.

REFERENCES

1. Baranov, V.S. and Kuznetsova, T.V., *Tsitogenetika embrional'nogo razvitiya cheloveka* (Cytogenetics of Human Embryonic Development), St. Petersburg, 2007.
2. Galitskii, V.A., Epigenetic nature of aging, *Tsitologiya,* 2009, vol. 51, no. 5, pp. 388–397.

3. Kiselev, O.I., Endogenous retroviruses: structure and functions in the human genome, *Vopr. Virusol.*, 2013, vol. 1, pp. 102–115.
4. Moskalev, A.A., *Starenie i geny* (Aging and Genes), St. Petersburg, 2008.
5. Mustafin, R.N. and Khusnutdinova, E.K., The interaction of transposons with epigenetic factors in aging, *Usp. Gerontol.,* 2017, vol. 30, no. 4, pp. 516–529.
6. Mustafin, R.N. and Khusnutdinova, E.K., Epigenetic hypothesis of the role of peptides in aging, *Adv. Gerontol.,* 2018, vol. 8, no. 3, pp. 200–209.
7. Khavinson, V.Kh. and Anisimov, V.N., 35 Years experience in peptide regulation of aging, *Usp. Gerontol.,* 2009, vol. 22, no. 1, pp. 11–23.
8. Khavinson, V.Kh., Solov'ev, A.Yu., Zhilinskii, D.V., et al., Epigenetic aspects of peptide-mediated regulation of aging, *Adv. Gerontol.,* 2012, vol. 2, no. 4, pp. 277–286.
9. Khavinson, V.Kh., Peptides, genome, aging, *Adv. Gerontol.,* 2014, vol. 4, no. 4, pp. 337–345.
10. Khavinson, V.Kh., Kuznik, B.I., Ryzhak, G.A., et al., Irisin, betatrophin, diabetes mellitus, obesity, and metabolic syndrome: epigenetic regulation mechanisms, *Usp. Fiziol. Nauk,* 2018, vol. 49, no. 1, pp. 72–86.
11. Chen, H., Zheng, X., Xiao, D., and Zheng, Y., Age-associated de-repression of retrotransposons in the *Drosophila* fat body, its potential cause and consequence, *Aging Cell*, 2016, vol. 15, no. 3, pp. 542–552.
12. De Cecco, M., Criscione, S.W., Peckham, E.J., et al., Genome of replicatively senescent cells undergo global epigenetic changes leading to gene silencing and activation of transposable elements, *Aging Cell,* 2013, vol. 12, no. 2, pp. 247–256.
13. de Souza, F.S., Franchini, L.F., and Rubinstein, M., Exaptation of transposable elements into novel cis-regulatory elements: is the evidence always strong?, *Mol. Biol. Evol.,* 2013, vol. 30, no. 6, pp. 1239–1251.
14. Faulkner, G.J., Retrotransposons: mobile and mutagenic from conception to death, *FEBS Lett.*, 2011, vol. 585, no. 11, pp. 1589–1594.
15. Feng, G., Leem, Y.E., and Levin, H.L., Transposon integration enhances expression of stress response genes, *Nucleic Acids Res.,* 2013, vol. 41, no. 2, pp. 775–789.
16. Feschotte, C., Transposable elements and the evolution of regulatory networks, *Nat. Rev. Genet.*, 2008, vol. 9, pp. 397–405.
17. Fujiwara, H., Site-specific non-LTR retrotransposons, *Microbiol. Spectr.*, 2015, vol. 3, no. 2. MDNA3-0001-2014. https://doi.org/10.1128/microbiolspec.MDNA3-0001-2014
18. Garavis, M., González, C., and Villasante, A., On the origin of the eukaryotic chromosome: the role of non-canonical DNA structures in telomere evolution, *Genome Biol. Evol.*, 2013, vol. 5, pp. 1142–1150.
19. Garcia-Perez, J.L., Marchetto, M.C., Muotri, A.R., et al., LINE-1 retrotransposition in human embryonic stem cells, *Hum. Mol. Genet.,* 2007, vol. 16, pp. 1569–1577.
