Вавиловский журнал генетики и селекции. 2019;23(4):380-389
DOI 10.18699/VJ19.506

The role of transposable elements in the ecological morphogenesis under the influence of stress

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In natural selection, insertional mutagenesis is an important source of genome variability. Transposons are sensors of environmental stress effects, which contribute to adaptation and speciation. These effects are due to changes in the mechanisms of morphogenesis, since transposons contain regulatory sequences that have *cis* and *trans* effects on specific protein-coding genes. In variability of genomes, the horizontal transfer of transposons plays an important role, because it contributes to changing the composition of transposons and the acquisition of new properties. Transposons are capable of site-specific transpositions, which lead to the activation of stress response genes. Transposons are sources of non-coding RNA, transcription factors binding sites and protein-coding genes due to domestication, exonization, and duplication. These genes contain nucleotide sequences that interact with non-coding RNAs processed from transposons transcripts, and therefore they are under the control of epigenetic regulatory networks involving transposons. Therefore, inherited features of the location and composition of transposons, along with a change in the phenotype, play an important role in the characteristics of responding to a variety of environmental stressors. This is the basis for the selection and survival of organisms with a specific composition and arrangement of transposons that contribute to adaptation under certain environmental conditions. In evolution, the capability to transpose into specific genome sites, regulate gene expression, and interact with transcription factors, along with the ability to respond to stressors, is the basis for rapid variability and speciation by altering the regulation of ontogenesis. The review presents evidence of tissue-specific and stage-specific features of transposon activation and their role in the regulation of cell differentiation to confirm their role in ecological morphogenesis.
Key words: variability; morphogenesis; stress; transposable elements; evolution.

For citation: Mustafin R.N., Khusnutdinova E.K. The role of transposable elements in the ecological morphogenesis under the influence of stress. Vavilovskii Zhurnal Genetiki i Selektsii = Vavilov Journal of Genetics and Breeding. 2019;23(4):380-389. DOI 10.18699/VJ19.506

Стресс-индуцированная активация транспозонов в экологическом морфогенезе

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Инсерционный мутагенез, обусловленный транспозициями мобильных элементов, лежит в основе изменений геномов в естественном отборе. Транспозоны являются сенсором экологических стрессовых воздействий, благодаря чему воздействия стрессоров на организмы потенцируют изменения расположения транспозонов, что способствует адаптации и видообразованию. Это обусловлено изменением механизмов морфогенеза, так как транспозоны содержат в своем составе регуляторные последовательности, оказывающие *цис*- и *транс*-воздействие на экспрессию специфических белок-кодирующих генов. Мобильные генетические элементы способны также к сайт-специфическим перемещениям, которые приводят к активации генов стрессового ответа. Кроме того, транспозоны служат источниками микроРНК, siРНК, длинных некодирующих РНК и сайтов связывания с транскрипционными факторами. В эволюции благодаря мобильным генетическим элементам возникают новые белок-кодирующие гены путем одомашнивания, экзонизации и дупликации. Данные гены содержат нуклеотидные последовательности, которые взаимодействуют с процессированными из транспозонных транскриптов некодирующими РНК, в связи с чем они находятся под управлением эпигенетических регуляторных сетей с участием мобильных генетических элементов. Поэтому наследуемые особенности расположения и состава транспозонов могут иметь значение в характере реагирования на определенные экологиче-

ские стрессорные воздействия. Это служит основой для отбора и выживания особей со специфическим составом и характером расположения транспозонов, способствующих адаптации при определенных средовых условиях. В эволюции свойство транспозонов перемещаться в специфические сайты генома, регулировать экспрессию генов и взаимодействовать с транскрипционными факторами, наряду со способностью реагировать на экологические стрессоры, является основой для быстрой изменчивости и видообразования за счет модулирования управления онтогенезом. Роль транспозонов в экологическом морфогенезе подтверждена данными об их ткане- и стадиеспецифических особенностях активации и участии в управлении дифференцировкой клеток в эмбриогенезе и постнатальном развитии. Дополнительным источником изменчивости служит горизонтальный перенос транспозонов, способствующий изменению их состава в геномах.
Ключевые слова: изменчивость; морфогенез; стресс; транспозоны; эволюция.

