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REVIEWS AND THEORETICAL ARTICLES

Epigenetic Regulation and Role of LINE-1 Retrotransposon in Embryogenesis

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Abstract—LINE-1 retrotransposon is the most common mobile genetic element in the genomes of various mammals, including humans. Its genes are represented by the greatest number of copies. For a long time, it has been considered that the presence of LINE-1 in genome reflects the limited ability of cells to eliminate it, and the retrotransposon activity is negative owing to the insertional mutagenesis. In recent years, the increased expression of LINE-1 retrotransposon and the activity of their encoded proteins observed in mammalian cells at different stages of development and, first of all, in early embryogenesis have been discussed in the literature. Is early embryogenesis the stage of development when the organism is more susceptible to the activity of retrotransposons, or does LINE-1 play some positive role in early embryonic development? This review is aimed at classifying the available data on the epigenetic regulation and the role of LINE-1 retrotransposon in embryogenesis of mammals. The link between the mechanisms of regulation of LINE-1 expression and the waves of epigenetic reprogramming is tracked in germ cells, during fertilization, and in blastocyst, as well as during the differentiation of embryonic and extraembryonic tissues.

Keywords: LINE-1, DNA methylation, retrotransposon, embryogenesis, epigenetic regulation, epigenetic reprogramming of the genome

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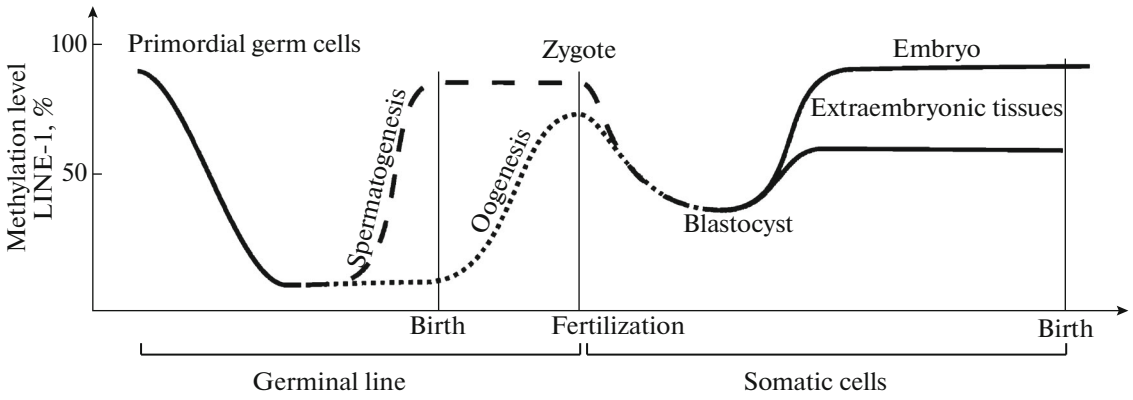
INTRODUCTION

About half of the mammalian genome is occupied by repetitive sequences, among which retrotransposons are well represented. The family of LINE-1 retrotransposons (long interspersed nuclear element 1) occupies about 20% of the human genome [1]. Traditionally, retrotransposons have been considered to be useless elements and, in some cases, because of their capability of recombination and induction of insertional mutagenesis, harmful parasitic elements that can cause hereditary diseases in humans and animals [2–4]. Recently, the noticeable role of LINE-1 in the regulation of the global profile of gene expression in eukaryotes [5–7], as well as in such fundamental morphogenetic processes as early embryogenesis, development, and differentiation [8], and in the formation of extensive structural variations of the genome during evolution [9, 10] has been shown.

Participation of LINE-1 in these processes is possible because of the unique and diverse functions of retroelements. Firstly, at the DNA sequence level, the retrotransposons can act as alternative strong promoters and participate in promotion of monoallelic expression of individual genes and X-chromosome inactivation in females; secondly, at the level of RNA transcripts, they may be involved in the activation of the embryonic genome, X chromosome inactivation, and maintaining of the pluripotent state of the cells; and, finally, the retrotransposons proteins may contribute to the displacement of transcriptional profiles owing to the action of the reverse transcriptase and maintain the stability of telomeres [11]. These properties play an important role in the development of an individual organism. Taking into consideration that the mechanisms of regulation of LINE-1 expression are epigenetic in nature, they are closely associated with the waves of epigenetic reprogramming of the genome in germ cells, during fertilization, and in blastocyst, as well as during the establishment of a differentiated state of embryonic and extraembryonic tissues [12] (figure). Therefore, variations in these processes can cause significant disruption of normal expression of mobile elements at each stage of development. On the other hand, aberrant epigenetic modifications of LINE-1 often indicate the global epigenetic abnormalities in the genome. This review is devoted to the still few data on the role of the LINE-1 retrotransposon in embryogenesis and the consequences of its epigenetic deregulation.