20. Gerdes, P., Richardson, S.R., Mager, D.L., and Faulkner, G.J., Transposable elements in the mammalian embryo: pioneers surviving through stealth and service, *Genome Biol.,* 2016, vol. 17, p. 100. https://doi.org/10.1186/s13059-016-0965-5
21. Han, M.J., Xu, H.E., Zhang, H.H., et al., Spy: a new group of eukaryotic DNA transposons without target site duplications, *Genome Biol. Evol.,* 2014, vol. 6, no. 7, pp. 1748–1757.
22. Henaff, E., Vives, C., Desvoyes, B., et al., Extensive amplification of the E2F transcription factor binding sites by transposons during evolution of *Brassica* species, *Plant J.,* 2014, vol. 77, pp. 852–862.
23. Henssen, A.G., Henaff, E., Jiang, E., et al., Genomic DNA transposition induced by human PGBD5, *eLife*, 2015, vol. 4, p. e10565. https://doi.org/10.7554/eLife.10565
24. Ito, J., Suqimoto, R., Nakaoka, H., et al., Systematic identify cation and characterization of regulatory elements derived from human endogenous retroviruses, *PLoS Genet.,* 2017, vol. 13, p. e1006883.
25. Jiang N., Du G., Tobias E., et al., Dietary and genetic effects on age-related loss of gene silencing reveal epigenetic plasticity of chromatin repression during aging, *Aging,* 2013, vol. 5, pp. 813–824.
26. Jjingo, D., Conley, A.B., Wang, J., et al., Mammalian-wide interspersed repeat (MIR)-derived enhancers and the regulation of human gene expression, *Mobile DNA,* 2014, vol. 5, pp. 5–14.
27. Johnson, R. and Guigó, R.J., The RIDL hypothesis: transposable elements as functional domains of long noncoding RNAs, *RNA,* 2014, vol. 20, pp. 959–976.
28. Kapusta, A., Kronenberg, Z., Lynch, V.J., et al., Transposable elements are major contributors to the origin, diversification, and regulation of vertebrate long noncoding RNAs, *PLoS Genet.,* 2013, vol. 9, p. e1003470.
29. Lee, K.H., Yee, L., Lim, D., et al., Temporal and spatial rearrangements of a repetitive element array on C57BL/6J mouse genome, *Exp. Mol. Pathol.*, 2015, vol. 98, pp. 439–445.
30. Li W., Prazak L., Chatterjee N., et al., Activation of transposable elements during aging and neuronal decline in *Drosophila*, *Nat. Neurosci.,* 2013, vol. 16, no. 5, pp. 529–531.
31. Lowe, C.B. and Haussler, D., 29 mammalian genomes reveal novel exaptations of mobile elements for likely regulatory functions in the human genome, *PLoS One,* 2012, vol. 7, p. e43128.
32. Lu, Y., Feng, F., Yang, Y., et al., LINE-1 ORF-1p functions as a novel androgen receptor co–activator and promotes the growth of human prostatic carcinoma cells, *Cell. Signal.,* 2013, vol. 25, no. 2, pp. 479–489.
33. Lynch, V.J., Nnamani, M.C., Kapusta, A., et al., Ancient transposable elements transformed the uterine regulatoty landscape and transcriptome during the evolution of mammalian pregnancy, *Cell. Rep.,* 2015, vol. 10, no. 4, pp. 551–561.
34. Macfarlan, T.S., Gifford, W.D., Driscoll, S., et al., Embryonic stem cell potency fluctuates with endogenous retrovirus activity, *Nature,* 2012, vol. 487, no. 7405, pp. 57–63.

