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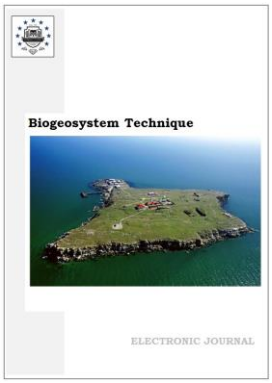

Articles

Interphase Nucleus and Transposable Elements (Review)

Tatiana T. Glazko [a], Galina V. Glazko [b], Gleb Yu. Kosovsky [a], Boris L. Zybaylov [b, *], Valery I. Glazko [a]

[a] FSBSI V.A. Afanasyev RI for Fur and Rabbit Farming, Moscow, Russian Federation
[b] University of Arkansas for Medical Sciences, Little Rock, AR, USA

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Abstract

How the nuclear architectonic is influencing gene expression programs is a fast developing area of research. In this review we track the accumulated data about interphase nucleus architectonic and how it is changing in various cellular populations of eukaryotes. We also discuss in details how major structural components of chromosomes – centromeres and telomeres – are organized. They consist of tandem repeats and transposons, closely related with each other. Mobile genetic elements play a key role in creating ectopic chromosomal contacts and laminal attachments of genomic elements. We note that retrotransposons autonomous long repeats LINE and non-autonomous short repeats SINE are localized differently over chromosomes. LINEs are preferably located in heterochromatin while SINEs are associated with euchromatin. They are involved in nuclear architectonic dynamic while gene expression programs are changing. We also consider the data about retrotransposons' high evolutionary rate and their involvement into decreasing reproduction of inter-species hybrids. The relationship between genomic 'resistance' toward retrotransposition and the success insertion rate of several viruses is also discussed. The relationship between the variability of retrotranspositions, morphogenesis and speciation, as well as resistance to natural selection is a big question in contemporary medicine and biology given recent pandemic.

Keywords: Interphase nucleus, architectonic, hetero- and euchromatine, lamina, transposons, gene expression programs.

1. Introduction

Answering questions about the mechanisms of gene expression regulation, in particular epigenomics, is a top priority for contemporary biology. One of the most enigmatic questions is: what are the control mechanisms behind activation and termination of gene expression programs in different tissues and organs of multicellular organisms? While active studies of specific

* Corresponding author
E-mail addresses: blzybaylov@uams.edu (B.L. Zybaylov)

regulatory mechanisms, such as differential DNA and histone methylation, microRNA regulatory networks, are ongoing, the system regulation of gene expression programs remains poorly understood. The importance of understanding these mechanisms was obvious for a while already. Just to mention that aneuploidy – the balance change between chromosome dosages – leads to deep developmental damages, for example, trisomy of 13, 18 and 21 chromosomes result in Patau, Edwards and Down syndromes, respectively while, haploid chromosomal dosage preserves its ontogenetic potential (Li et al., 2014; Cui et al., 2020). Rapidly accumulating data suggests that system regulation of gene expression programs interaction and functioning is being affected via interphase nucleus architectonic.

2. Methods

Currently, the main and widely used methods of studying the architectonics of the interphase nuclei are Hi-C method and sites of chromatin interaction analysis by paired-end tag sequencing, that measure the 3D proximity of pairs of DNA loci by cross-linking, ligating, and sequencing the DNA. Using such methods, researchers have reconstructed the 3D conformation of chromatin in vivo in a wide variety of species in different cell types.

3. Discussion

Besides individual chromosomal territories interphase nucleus contains several other domains, some of them concentrating around nuclear periphery and some around the nucleolus, both in heterochromatin state, while others are located inside the nucleus and in euchromatine state (Figure 1).