Introduction

The concept of "ecological morphogenesis" includes the features of growth and development of organisms under the influence of key adaptation mechanisms that are formed under the influence of environmental factors (Curran, 2015). The basic principles of ecological morphogenesis are due to the differentiation and development of tissues under the control of genetic programs that have evolved under the influence of certain environmental factors with the selection of the optimal adaptive morphofunctional capabilities of the organism (Deng et al., 2014). In 1942, Conrad Waddington discovered that some phenotypic traits induced by heat shock in *Drosophila* pupae and then selected over several generations become inheritable in the presence of heat shock (Waddington, 1942). This means that changes in phenotypic traits that were acquired under the influence of environmental stressors (ES) can be inherited through the germ line. Waddington developed the concept of "canalization and assimilation" to explain his concept in the framework of Darwin's evolutionary theory. He called the "canalization" of stress resistance of organisms and their ability to maintain a constant phenotype. With these processes, genetic variations of genes of organisms of the same species that can change the phenotype remain hidden. If stress is strong enough to overcome this resistance, the path of development may change due to the expression of a particular gene from the existing hidden variations. This variant of the gene can be preserved during the selection and become inherited through the process of "assimilation" (Waddington, 1959).

The literature provides enough data to suggest that transposons (TE, transposable elements) can serve as hidden genetic structures capable of changing the expression of specific genes in response to certain ES (which overcome resistance to the constancy of the phenotype). This is due to the fact that TEs play an important role in the regulation of gene expression in ontogenesis (de Souza et al., 2013; Pavlicev et al., 2015; Wang et al., 2016; Ito et al., 2017; Ramsay et al., 2017; Saze, 2018) and serve as sources of changes in epigenetic (EG) factors (Li et al., 2011; Ito, 2012; Kapusta et al., 2013; Gim et al., 2014; Cho, 2018).

TEs are genetic elements that transpose from one locus in the genome to another. They can be simple (for example, insertion elements, IS) or complex (for example, TE, which contain genes involved in conjugation and drug resistance in prokaryotes). TE sizes range from 0.7 to 500 thousand base pairs (Zhang, Saier, 2012). The nomenclature system of IS-elements of prokaryotes is presented in the database (http://www-IS.biotoul.fr). The system proposed in 2008 is still used to classify transposons of bacteria and archaea (Roberts et al., 2008). TE classified into two classes. Class I includes retroelements (RE), which are moved by the "copy-and-paste" mechanism. They are divided into LTR-RE, which contain long terminal repeats (LTR, long terminal repeat) and non-LTR-RE (not containing LTR). Different members of RE contain transcriptase (RT, reverse transcriptase) for replication, but they differ in the composition of the catalytic components responsible for integration into the host genome. Class II includes DNA-TE, which are moved by "cut-and-paste" or "rolling circle". Their transposition is possible due to 3 different mechanisms: DDD/E transposase, tyrosine recombinase and endonuclease HUH in combination with helicase (Kojima, 2018). The most common TE classification is presented in Repbase (http://www.girinst.org/repbase/). TE occupy a significant part of the genomes of plants (more than 80 %), fungi (3–20 %) and animals (3–45 %) (Wicker et al., 2007).

A significant contribution to the study of TE, their systematization and the definition of a regulatory role was made by Russian researchers. R.B. Khesin in 1984 in his monograph "Genome inconsistency" described and systematized prokaryotic and eukaryotic TE in detail. The author noted the role of TE in genetic recombination, leading to an increase in the number of genes. Parallel variability Khesin explained the influence of TE with similar site-specificity of integration (Khesin, 1984). In further experimental works on *Drosophila*, the role of site-specific integration of TE as the adapting ability of genomes was confirmed (Kaidanov et al., 1996). If TEs are located near specific genes, which is associated with their peculiarities of germinative insertions, a specific reaction to ES is possible, which explains the concepts of "canalization and assimilation" at the genetic level. This is due to the activation of the TE in response to stress (Todeschini et al., 2005; Markel, 2008; Ito et al., 2016) and the effect of the TE on stress-sensitive genes due to the content of regulatory nucleotide sequences in transposons (de Souza et al., 2013; Feng et al., 2013). For example, the human genome contains 794 972 binding sites with transcription factors (TF) derived from LTR-RE, which are characterized by specific activation at different stages of development and depending on the tissue (Ito et al., 2017). Moreover, during evolution, the ability of TE to site-specific transposition was formed (Markel, 2008; Feng et al., 2013), thanks to which TE can dynamically regulate the expression of protein-coding genes (BCG) *in cis* and *in trans*, as well as stably alter gene regulation due to structural rearrangements (de Souza et al., 2013; Sahebi et al., 2018). The basis of the evolutionary processes is the variability, which is

induced by the ES (Markel, 2008), which caused the speciation of eukaryotes due to "outbreaks of transpositions" during interspecies hybridization, acting as a "genomic shock" (Cheresiz et al., 2008).