Variation of LINE-1 methylation level against the waves of epigenetic reprogramming in ontogenesis of mammals (from [12]).

LINE-1 MOLECULAR STRUCTURE

In sequenced genomes of the human, mouse, and rat, about 500000 copies of LINE-1 repeats have been found, but the overwhelming number of them are inactive owing to numerous structural rearrangements. LINE-1 consists of 5'- and 3'-untranslated regions, two open reading frames (ORF1 and ORF2), and poly(A) tract. Promoter sequences, which are located in the 5'-untranslated region, are responsible for the transcriptional activity of retrotransposons. LINE-1 sense RNA is a matrix to LINE-1 DNA synthesis and at the same time it encodes ORF1p and ORF2p proteins [13, 14]. ORF1p is able to form multimeric complexes, to bind single-stranded RNA, and to participate in the exchange of the strand during reverse transcription of LINE-1 element [15–17]. The ORF2p protein has an endonuclease and reverse transcriptase activity [18, 19].

One of the main mechanisms of regulation of LINE-1 retrotransposon expression is DNA methylation. Promoter regions of retrotransposon contain a large number of CpG sites, which are usually characterized by high levels of methylation in both mice and humans. Elevated expression of mobile element is accompanied by partial demethylation of LINE-1 promoters in the 5'-UTR region. Methylation of cytosine in vitro at CG dinucleotides of the promoter regions of LINE-1 elements reduces their expression by over 70%. In addition, LINE-1 expression is controlled by small noncoding RNAs—piRNA, microRNA, and small interfering RNA; and small RNAs operate primarily in gametogenesis and immediately after fertilization, when the genome undergoes global epigenetic reprogramming [8].

EPIGENETIC REGULATION OF LINE-1 IN GERM CELLS

Expression of LINE-1 and its regulation are different in male and female germ cells of mammals. During the epigenetic reprogramming of the genome in the male primordial germ cells, when the genome is almost demethylated, the transcription of LINE-1 is controlled by piRNA, which, on one hand, suppress the transcriptional activity and, on the other hand, determine methylation of LINE-1 promoter [20, 21].

In oogenesis, in contrast to spermatogenesis, piRNA are unlikely to be involved in the control of expression of retrotransposons, since loss of PIWI proteins does not lead to the increase in retrotransposon expression. Perhaps, in this case, the role of regulatory elements is played by some other small RNA—microRNA and small interfering RNA. A similar situation exists in the blastocyst and in embryonic stem cells, where there is an increase in the level of expression of small RNAs of different types, including noncoding RNA, originating from LINE-1 transcripts [8].

Regulation of the expression of LINE-1 by DNA methylation is also different in male and female germ cells. Thus, LINE-1 promoter is hypermethylated in mature spermatozoa, whereas in primary oocytes it is hypomethylated at the diplotene stage, and secondary oocytes at the ovulation stage have a medium index of LINE-1 promoter methylation [22] (figure).

Almost nothing is known about LINE-1 functions in germ cells, but it is clear that its expression should be maintained at a certain level, as the increased activity of LINE-1 is associated with a variety of abnormalities in the gametes (table). For example, it was shown that ORF1p overexpression in mouse oocytes leads to an arrest at the stage of the first meiotic division and is accompanied by disorders of the chromosome alignment at the cell equator and defects of spindle organization [23, 24], resulting in preferential elimination of oocytes overexpressing ORF1p before birth [23]. It is known that the abnormal piRNA functioning in spermatogenesis in mice germline cells leads to the release from the repression of various families of transposons and is associated with sterility [25]. In men with impaired sperm production, the hypermethylation of genes associated with piRNA processing was found, leading, in particular, to a decrease in methylation lev-

Supposed LINE-1 functions and the consequences of the decrease and increase in its expression at different stages of ontogenesis