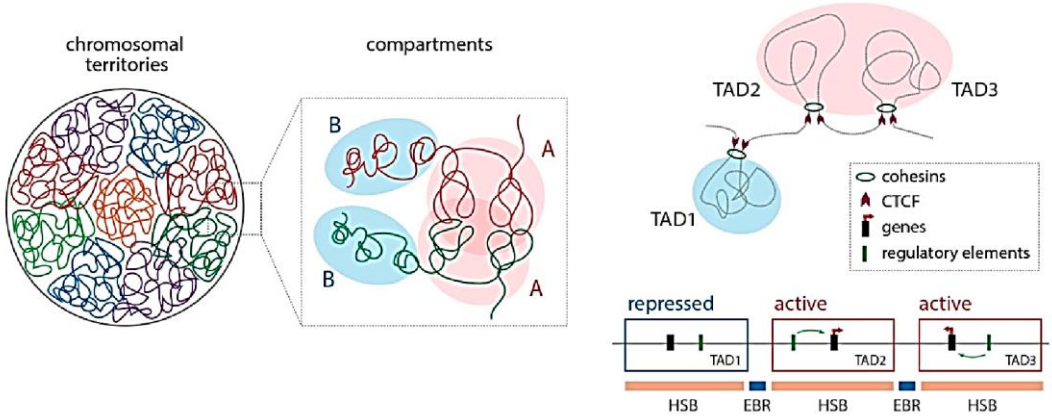


Fig. 1. Genomes are compartmentalized into different levels of organization, including: (i) chromosomal territories, (ii) 'open' (termed 'A')/'closed' (termed 'B') compartments inside chromosomal territories, (iii) topologically associated domains (TADs) and (iv) looping interactions (Deakin et al., 2019)

TADs, which are delimited by insulating factors such as CTCF and cohesins, harbor looping topologies that permit long-range interactions between target genes and their distal enhancers, thus providing 'regulatory neighborhoods' within homologous syntenic blocks (HSBs). In this context, the integrative breakage model proposes that genomic regions involved in evolutionary reshuffling (evolutionary breakpoint regions, EBRs) that will be likely fixed within populations are (i) those that contain open chromatin DNA configurations and epigenetic features that could promote DNA accessibility and therefore genomic instability, and (ii) that do not interfere with essential genes and/or gene expression (Deakin et al., 2019).

Spatial positioning is a fundamental principle governing many processes in the nucleus. Chromatin is hierarchically organized, from nucleosomes to chromatin domains (CDs), or topologically associated domains (TADs), to higher-order compartments, the apex of which is chromosome territories (CT) (Figure 2).

Accumulating evidence suggests that chromatin organization is a critical factor in regulating gene expression. For example, enhancers interact with their target genes almost exclusively within the TAD, distally co-expressed genes are recruited into shared protein aggregates upon activation, and compact domains exhibit dynamic movement and configurational changes *in vivo*.

Nonrandom radial positioning of CTs in the nucleus suggest that there are preferential interaction patterns between chromosomal territories. These specific inter-chromosomal network patterns are changing during the cell cycle, cell differentiation as well as neoplastic transformation. The dynamics of these networks supposedly correlates with the global level of genome regulation. The proximity of certain chromosomal regions in cells (related to their genes co-expression), probably can explain the tendency for different translocations in pathologies.