The activation of TE by stress is first described by Barbara McClintock. In her early observations, McClintock showed that TE transpositions are associated with heterochromatinization phenomena, and mobilization of heterochromatic domains can alter gene expression. McClintock suggested that the TE, which she called controlling elements, allows the genome to react more flexibly to stress (McClintock, 1984). Indeed, TEs play an important role in adaptation. TE insertions can affect host gene expression patterns and provide organisms with mechanisms for rapid genetic variation through the TE response to stress. For example, in *Arabidopsis thaliana*, the transposition of the heat-activated TE ONSEN causes a mutation of a gene that is sensitive to abscisic acid (ABA). As a result, plant insensitivity to ABA and tolerance to the stressor arise. That is, activation of TE under the action of ES can cause modulation of the host's reaction to environmental influences. Epigenetic mechanisms usually cause a silencing effect of a new insertion (for example, for ABA using IBM2), but they can selectively activate TE under stress (Ito et al., 2016). Induction of integration events under the influence of ES was detected in fungi. For example, in *Saccharomyces cerevisiae*, Re *Ty1* is activated under the influence of various ES, including the lack of adenine (Todeschini et al., 2005).

The role of TE in evolutionary variability is also associated with their ability to induce chromosomal rearrangements, including deletions, inversions, and replicon fusion – the central events of many evolutionary processes. Moreover, TEs contribute to a significant reorganization of genes from the initial random order under the pressure of selection. TE contributed to the emergence of adaptive mutations that occur randomly, but with increased speed under the influence of stress in eukaryotes in the course of evolution (Zhang, Saier, 2012). Large-scale changes in DNA methylation in response to stress (Dowen et al., 2012) may reflect the dynamics of expression of TE, sensitive to ES and to the stress response of the organism (Todeschini et al., 2005; Markel, 2008; Ito et al., 2016). This is due to the important role of TE as sources of non-coding RNA (ncRNA) (Li et al., 2011; Gim et al., 2014; Cho, 2018), which have a regulatory effect on chromatin structure and genome methylation (Ito, 2012; Zhang et al., 2015).

In addition, the ability of the animated TE to enhance the transcription of the stress response genes, as well as exert a regulatory effect *in cis* and *in trans* on various BCGs, makes the TE universal mediators of the interaction of the genome with ES (de Souza et al., 2013; Feng et al., 2013; Ito et al., 2016). For example, in the study of DNA demethylases in plants, it was revealed that their primary function is to regulate the expression of stress response genes due to the effect of TE on their promoters (Le et al., 2014). In addition, the key influence of the TE on the regulation of the genome is due to the origin of the transcription factors from the TE (Lin et al., 2007; Feschotte, 2008) and TF binding sites (TFBS) from the TE in the evolution. Specific activation of these TFBSs was detected by switching gene expression during cell differentiation during ontogenesis (de Souza et al., 2013; Ito et al., 2017).

TEs possess the sensitivity of their expression both to ES and to the stress reactions of the organism itself. At the same time, TEs can cause local regulation of certain genes, acting as enhancers (Makarevitch et al., 2015). In addition, TEs can alter the expression of specific genes using ncRNA (Cho, 2018). TEs can act as stress-sensitive regulators, affecting *in cis* and *in trans* the functioning of BCG (de Souza et al., 2013; Sahebi et al., 2018). In the course of evolution, host genomes have developed the ability to regulate the activity and specificity of integration for TE. This mitigates the instability of the genome caused by uncontrolled transpositions. Recent studies have shown the key role of small ncRNAs in the regulation of transpositions in fungi, plants and animals through a conservative mechanism. Signals about the presence of transposon RNA or about the integration of TE into specific loci of the genome are transmitted to small ncRNAs that send epigenetic modifications and gene silencing back to TE (Wheeler, 2013). The regulation of the host genome by means of TE is global with the involvement of all ncRNA species (Mustafin, Khusnutdinova, 2017). The origin of ncRNA from TE suggests that during the course of evolution, TE developed the ability to self-regulate with the help of processed products of their own transcription, which ensure their optimal interaction with the host genome. TEs can induce mutations under the control of host factors in a process that phenotypically and mechanistically corresponds to the definition of "directional mutations" that occur with high frequency when exposed to stress if they are beneficial to the host. Prototypes of "directed mutations" are found in bacteria, for example, *E. coli* strains with a deletion of the *crp* gene cannot grow on glycerol (Glp(–)). However, insertions of the IS5 into a specific region immediately prior to the glpFK promoter lead to the efficient use of glycerol (Glp(+)) at rates that are significantly increased by the presence of glycerin or loss of the glycerin repressor (GlpR) (Zhang, Saier, 2012). The non-random TE integration was found in the *Schizosaccharomyces pombe* genome, in which the *Tf1* LTR-PE is inserted into promoters with a preference for stress response genes (Feng et al., 2013). In addition, sites of preferred stress-induced TE integration in *D. melanogaster* were identified (Vasileva et al., 1997). In *D. melanogaster*, 94 % of all insertions of the *P*-element and all insertions of other elements (*jockey*, *gipsy*) in the field of gene promoters were in the heat shock gene *hsp70* (Walser et al., 2006). That is, transposon-mediated changes are "directed mutations" (Cheresiz et al., 2008).