Stage of development	Possible LINE-1 functions	Consequences of the increase in methylation/decrease in expression	Consequences of the decrease in methylation/increase in expression
Oogenesis	?	Arrest of division at the stage of germinal vesicle, DNA lesions, and chromatin conformation abnormalities [24]	Meiosis arrest and spindle defects [23, 24]
Spermatogenesis	?	Reduced sperm motility [29] and low sperm quality [30]	Abnormal sperm production and sterility [25, 26]
Zygote and cleavage	Embryonic genome activation [32, 41], heterochromatin formation [46, 47], and telomere stabilization?	Division arrest and abnormal gene expression [41, 42]	?
Embryogenesis placenta	Placenta functioning?	Spontaneous abortion?	Mosaicism origin?

els of LINE-1 [26]. Increasing retrotransposon expression can lead to DNA double strand breaks [27]. So, the abnormalities appearing owing to retrotransposon activation indicate a danger to a cell of the removal of repression of these sequences and are in good agreement with the traditional consideration of LINE-1 as "dangerous passenger" in the genome.

Considering the possible functions of LINE-1, data on the necessity of LINE-1 expression in germ cells seem more interesting. In mouse oocytes, the ORF1p protein is present at the early stages of gametogenesis both in the cytoplasm and in the nucleus [24], and the suppression of its synthesis leads to the arrest of oocytes at the germinal vesicle stage and also to the suppression of expression of cyclin B1 and cyclin-dependent kinase CDC2, necessary for the initiation of division. In addition, when the lack of ORF1p is induced, DNA lesions and chromatin conformation abnormalities occur [24]. Recently, the presence of reverse transcriptase encoded by LINE-1 was observed near sperm acrosome [28]. Its presence in the sperm indicates the need for reverse transcription either in the sperm or immediately after fertilization, when the embryo genome is not yet active. Lowering of the reverse transcriptase expression in spermatozoa has not been associated with abnormalities in germ cells directly; however, LINE-1 hypermethylation has been associated with reduced sperm motility [29] and low sperm quality from donors [30], indicating the need for expression of LINE-1 not only after fertilization but also to ensure the sperm functioning.

EXPRESSION AND FUNCTIONS OF LINE-1 IN EARLY EMBRYOGENESIS

In mouse embryos, LINE-1 is highly expressed at the first cleavage stage, constituting 13% of the total cDNA pool in the cell [31–33]. In turn, the increased reverse transcriptase activity of LINE-1 in a murine zygote and at the first cleavage stage is accompanied by the increase in the number of copies of the retrotransposon itself independently of nuclear DNA replication. Moreover, LINE-1 amplification is observed in both pronuclei immediately after fertilization, which indicates, firstly, the presence of LINE-1 RNA in both oocytes and spermatozoa and, secondly, the need for reverse transcriptase activity even in the zygote [28]. Interestingly, the reverse transcription is performed, apparently, by LINE-1 reverse transcriptase, located near the acrosome of sperm [28].

High transcriptional activity of LINE-1 at the cleavage stage is confirmed by a rapid decline of its methylation during reprogramming of the embryonic genome in the zygote and cleavage stage (figure). So, during the paternal genome demethylation in the mouse zygote, the methylation index of LINE-1 retrotransposons decreases the most significantly (by 18%) (in particular, L1Md_T and L1Md_Gf families) compared with other classes of transposons. Further, during the first cleavage of the zygote, the index of LINE-1 methylation continues to decline owing to the passive loss of DNA methylation, reaching a minimum by the blastocyst stage [22]. Taking into consideration the global genome demethylation during reprogramming, the expression of LINE-1 in this period is regulated, apparently, owing to the RNA interference mechanism using short noncoding LINE-1 RNA [34].

Activation of the mobile element expression can be a side effect of genome hypomethylation during the global epigenetic reprogramming that occurs in this period of development of the organism. As a result of such activation, LINE-1 retrotransposition may occur in mammalian germ cells and at the early stages of embryo development prior to the germ line compartmentalization [35–40]. On the other hand, the increased expression of LINE-1 may be of nonrandom nature and be linked to the specific functions of LINE-1 in early embryonic development.