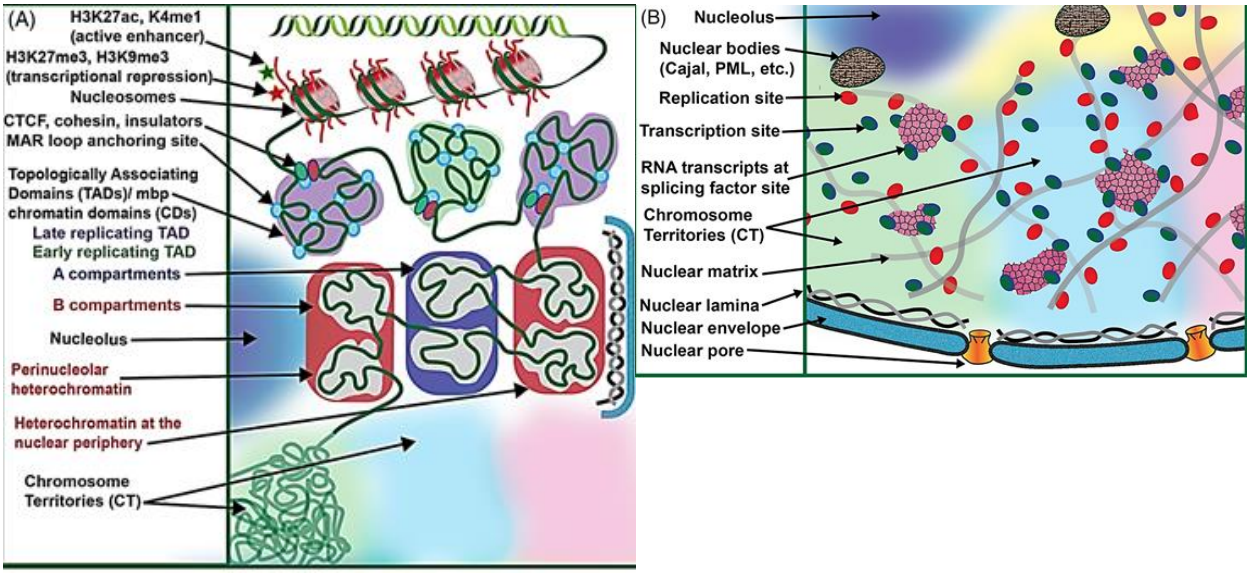


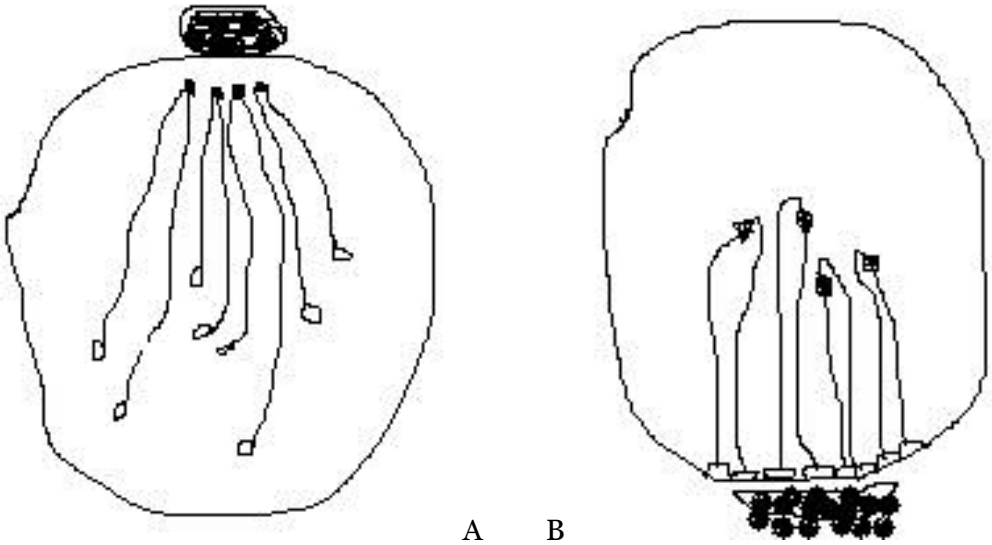
Fig. 2. Higher order chromatin organization and functioning nuclear architecture. A. Shows the hierarchical levels of chromatin organization, including: nucleosomes, chromatin fibers, chromatin loops, CD – chromatin domains, topologically associated domains (TADs), compartments A and B and chromosomal territories (CT). B. Functional nuclear architectonics. Replication sites and nuclear accumulations of proteins are associated with the nuclear matrix. Transcription sites are associated with nuclear matrix or nuclear protein assemblies. Other nuclear bodies and structural elements of the nucleus are shown, such as the nuclear envelope, nuclear lamina, nuclear pore complex and nucleolus (Fritz et al., 2019)

Replication sites and nuclear accumulations of proteins are associated with the nuclear matrix. Transcription sites are associated with nuclear matrix or nuclear protein assemblies. Other nuclear bodies and structural elements of the nucleus are shown, such as the nuclear envelope, nuclear lamina, nuclear pore complex and nucleolus (Fritz et al., 2019).

Genomic regions, involved in evolutionary breakpoint regions (EBRs) are mostly divided into: (1) those, containing 'open' chromatin that allows easy DNA access for regulating genomic instabilities and (2) those, that do not interfere with gene expression and/or interactions (Deakin et al., 2019). Thus, it is imperative to understand underlying principles of the formation of these different genomic regions.

The most obvious eukaryotic chromosomal regions are telomeres and centromeres, playing the central role in interphase nucleus architectonic as well as meiosis and mitosis (Figure 3).

Telomeres consist of highly conserved microsatellite – a thousand-fold tandem repeat – hexanucleotide TTAGGG, which interacts with a number of proteins, protecting telomeres from damages and "illegitimate" fusion with other telomeres. These proteins are part of the shelterin protein complex, which facilitates the formation of a lasso-like structure to protect the open ends of telomeric DNA from damage (Shay, 2018). The protein complex consists of six shelterin members (Figures 4, 5) and includes TRF1 (telomeric repeat binding factor 1), which binds to the canonical TTAGGG double-stranded telomeric repeat and interacts with TIN2 (TRF1-interaction nuclear factor 2). Another shelterin protein is TRF2, which also binds double-stranded telomeric repeats and interacts with RAP1 (repressor/activator protein 1). POT1 (protection of telomeres 1) binds to TTAGGG single-stranded repeats and binds to TRF1 and TRF2 through a binding partner, TPP1, which also binds to TIN2.