The effect of stress on the activation of transposable elements in plants

Plants are characterized by the peculiarities of the composition of TE in their genomes, the distribution of TE, as well as the characteristics of microRNA, which is reflected in their morphogenesis under the influence of stress (Mustafin, 2018). The effect of TE on the dynamics of gene expression during tissue formation is mediated by interaction with epigenetic factors (ncRNA, DNA methylation and histone modification). In plants, siRNAs are responsible for RNA-dependent DNA methylation (RdDM), which suppresses TE when they are activated by stress and hybridization events (Ito, 2012). The ability to regulate gene activity by exposure to target methylation and histone modifications was also detected in

miRNAs and long ncRNAs (Zhang et al., 2015). Important sources of these non-coding RNAs are TE (Li et al., 2011; Kapusta et al., 2013; Lorenzetti et al., 2016; Cho, 2018). That is, in the course of evolution, TE acquired the ability of self-regulation by the products of processing their own transcripts, which is important in controlling the functioning of genes *in cis* and *in trans* (de Souza et al., 2013) and through site-specific transpositions (Markel, 2008; Feng et al., 2013; Sahebi et al., 2018).

NcRNAs, which are derived from TE, are able to exert a regulatory effect directly on the expression of BCG, which contain sequences identical to TE (Fig. 1). This is due to the important role of the TE in the emergence of BCG in the course of evolution due to their domestication (Zdobnov et al., 2005; Lin et al., 2007; Feschotte, 2008; Dupressoir et al., 2012), retrogenes generation (Kubiak, Makalowska, 2017) and exonization (Lin et al., 2008; Sela et al., 2010; Schmitz, Brosius, 2011; Tajnik et al., 2015). The correlation between stress induction of TE and activation of cell defense mechanisms against stress is associated with the presence of TF binding sites in TE, which induce the genes of cell defense systems and are often co-opted by host genomes for their own needs due to their adaptive role (Cheresiz et al., 2008). The conservation of TEs in the host genomes is due to their participation in the activation of responses to the stress response for survival (Feschotte, 2008; de Souza et al., 2013; Ito et al., 2017).

In plants, the major part of the genomes is occupied by LTR-RE, which are regulated by various ESs, displaying finely tuned responses to these stimuli, mainly in the form of activation. LTR regions contain regulatory motifs similar to cellular genes and are involved in the functional plasticity of host genomes, acting as dispersed regulatory modules that can reorient stress stimuli for neighboring genes (Grandbastien, 2015). In response to stress, both TE and genes located near insertions can be transcriptionally activated. TEs are important sources of epigenetic factors (Mustafin, Khusnutdinova, 2017), and most plant miRNAs are identical or homologous to TE (Lorenzetti et al., 2016; Cho, 2018). Therefore, to determine the response of plants to stress, miRNAs are investigated, which play an important role in controlling the activity of BCG and TE. For example, in rice microRNAs were identified that are subject to regulatory effects by stressors, such as drought, cold and insolation. Of these newly identified 227 miRNAs, 80 were derived from TE (Barrera-Figueroa et al., 2012). The activation of LTR-RE in rice was revealed under the influence of an excess of iron in the soil. It was shown that LTR-RE can enhance the expression of genes involved in iron homeostasis (Finatto et al., 2015).

The ideal system for studying the effect of TE on gene regulation is the maize genome, since it contains many different TEs alternating with BCG. An analysis of the location of genes near TE and stress-induced transcripts has shown that these TEs can perform enhancer activity that stimulates the expression of stress-sensitive genes. It was reported that TE are important sources of regulation of alleles of genes sensitive to abiotic ES (Makarevitch et al., 2015). Therefore, TFBS, which are derived from the TE, can rewrite existing transcriptional networks. This leads to the emergence of new adaptive traits, which is important for the formation of new species. For example, during speciation of cabbage, TE amplified binding sites with the transcription factor E2F, therefore