The potential role of LINE-1 in early embryogenesis of mammals can be implemented at the level of DNA sequence, expressed transcripts, and proteins synthesized on their basis. The most important event taking place at the cleavage stage is the activation of the embryonic genome (table). It is assumed that retroelements are able to play the role of "alternative" strong promoters that provide stable expression of genes of the embryonic genome at the early stages of blastomere cleavage when there is total epigenetic reprogramming. This is confirmed by the fact that the suppression of the activity of one of the LINE-1 families led to abnormalities of the first divisions of the embryo at the cleavage stage [41, 42]. At the same time, the inhibition of LINE-1 expression in the zygote and blastocysts induced the reduction or complete termination of expression of certain genes necessary for the division of normal blastocyst, including the *TP53* gene, whereas two genes (*HSP70.1* and *CCND1*), whose transcription is normally decreased at these stages of development, began to be actively expressed [41]. A similar effect was also observed when the activity of reverse transcriptases was blocked by chemical agents in mouse cells and transformed human cell cultures; i.e., the reduction of reverse transcriptase activity led to the disruption of cell division [43, 44]. Furthermore, it is possible that LINE-1 promotes an open chromatin configuration at the early stages of embryo development to ensure the processes of epigenetic reprogramming and activation of embryonic genome [45].

The role of LINE-1 in the regulation of embryonic genome expression may also be associated with the induction of heterochromatin formation (table). For example, it is suggested that LINE-1 participates in the X-chromosome inactivation in female mammals [46, 47]. In the mouse, rat, and human, the X chromosome contains approximately 2 times more copies of LINE-1 compared with other chromosomes [48, 49]. In addition, on the X chromosome of eutherians, LINE-1 are relatively uniformly distributed, and their proportion is reduced only in the areas that contain genes that avoid inactivation [50, 51]. Interestingly, complete and evolutionarily younger elements are largely represented on the X chromosome [52]. The relationship between the LINE-1 and its function for transcription suppression also follows from evolutionary reasons, because the evolutionary period, when the increase in the number of copies of LINE-1 on the X chromosome occurred, coincides with the origin of random inactivation of the X chromosome in eutherians [51]. Known enrichment with complete copies of LINE-1 near genes with random monoallelic expression also supports the idea that they can play a role in the inactivation of one of the copies of a gene or even the whole chromosome [53]. In addition, a role of LINE-1 in imprinting was suggested [54]; however, the experimental proof of this hypothesis has not been obtained.

LINE-1 participation in the induction of heterochromatin formation is, presumably, realized through RNA-dependent mechanisms. It was found that LINE-1 together with Xist RNA participates in X-chromosome heterochromatinization [55]. It is known that LINE-1 transcripts can serve as substrates for small interfering RNA. This process is observed during the differentiation of embryonic stem cells, when evolutionarily young LINE-1 elements are transcribed in the regions of the inactive X chromosome, which are not exposed to the inactivation, and induces a local heterochromatinization following the RNA interference mechanism [55]. Large-scale changes in chromatin conformation, ranging from the establishment of the so-called "open" configuration in blastomeres and to the selective suppression of the expression of single genes during differentiation, may explain the presence of LINE-1 RNA in the cells in these periods of development of the organism.

An important factor for maintaining pluripotency of embryonic stem cells is the ensuring of telomerase activity. Interestingly, the expression of LINE-1 in tumor cells appears to be responsible for the maintenance of telomerase activity and telomere stability [11]. This is achieved by the LINE-1 regulation of the expression of the c-Myc and KLF-4 transcription factors, activating the expression of telomerase. c-Myc and KLF-4 also activate the expression of LINE-1, indicating the regulation with feedback mechanism [11]. Possibly, as in tumor cells, the expression of LINE-1 at early stages of development is responsible for the maintenance of the pluripotency of embryonic stem cells and its disruption can lead to anomalies of differentiation of embryonic tissues.

EPIGENETIC STATUS AND ROLE OF LINE-1 IN PLACENTA

During the preimplantation development of the embryo, the LINE-1 methylation index gradually decreases to the lowest level at the late blastocyst stage (figure). Then *de novo* methylation occurs, and in most epiblast derivatives, including the cells of the embryo, LINE-1 is hypermethylated, whereas in the cytotrophoblast and in certain derivatives of epiblast, further belonging to the placental tissues, it remains less methylated [56]. According to our results and the literature [57, 58], placental tissues at the first trimes-

ter of pregnancy are characterized by a reduced methylation index of this element in comparison with somatic tissues of the adult organism, for example, with peripheral blood lymphocytes (50% in placenta and 80% in lymphocytes). Moreover, there is a decrease of the level of LINE-1 methylation in placental tissues during fetal development, resulting in the increase of its expression [59].