A B

Fig. 3. A – Telophase of mitosis with a restored nuclear envelope, centromeres (stained areas of chromosomes) accumulate towards the centrosome (accumulation of stained fragments on the nuclear envelope). B – Prophase I of meiosis, telomeres (unstained areas of chromosomes) accumulate on the nuclear envelope towards the centrosome (accumulation of colored fragments on the nuclear envelope).

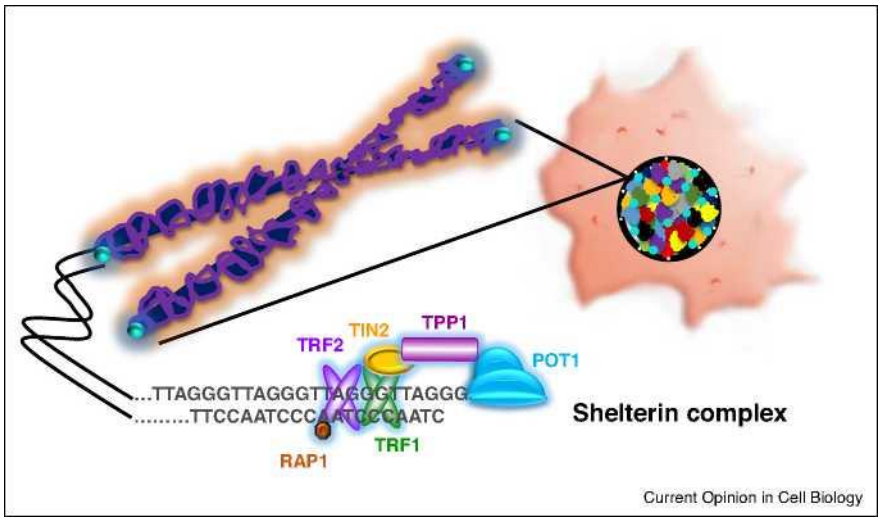


Fig. 4. Telomeres are repetitive DNA sequences at the ends of linear chromosomes (Shay, 2018)

Telomeres are key elements of nuclear architectonics, determining the positioning of chromosomes in nuclear space and often associated with the nuclear envelope, and also protect the linear ends of chromosomes from DNA damage. The end of telomeric DNA consists of a single strand of G-rich DNA sequence forming a lasso-like structure, and this strand invades TTAGGG repeats to form a T-loop. In total, telomere ends make up only ~ 1/6000 of the total genomic DNA in a cell. Telomeres are gradually shortened with each cell division in the absence of a mechanism for maintaining telomeres, which ultimately leads to proliferation end. Loss of telomere protection can lead to a telomere damage, which can be overcome by the activation of telomerase (reverse transcriptase), which increases telomere repeats (Shay, 2018).

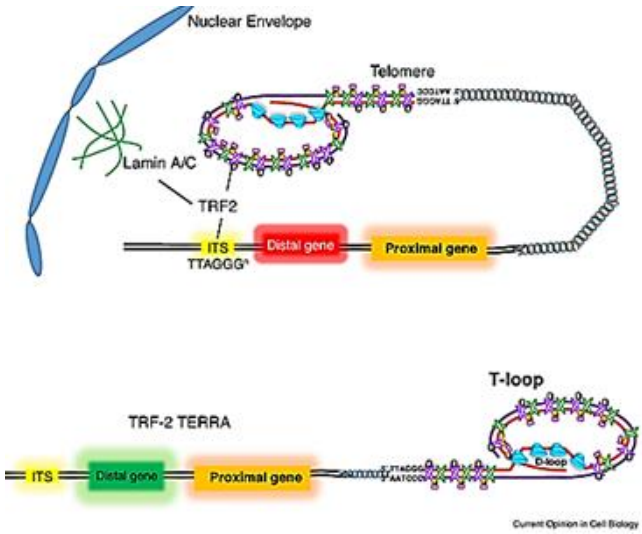


Fig. 5. Model of interactions between telomere and a distant gene (Shay, 2018)

When cells have long telomeres, the 3D chromosomal loop positions the distal gene close to the telomere through interactions with interstitial telomere sequences (ITS), facilitated by shelterin proteins (such as TRF2) and proteins that are associated with the inner nuclear envelope (lamin A/C) ... The 3D telomere loop changes the chromatin structure near the distal gene, which leads to a change in gene expression. When cells have short telomeres, these associations are lost and distal gene expression is altered. There is also support for telomere repeat RNA (TERRA), which is a long non-coding RNA transcribed on telomere repeats that increases in cells with short telomeres, and TERRA can sequester TRF2 from a gene regulated by the length of the distal telomere (Shay, 2018).

Telomeres play an essential role in the architectonics of the interphase nucleus (Figure 6).