35. Macia, A., Muñoz-Lopez, M., Cortes, J.L., et al., Epigenetic control of retrotransposons expression in human embryonic stem cells, *Mol. Cell. Biol.,* 2011, vol. 31, pp. 300–316.

36. Mak, K.S., Burdach, J., Norton, L.J., et al., Repression of chimeric transcripts emanating from endogenous retrotransposons by a sequence-specific transcription factor, *Genome Biol.*, 2014, vol. 15, p. R58. https://doi.org/10.1186/gb-2014-15-4-r58

37. Mikkelsen, T.S., Ku, M., and Jaffe, D.B., Genome-wide maps of chromatin state in pluripotent and lineag-committed cells, *Nature,* 2007, vol. 448, pp. 553–560.

38. Orr, W.C., Tightening the connection between transposable element mobilization and aging, *Proc. Natl. Acad. Sci. U.S.A.,* 2016, vol. 113, pp. 11069–11070.

39. Packer, A., Manova, K., and Bachvarova, R.F., A discrete LINE-1 transcript in mouse blastocysts, *Dev. Biol.,* 1993, vol. 157, no. 1, pp. 281–283.

40. Pal, S. and Tyler, J.K., Epigenetics and aging, *Sci. Adv.,* 2016, vol. 2, no. 7, p. e1600584.

41. Pavlicev, M., Hiratsuka, K., Swaggart, K.A., et al., Detecting endogenous retrovirus-driven tissue-specific gene transcription, *Genome Biol. Evol.,* 2015, vol. 7, pp. 1082–1097.

42. Polavarapu, N., Mariño-Ramírez, L., Landsman, D., et al., Evolutionary rates and patterns for human transcription factor binding sites derived from repetitive DNA, *BMC Genomics,* 2008, vol. 9, p. 226. https://doi.org/10.1186/1471-2164-9-226

43. Ramsay, L., Marchetto, M.C., Caron, M., et al., Conserved expression of transposon-derived non-coding transcripts in primate stem cells, *BMC Genomics,* 2017, vol. 18, pp. 214–226.

44. Rodić, N. and Burns, K.H., Long interspersed element-1 (LINE-1): passenger or driver in human neoplasms?, *PLoS Genet.,* 2013, vol. 9, no. 3, p. e1003402.

45. Ruiz-Orera, J., Messeguer, X., Subirana, J.A., and Mar Alba, M., Long non-coding RNAs as a source of new peptides, *eLife*, 2014, vol. 3, p. e03523. https://doi.org/10.7554/eLife.03523

46. Saghatelian, A. and Couso, J.P., Discovery and characterization of smORF encoded bioactive polypeptides, *Nat. Chem. Biol.,* 2015, vol. 11, no. 12, pp. 909–916.

47. Samantarrai, D., Dash, S., Chhetri, B., et al., Genomic and epigenomic cross-talks in the regulatory landscape of miRNAs in breast cancer, *Mol. Cancer Res.,* 2013, vol. 11, pp. 315–328.

48. Sedivy, J.M., Kreiling, J.A., Neretti, N., et al., Death by transposition—the enemy within?, *BioEssays,* 2013, vol. 35, pp. 1035–1043.

49. Schon, U., Diem, O., Leitner, L., et al., Human endogenous retroviral long terminal repeat sequences as cell type-specific promoters in retroviral vectors, *J. Virol.,* 2009, vol. 83, no. 23, pp. 12643–12650.

50. Singh, D.K. and Rath, P.C., Long interspersed nuclear elements (LINEs) show tissue-specific, mosaic genome and methylation-unrestricted, widespread expression of noncoding RNAs in somatic tissues of the rat, *RNA Biol.,* 2012, vol. 9, pp. 1380–1396.

51. Sinzelle, L., Izsvák, Z., and Ivics, Z., Molecular domestication of transposable elements: from detrimental parasites to useful host genes, *Cell. Mol. Life Sci.,* 2009, vol. 66, pp. 1073–1093.

52. Trelogan, S.A. and Martin, S.L., Tightly regulated, developmentally specific expression of the first open reading frame from LINE-1 during mouse embryogenesis, *Proc. Natl. Acad. Sci. U.S.A.,* 1995, vol. 92, no. 5, pp. 1520–1524.

53. van Meter, M., Kashyap, M., Rezazadeh, S., et al., SIRT6 represses LINE1 retrotransposons by ribosylating KAP1 but this repression fails with stress and age, *Nat. Commun.,* 2014, vol. 5, p. 5011. https://doi.org/10.1038/ncomms6011

54. Volff, J.N., Turning junk into gold: domestication of transposable elements and the creation of new genes in eukaryotes, *BioEssays,* 2006, vol. 28, pp. 913–922.

55. Wang, J., Vicente-García, C., Seruggia, D., et al., MIR retrotransposons sequences provide insulators to the human genome, *Proc. Natl. Acad. Sci. U.S.A.,* 2015, vol. 112, pp. 4428–4437.

56. Wang, J., Li, X., and Wang, L., A novel long intergenic noncoding RNA indispensable for the cleavage of mouse two-cell embryos, *EMBO Rep.,* 2016, vol. 17, pp. 1452–1470.

57. Wheeler, B.S., Small RNAs, big impact: small RNA pathways in transposon control and their effect on the host stress response, *Chromosome Res.,* 2013, vol. 21, pp. 587–600.

58. Wood, J.G., Jones, B.C., Jiang, N., et al., Chromatin-modifying genetic interventions suppress age-associated transposable element activation and extend life span in *Drosophila, Proc. Natl. Acad. Sci. U.S.A.,* 2016, vol. 113, pp. 11277–11282.

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