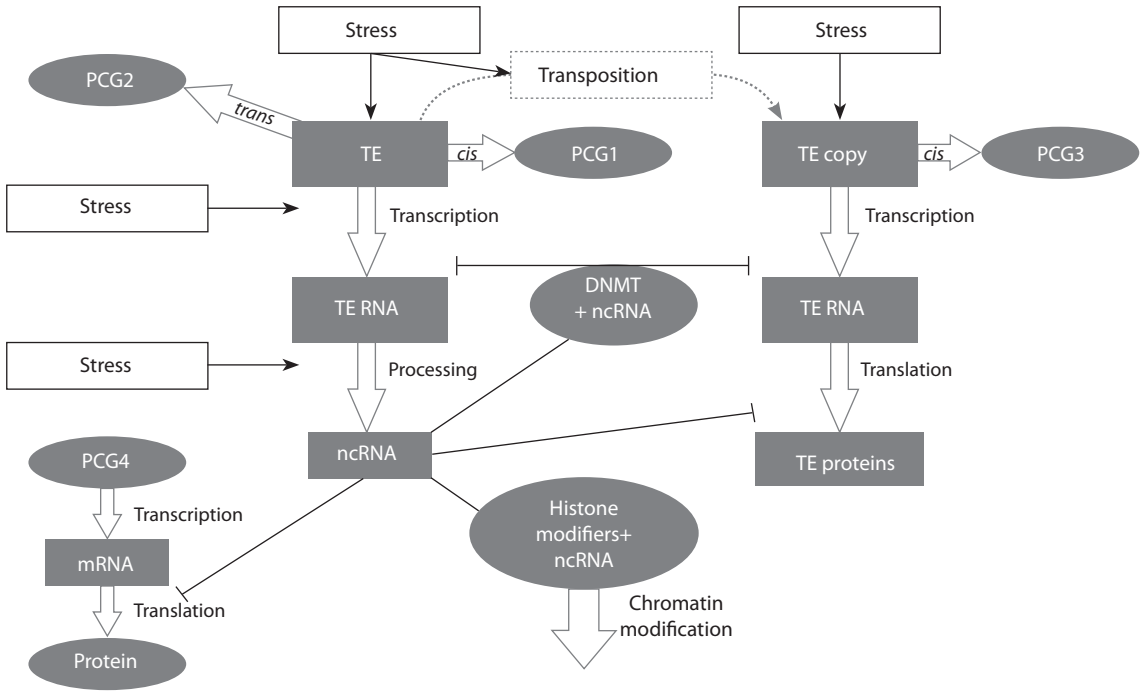

Fig. 1. Role of transposable elements in the regulation of genomic functioning under the action of stress.
TE, transposable elements; PCG, protein-coding gene; ncRNA, non-coding RNA; mRNA , messenger RNA; DNMT, DNA methyltransferase.

in some species of cabbage more than 85 % of all E2F are inside the TE (Henaff et al., 2014).

The effect of stress on the activation of transposable elements in animals

In 1985, it was shown that heat shock in *D. melanogaster* enhances the expression of RE *copia* and the *hsp-10* gene (Strand, McDonald, 1985). Further studies revealed that the features of *copia* activation are specific for different lines of *D. melanogaster* (Cheresiz et al., 2008). These results indicate the variation in TE sensitivity to stress, even in individuals within the same species. The probable causes of such variability may be a violation of the relationship of TE with various TFs. It can be suggested that the sensitivity of TE to environmental stressors and stressful changes in the organism may vary in different cell lines of one organism under the influence of varying gene expression during differentiation. In this regard, cells of different organs and tissues may exhibit the specific susceptibility of TE in the composition of their genomes to stress. The most highly stress sensitive cells are brain neurons (Hunter, McEwen, 2013). One of the ways that the ES affects the brain is the change in epigenetic marks at different stages of development in ontogenesis, thereby regulating the expression of specific TE depending on their location (Hunter, McEwen, 2013). The possible reason for the inheritance of stress resistance can be the peculiarities of the composition, distribution, and peculiarities of TE activation in individual development, which are important factors of EG regulation of morphogenesis (Mustafin, Khusnutdinova, 2018b). That is, individuals survive in natural selection, whose location and composition of TEs in the genome of which contribute to the effect of ES contributing to the adaptation and survival.

Epigenetic factors may explain the mechanism by which ES causes long-term changes in physiology and behavior. Stress, as well as steroid hormones, due to changes in epigenetic markers (DNA methylation and histone modifications) affect plasticity in a number of brain regions (Hunter et al., 2015). These areas include the hippocampus, which contains neuronal stem cells and is characterized by TE activity necessary for their differentiation into specific neurons for different areas of the brain (Mustafin, Khusnutdinova, 2018a). It has been shown, for example, that acute stress in rats causes significant and hippocampal-enhanced enhancement of H3K9me3 levels that target LTR-RE in order to contain potential genomic instability (Hunter et al., 2012). In addition, some TEs are activated under the influence of stress caused by viral infections of host cells. For example, infection of cell cultures with the herpes virus, human immunodeficiency and adenovirus induces the transcription of SINE elements (Cheresiz et al., 2008).