Probably, the LINE-1 activity is required for normal development of the placenta, but so far studies have not been performed to assess the activity of retrotransposon in placental tissues (table). It is known that genes of retroviral origin play a key role in the differentiation of human placental trophoblast. The balance of the expression of two genes of endogenous human retrovirus—syncytin [60] and suppressin [61]—defines the way of differentiation of cells from trophoblast to syncytiotrophoblast, characterized by the formation of syncytium from cells with fused cytoplasm, or invasive trophoblast migrating in decidua of the uterus. It is possible that the proteins encoded by LINE-1 may also be involved in ensuring the functioning of the placenta.

Normal functioning of the extraembryonic tissues is a prerequisite for nutrition and development of the fetus. Therefore, the excessive activation of LINE-1 in the extraembryonic tissues associated with the occurrence of double-strand DNA breaks and insertional mutagenesis could potentially be the cause of abnormal embryo development and lead to abortion. Indeed, we found a decreased level of methylation of LINE-1 in placental tissues of first trimester spontaneous abortions with normal karyotype compared with normally developing embryos [58]. Interestingly, earlier in the tissues of spontaneous abortions with normal karyotype, decreased activity of DNMT1, which is the DNA methyltransferase maintaining the methylation pattern, was observed, which could lead to both LINE-1 hypomethylation and spontaneous abortion [62].

Hypermethylation of LINE-1 also can potentially be associated with impaired fetal development, but, apparently, it does not lead to pregnancy loss itself, since it does not occur among spontaneous abortions with normal karyotype [58]. However, hypermethylation of LINE-1 is observed in the cytotrophoblast with karyotype anomalies. So, in the case of partial molar pregnancy, which is caused by the fertilization of an egg by two sperms and the resulting triploidy, the LINE-1 retrotransposon is hypermethylated in trophoblast cells [63]. In addition, the level of LINE-1 methylation is increased in cytotrophoblast of spontaneous abortions with mosaic aneuploidy in contrast to pure aneuploidy [58]. However, it is unlikely that the abnormal expression of LINE-1 in the tissues with abnormal karyotype is a determining factor in the mechanisms that lead to fetal death. The increase in the methylation index of mobile element in the cytotrophoblast of embryos with aneuploid karyotype likely reflects more global epigenetic abnormalities at the genomic level and is in agreement with previous studies of increased portion of methylated CpG sites of promoter regions of genes in the same tissue with trisomy 16 [64, 65].

CONCLUSIONS

The methylation index of LINE-1 retrotransposon is often used as an indicator of the level of global methylation of the genome, including also the embryogenesis impairment [58], while the role of retrotransposons from this family in mammalian development is poorly understood. Almost nothing is known about the role of retrotransposon in gametogenesis, except that the products of its expression are detected in sperm and oocytes. Probably reverse transcriptase activity is required to start the embryonic genome functioning. Clearly, these elements owing to their functions are involved in the formation of chromatin structure and are necessary for the expression of genes controlling blastocyst cleavage. In addition, a high level of transcription of LINE-1 in the zygote and blastocyst indicates the essential role of retrotransposon in maintaining the pluripotent state of cells. The high concentration of LINE-1 in DNA regions with monoallelic expression in differentiated cells also indicates that this element in *cis*-position affects the inactivation of the X chromosome. The role of this mobile element in the placental tissues is poorly investigated. Although they are fully differentiated structures, LINE-1 promoter regions have a low level of methylation compared to somatic tissues at the same stage of development, potentially indicating the higher transcriptional level of retrotransposon in provisory embryonic tissues.

Undoubtedly, the errors in the process of global epigenetic reprogramming in germ cells and later in the zygote primarily affect such widely represented sequences in the genome as LINE-1. Despite the fact that DNA methylation is not the main mechanism of the control of retrotransposon expression in primordial germ cells, the impairment of the global demethylation of the genome and the subsequent *de novo* methylation of more mature gametes during the first wave of reprogramming, apparently, reflect the level of LINE-1 expression. The consequences of errors during the second wave of reprogramming after fertilization are even more dramatic, since, on one hand, LINE-1 activity is essential for the cleavage process and, on the other hand, retrotransposon overexpression leads to genetic instability.

Despite the small number of studies, it is clear that the significance of LINE-1 for embryogenesis is not limited to the negative effects of the removal of its epigenetic repression. On the contrary, this retrotransposon has a number of functions in mammalian

embryogenesis required at different stages of development.

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