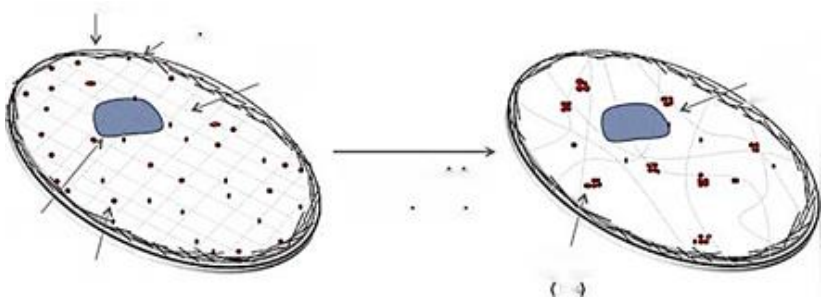


Fig. 6. Distribution of telomeres in the interphase nucleus (Novo, Londono-Vallejo, 2013)

In normal cells (left), telomeres are scattered throughout the nucleus, with some telomeres showing preferential associations with the nuclear periphery or nucleolus. During oncogenic transformation, aging, or deregulation of lamins (proteins of the lamina underlying the inner membrane of the nuclear envelope), the distribution of telomeres changes, either increasing their connection with each other (telomere aggregates) or with the nuclear envelope (Novo, Londono-Vallejo, 2013).

Progeria – premature ging – is an example of a violation of the contacts of telomeres with progerin – lamine A. Mutated protein leads to an accelerated shortening of telomeres and premature aging (Rahman et al., 2021).

Even without mutations in lamina proteins there is a progressive shortening of telomeres with increasing age, which is associated with shifts in gene expression through changes such as the telomere position effect (TPE), suggesting a decrease in telomere interference with the transcriptional activity of more distant genes (Figure 7). Changes in telomeres positioning, because of shortening, affect the expression of a number of genes, so called telomere long distance effects

(TPE-OLD). This is why some genes far away from telomere (1-10 megabases, MB) are still affected by TPE, but genes closer to the telomere are not (Figure 7). With aging, shortening of telomere lengths lead to a change in the effect of gene expression (Zhang et al., 2021).

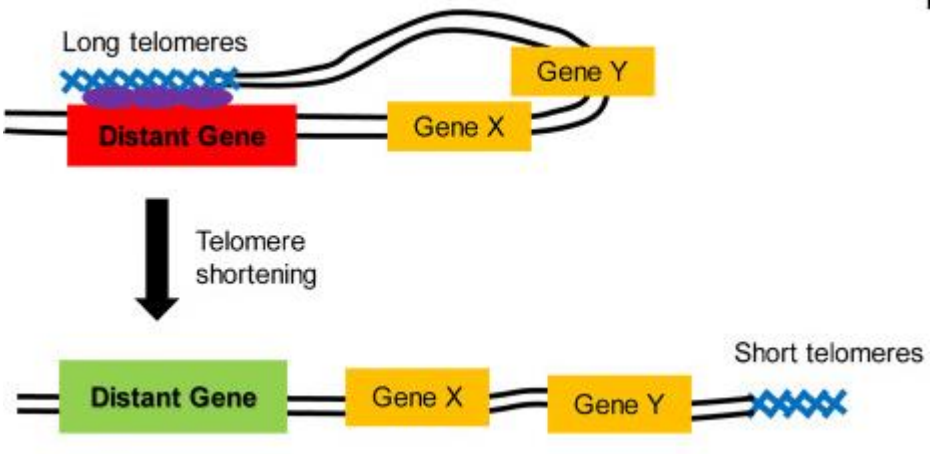


Fig. 7. Schematic of the distant effect of telomeric repeat shortening on gene distant expression (TPE-OLD) (Zhang et al., 2021)

Long telomeres can form a loop and interact with target genes that are far away. Red indicates inhibition of gene expression, green indicates an activated state. Other genes (yellow) in between are not affected. The distant interaction of the telomere and the gene can be mediated by the shelterin protein complex (purple) and weaken as the telomeres are shortened. Old cells, as a rule, have a smaller average telomere length (Zhang et al., 2021).

It should be noted that the telomerase, controlling the growth of telomeric repeats, is a specialized RNA-dependent DNA polymerase (reverse transcriptase). It means that telomeric repeats are evolutionary related with exogenous retroviruses, precursors of endogenous retrotransposons. The fact that telomeric repeats in Drosophila are represented by specific endogenous retroviruses further confirms this observation (Cacchione et al., 2020).