The relationship of hormones with stress-induced transposon activity

The expression pattern of TE is influenced by the type of cells and tissues (with particular importance in the placenta and germ cells), aging and differentiation factors, cytokines, agents and steroids disrupting the function of cells (Taruscio, Mantovani, 2004). TEs are highly sensitive to hormones, the level of which, in turn, reflects the body's response to stress. Based on this, it can be suggested that the management of ontogenesis with the participation of hormones was formed under the influence of environmental changes during the adaptation of organisms using TE, participating in the regulation of gene expression in various cells depending on the tissue and developmental stage. This assumption is based on data on the key role of epigenetic factors in the regulation of TE activity. At the same time, TE themselves are sources of ncRNAs (Lorenzetti et al., 2016; Cho, 2018), which are capable of being translated into functional peptides (miPEP) (Couzigou et al., 2016), that regulate gene expression. It is assumed that peptide hormones can affect the tissue- and stage-specific TE activation, which is used to control gene expression during the growth and development of the organism (Mustafin, Khusnutdinova, 2018a). This is due to the ability of miPEP to enhance the expression of its own miRNAs (Couzigou et al., 2016), which are involved in the epigenetic regulation of TE (Mustafin, Khusnutdinova, 2017) (Fig. 2).

Stress and steroid hormones affect brain structures, where a high TE activity has been identified (Hunter et al., 2015), presumably related to the regulatory effect of transposons on the differentiation of neuronal stem cells (Mustafin, Khusnutdinova, 2018a). The relationship of TE with hormones is determined both in their sensitivity to steroids and peptides, and in the regulatory effect of TE insertions on genes that affect hormone production. For example, the insertion of TE *Taguchi* occurs to the *cis*-regulatory region of the ecdysonoxidase gene, which encodes a key enzyme to reduce the level of the molt hormone 20-hydroxyecdysone. Phylogenetic analysis showed that the TE insertion occurred during the domestication of the silkworm and was adaptive for *Bombyx mori*, as it is used as an enhancer that induces the expression of 20-hydroxyecdysone (Sun et al., 2014). For the final stages of cortisol and aldosterone synthesis in humans, the *CYP11B1* and *CYP11B2* genes, respectively, are responsible. These two genes are homologous in the proximal regions, however, the insertions of *Alu* and L1 caused the divergence of promoters (Cheng et al., 2012). In the human genome, a micro-transcriptional mechanism regulating the expression of the *Tspo* gene was detected. In the intron of the *Tspo* gene, SINE B2 is located, which regulates steroidogenesis specific for the *Tspo* gene. High levels of TSPO are expressed in Leydig cells in the testes, and their expression levels dictate the ability of cells to form androgens (Fan, Papadopulos, 2012).

An *in vitro* transfection study with human *DMBT1* (deleted in malignant brain tumors 1) promoter constructs showed that an *Alu* site approximately 3000 nucleotides upstream of the gene mediates estrogenic regulation. Estrogen antagonists tamoxifen, raloxifene and ICI 182,780 also induce the expression of *DMBT1* gene through this *Alu* site (Tynan et al., 2005). It was found that the ORF-1p L1 element enhances the transcriptional activity of androgen receptors (AR) and the expression of the prostate-specific antigen (PSA) (Lu et al., 2013). Plants produce a large amount of hormonal substances – phytosterols, which have a diverse effect on their development. Currently, mutants of *Arabidopsis* for transposons are widely available for studying phytosterols (Suzuki, Muranaka, 2007). Thus, various independent studies have shown that hormones can affect TE expression, while transposons affect hormone production by insertions into specific loci and effects on the epigenetic regulation of morphogenesis.

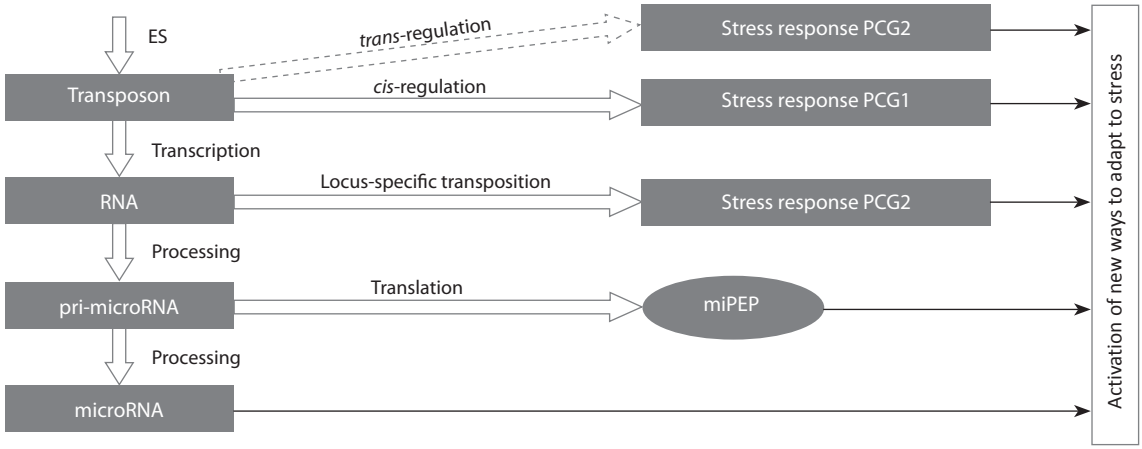

Fig. 2. Scheme of the role of transposon self-regulation in the regulation of stress-induced adaptive variability of genomes.
ES, environmental stressors; miPEP, product of microRNA translation; PCG, protein-coding gene.

Tissue-specific and stage-specific activation of transposons

TEs are successfully preserved in evolution, they respond to certain ES and stress changes in the organism, and also have a global regulatory effect on the genome. This indicates the universality of stress-induced TE activity in evolution and ontogenesis. As stress signals affecting the activity of certain TE, there may be changes in the intracellular environment during successive cell divisions, starting with the first division of the zygote. The specific composition and distribution of TE for each species suggests that activation of certain TE may cause activation of some BCG by *cis* and *trans* regulation (de Souza et al., 2013; Sahebi et al., 2018) and silencing of other BCG via ncRNA formed by processing TE transcripts (Gim et al., 2014; Cho, 2018). As a result, a cascade of sequential changes in BCG expression necessary for cell differentiation may form. The existence of such evolutionary-established mechanisms of regulation of ontogenesis with the help of TE can be confirmed if the suppression of the activity of specific TE required for further regulation of cell differentiation will stop the further development of the organism. Indeed, in experiments on mouse embryos, it was shown that depletion of the long *LincGET* ncRNA associated with LTR-RE leads to a complete arrest of further development at the two-cell stage (Wang et al., 2016). In this stage, many transcripts are initiated from the LTR-RE (Macfarlan et al., 2012) and are associated with enhancers that support the polypotency (Fort et al., 2014).

In embryogenesis, TEs can redistribute the regulation of BCG expression depending on the developmental stage and the type of tissue (Pavlicev et al., 2015). In mouse and human genomes, TE are sources of at least 30 % of transcription start sites with tissue-specific activation features (Gerdes et al., 2016). In mice, in early embryogenesis, up to 20 % of the transcriptome is initiated from RE. In evolution, specific transpositions of retroelements became the basis for the distribution of tissue-specific binding sites for TF (Mak et al., 2014). On the basis of experimental data on the accumulation of LINE-1 insertions in human embryonic stem cells, accompanied by the suppression of the activity of certain genes, the role of the TE in regulating the work of the genome in cell differentiation was confirmed (Garcia-Perez et al., 2007). Profiles of specific TEs may indicate cellular identity. This suggests the importance of TE in controlling the work of the genome in cell differentiation. The active transcription of TE, which contributed to the maintenance of pluripotency, as well as the reactivation of certain REs in the early embryonic development of animals along stem cell lines was proven (Gerdes et al., 2016).

TEs are important sources of TFBS, which are characterized by their ability to be activated depending on the tissue and developmental stage (Lowe, Haussler, 2012; de Souza et al., 2013). TFBS, which originated from LTR-RE, differ in tissue- and stage-specific activation features (Ito et al., 2017). In addition, TEs can control tissue-specific features of gene expression by providing alternative splicing sites and UTR regions, since the alternative variants of the translated proteins have different properties (Lin et al., 2008; Tajnik et al., 2015). It was shown that epigenetic regulation of the function of transposons located in the introns of genes contributes to a change in their regulation in ontogenesis and in the peculiarities of expression (Saze, 2018). In human tissue cultures, a difference in tissue-specific gene expression was detected for 62 different LTR classes in 18 types of tissue. These results allowed to propose the role of TE as a tissue-specific regulator of gene expression in ontogenesis (Pavlicev et al., 2015). Non-LTR retroelements have functions similar to long ncRNAs, regulating BCG expression in stem cell differentiation during embryogenesis (Honson, Macfarlan, 2018). In addition, in humans, various long ncRNAs derived from the retrovirus HERVH are expressed and necessary for stem cell pluripotency (Ramsay et al., 2017).

Horizontal transfer of transposable elements in evolution

In addition to the distribution of transposons in the genomes of eukaryotes, TE composition plays an important role in speciation, which is modified by horizontal transfer. Horizontal transfer plays a major role in the evolution of prokaryotes, in which more than 81 % of their genes are involved in this process (Palazzo et al., 2017). In the evolution of animals, the

character of TE spreading by means of horizontal transfer is noted, like interspecies viral pandemics. For example, about 46 million years ago there was a major surge in the activity of DNA-TE of the *SPIN* family, making the sequences of these TE identical by 96 % in a wide variety of animals (african clawed frog, lizard anole, senegal galago, rat, mouse, brown bat) (Pace et al., 2008). In animals, for the first time, horizontal transposon transfer was detected in 1990 in *D. melanogaster* (Daniels et al., 1990). Further studies have revealed the ability of horizontal transfer of most TEs in insects, reptiles, jaws, lamprey and mammals (Zhang et al., 2014).