Centromeric regions of eukaryotic chromosomes contain another morphological element directly involved in the dynamics of the interphase nucleus architectonics (Liu et al., 2021; Bloom, Costanzo, 2017). In interphase nuclei centromeres form chromocenters, sometimes with tissue-specific dynamics. The small number of chromocenters is typical for rapidly dividing cells. There are many studies comparing the distributions of centromeres and chromocenters in animal and plant cells (Andrey et al., 2010). In one study, rabbit embryo cells, differentiated rabbit mammary gland epithelium cells during lactation, as well as differentiated cells of *Arabidopsis thaliana* were considered. The genomes of these species are significantly different. Rabbit genome has 44 chromosomes, while *A. thaliana* has only 10. Rabbit's genome size is 2.77 gigabases, while *A. thaliana* is 125 megabases. In *A. thaliana* differentiated cells, centromeres are grouped into chromocenters that are regularly distributed inside the nucleus. In rabbit's differentiated cells centromeres are also clustering more frequently as compared to embryonic cells. In the first prophase of meiosis, in wheat and mice, violations of the conjugation of homologous chromosomes are caused by mutations in orthologous genes. There is a high degree of homology between Ph1 and Cdk2 loci in mammals (Al-Kaff et al., 2008). The Cdk2 locus controls conjugation of homologs during meiosis in mice (Viera et al., 2009). Cdk2 is involved in initiating the onset of centrosome duplication (Schatten, 2008). Cdk2 is a part of the telomeric protein complex and prevents the fusion of sister chromatid telomeres (Konishi, de Lange, 2008).

The nucleotide sequence of centromeric regions is variable and consists of highly repeated tandem and dispersed repeats – minisatellites and mobile genetic elements (Balzano, Giunta, 2020). Thus, the eukaryotic genome, formed by linear chromosomes, is not only a symbiosis with archaeal and prokaryotic genomes, but also with mobile genetic elements that are presented, for example by retroelements, organizing telomeric and centromeric regions (Figure 8).

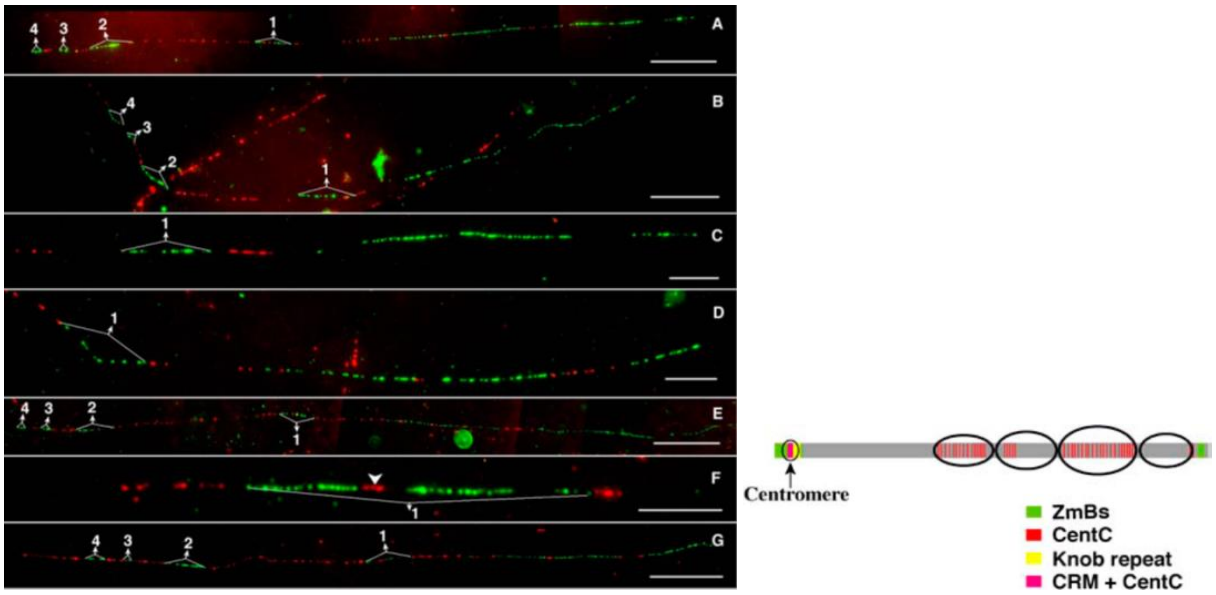


Fig. 8. The distribution of CentC repeats, retrotransposons CRM and ZmB in centromeric region of corn's chromosomes (Liu et al., 2020)

In several studies it was suggested that centromeres were derived from telomeres and the proof of concept was also provided (Villasante et al., 2007).

Thus, the formation of telomeres and centromeres, the two key elements of the interphase nucleus architectonics, is based on tandem repeats and exogenous retroviruses remnants. These genomic elements are closely related (Louzada et al., 2020). Those elements are prone to form secondary DNA structures, e.g. hairpins, quadruplex DNA structures, triplexes. Those structures may interfere with genome duplication, slowing down or even arresting replication fork, resulting in double strand breaks. Homological recombination can repair the breaks, but the presence of satellites and mobile genetic elements may lead to changes in nuclear architectonic and consequently gene expression programs. High recombination frequency between homological sequences of tandem repeats and transposable elements leads to the idea that these elements are an 'engine' promoting genome evolution. Genomic regions with these sequences are considered 'hot spots' for structural chromosome rearrangements, leading to species-specific changes in nuclear architectonic, creating new gene networks and gene expression programs.

Mammalian genomes are enriched with transposable elements (TE) (Percharde et al., 2020). There are not many DNA-transposons (< 3 %) and full-seized endogenous retroviruses (4-10 %), but the frequency of autonomous and non-autonomous retrotransposons is high.

Long interspersed repeated DNA LINE1 is the most successful TE family in terrestrial mammals (Percharde et al., 2020). Typical LINE1 family member is around 6,000 bp long and encode two proteins, ORF1 and ORF2, participating in transpositions. ORF1 is RNA-binding protein, ORF2 combines endonuclease (EN) and reverse transcriptase (RT) activities. Among ca 8868000 human and ca 599 000 mice LINE1 elements only 80-100 human LINE1 and 2300 mouse LINE1 still have transpositional activities in human and mouse genomes, respectively (Percharde et al., 2020).

LINE1 insertion happens mostly via endonuclease-dependent revers transcription. LINE1 RNA associates with several homotrimers of ORF1p and at least one dimer of ORF2p, forming ribonuclear protein RNP LINE1 in cytoplasm. RNP LINE1 then enters the nucleus where endonuclease ORF2p frees 3' hydroxyl group. This free 3' hydroxyl group then serves as a primer for cDNA LINE1 synthesis by reverse transcriptase ORF2p, starting from the polyA tail of mRNA LINE1. Short dispersed genomic element SINE also has polyA tail and it may compete with LINE1 polyA tail for LINE1 ORF2p reverse transcriptase, hijacking LINE1 transposition mechanism. Also LINE1 ORF2p can retrotranspose unique mRNA proteins and small nuclear RNAs (Percharde et al., 2020).

LINE1 retrotranspositions depend on other cellular proteins. There are positive regulators of transpositions, in particular nucleolin and heterogeneous nuclear riboproteins (hnRNPs), mitogen

activated proteinkinases and cyclin-dependent kinases. DNA repair mechanism concludes LINE1 insertion. Mammalian genomes have several mechanisms at transcriptional, post-transcriptional and posttranslational levels, restricting LINE1 transposition. CpG DNA methylation and histone modifications at the LINE1 promoter can limit LINE1 transcription. KRAB-ZFP proteins (zinc finger proteins with DNA interacting motif) specifically recognize ERV and LINE1 and attract KAP1 (heterochromatin protein). Posttranscriptional repression LINE1 RNA occurs through RNA-interference with small RNAs. LINE1 retrotransposition can also be restricted at the posttranslational level with interferon-induced genes (Percharde et al., 2020).

New LINE1 insertions happens approximately 1 in 100 human births and 1 in 8 mouse births. LINE1 interferes with genome homeostasis in many ways, in particular: i) LINE1 activity induces genome insertions; ii) LINE1 activity influence SINE/Alu retrotranspositions, which are also involved in genomic instability; iii) LINE1 ORF2 endonuclease activity may have some mutagenic effects independently on retrotransposition; iv) LINE1 and SINE elements may influence short tandem genome-abundant AT-rich repeat; v) repetitive property LINE1 and SINE elements can induce large-scale genomic rearrangements, such as inversions and duplications. On the average, any two haploid human genomes have approximately one thousand different TE insertions, mostly from LINE1 and Alu families (Percharde et al., 2020).