It is assumed that the genes of RAG, forming the complex necessary for recombination of the V(D)J, in the jawed vertebrates have arisen due to the horizontal transfer of TE (Sniezewski et al., 2018). In the insect *Helicoverpa zea*, Transib transposase was found, which has properties similar to RAG. This suggests the possibilities of horizontal transfer in the evolution and phylogenetic relationship of the TE genes domesticated by the genomes of various types of eukaryotes (Hencken et al., 2012). Phylogenetic studies have revealed a horizontal transfer of retroelements of the *An-RTE* family in angiosperms from ancestors of arthropods. In 42 animal species, retroelements were significantly identical with *An-RTE* flowering plants (Gao et al., 2018). In the Horizontal Transposon Transfer DataBase (http://lpa.saogabriel.unipampa.edu.br:8080/httdatabase/), great attention is paid to horizontal transfer in eukaryotes (Dotto et al., 2018).

Recently, mechanisms of horizontal transfer between different taxa are being actively studied. One of the ways of spreading TE by horizontal transfer was demonstrated by the example of TE *Bari* belonging to the *Tc1-mariner* superfamily, which in evolution acquired the property of "diffuse promoters" and can move between different genomes (Palazzo et al., 2017). Viruses can act as vectors for horizontal transposon transfer. For example, for the *Chapaev* transposon, the *Bracovirus* virus can act as a vector. Due to the horizontal transfer, *Chapaev* elements are widely distributed in the genomes of many animal species (Zhang et al., 2014).

TEs are found in the genomes of giant viruses, where they participate in the functioning and evolutionary transformations, and their transfer to the host genomes is not excluded (Filee, 2018). For example, the transposon *Submariner* was found in the genome of *Pandoravirus salinus*. For this pandoravirus, the host is the ameba *Acanthamoeba castellanii*, in the genome of which *Submariner* and its associated DNA-TE are found, which indicates the presence of a horizontal transfer between the virus and the host (Sun et al., 2015). In addition, viruses can activate TE, for example, a cytomegalovirus infection can cause the expression of HERV (Assinger et al., 2013). Moreover, TEs can participate in the integration of viral genomes into host DNA, as well as in protection against viral infections (Speiseder et al., 2014; Tarocchi et al., 2014). For example, in animals, the ability of ERV to cause restriction of related exogenous retroviruses was identified (Malfavon-Borja, Feschotte, 2015). At the same time, the ability to transform ERVs into exogenous retroviruses, and exogenous viruses to ERV in the genomes of various hosts has been proven (Zhuo, Feschotte, 2015). *Caulimoviridae* viruses in plants have evolved from LTR retroelements (Llorens et al., 2009). Analysis of the results of experimental work by various authors has shown that the relationship between TE and viruses in the evolution of eukaryotes is global and plays a crucial role in the variability of the host genomes. A number of studies have shown the interconversions of viruses and TE (Zhuo, Feschotte, 2015), as well as the existence of elements that combine the properties of viruses and transposons. Intermediate evolutionary link between DNA-TE and viruses are virophages (Fisher, Suttle, 2011). *RVP* virophages are known, which are a hybrid of polytone virophages that can cause viral infections (Yutin et al., 2015). Polintons are also known which possess the properties of TE. Polintons exist as both autonomous and non-autonomous elements. They are common among various species of animals, mushrooms and protists. It is assumed that many eukaryotic viruses, including megaviruses and adenoviruses, originated from polintons (Krupovic, Koonin, 2016).

Conclusion

In the scientific literature accumulated enough experimental data confirming the sensitivity of TE to stress in all living organisms. The activation of TE under the action of stress leads to a change and the emergence of new regulatory gene networks that contribute to variability. This is an important factor in the natural selection of individuals with a specific composition and location in their genomes TE, whose activation under the influence of stress during ontogenesis facilitates adaptation.

The study of TE activation in different tissues and at different stages of development under the influence of stress may be the key to clarifying the mechanisms of ecological morphogenesis. These studies are promising for diagnostic and therapeutic models in biology, genetics and biochemistry. Determining the role of miRNAs and hormones in changing cell differentiation under the influence of TE is promising for planning targeted therapy of pathologies associated with dysfunction of epigenetic factors, as well as a possible impact on the aging process. The key to modulating the growth and development of organisms can be the study of various TEs capable of site-specific transposition. These studies are promising for the controlled use of stem cells in organ-substituting technologies. Moreover, to study changes in regulatory gene networks in evolution, it is promising to compare the sensitivity to stress of certain TE different taxa of eukaryotes.

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Conflict of interest. The authors declare no conflict of interest.
Received November 21, 2018. Revised December 17, 2018. Accepted January 22, 2019.