LINE1 family high frequency in mammalian genomes positions these elements to play a central role in local chromatin organization and, further, higher level chromatin architecture. LINE1 and SINE elements, both depending on LINE1 ORF2 activity for transposition, have very different genomic distribution. LINE1 are frequent in gene poor, AT-rich heterochromatin regions while SINE elements are frequent in gene rich, GC-rich, euchromatin regions. In interphase nucleus there is similar subdivision between compartments: (B) – silence and (A) – expression. It is highly probable that LINE1 and SINE elements not only correlate with B and A compartments, respectively, but also can participate in formation of chromosomal domains in these two compartments. The high association of RNA repetitive sequences, including LINE1 RNA, with chromatin, and evidence that chromatin-bound RNA contributes to the global organization of chromatin, supports this hypothesis.

TEs such as LINE1 and various endogenous retroviruses (ERVs) become globally demethylated and expressed during major epigenetic reprogramming in the germline. This erasure of epigenetic memory occurs naturally *in vivo* in the course of normal embryonic development. Similarly, TE de-repression via H3K9me2 happens in induced pluripotent stem cells. Many TE families have cis-regulatory activity. Gradually it is becoming clear that transcribed TE genes are also important in early development. Transcribed HERVH RNA is important to maintain human embryonic stem cells (ESC) in non-differentiated state, presumably acting as lncRNAs. HERVK encoded protein Rec is highly expressed in human embryos increasing antiviral resistance by increasing IFITM1 proteins regulation. Rec also binds a subset of endogenous RNAs regulating they ribosome coverage and expression the way that can be important for early human development.

Actually, the relationship between many TEs and pathways limiting their mutagenic activity can be considered in terms of the balance between beneficial and negative functions of TE. The involvement of TE expression in the early stages of growth and development, increased genetic and epigenetic variability, thus providing an adaptation mechanism in ever-changing environment, are both beneficial TE functions. However, this metastable state of TEs in some cases results in a disease, if retrotransposition event goes wrong. In other words, potential reactivation of TEs in adult somatic cells and their association with diseases such as cancer may be the price to pay for their role in development and evolution (Percharde et al., 2020).

Many studies confirm that tandem and dispersed repeats are involved in the regulation of changes in gene expression programs through dynamic changes in interphase nucleus architectonics. The most appealing example is the work performed on the interphase nuclei of cylindrical photoreceptor cells of nocturnal mammals, where an inverted pattern of heterochromatin and euchromatin distribution, in comparison with other nuclei, was observed. Heterochromatin was located inside, euchromatin – on the periphery of the nucleus under the lamina (Figure 9) (Falk et al., 2019). The authors of this study came to the conclusion that, in particular, ectopic contacts between homologous dispersed repeats localized in different regions of chromatin can make a significant contribution to such an inverted variant.

Redistributions of hetero- and euchromatin have been described in rabbit embryos starting from the four cells stage (Bonnet-Garnier et al., 2018).

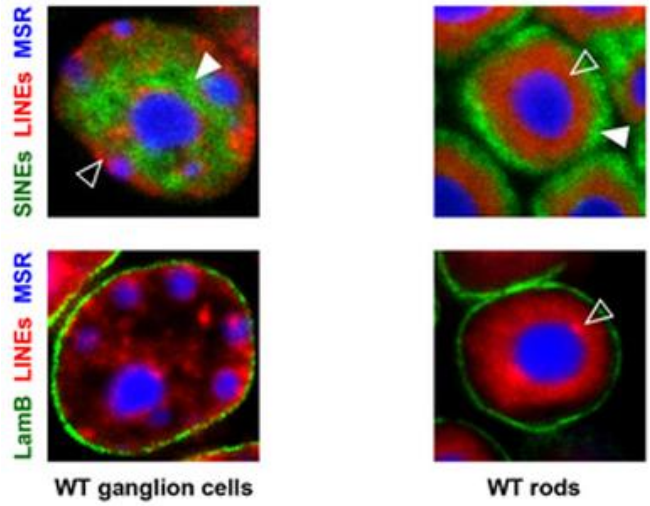


Fig. 9. The distribution of heterochromatin markers LINE (red), euchromatin marker SINE - green and MSR - microsatellite sequences in the nuclei of ganglion cells (left) and cylindrical photoreceptor cells (right) (Falk et al., 2019).

The significant importance of interchromosomal interactions is in a good agreement with our earlier data on two main types of chromatin contacts in the space of the interphase nucleus - with the periphery of the nucleus and between chromosomes (Figure 10).

Fig. 10. Contacts variants of 4 polytene chromosomes in the saliva gland of the *Chironomus thummi* larva after centrifugation (Glazko, Zayniev, 1986)

Chromosomes form long strands attached to the periphery of the nucleus; Tight interchromosomal contacts with each other; a – chromosome 4, bearing the nucleolus, maintaining contact with the periphery of the nucleus (40×12.5) (Glazko, Zayniev, 1986).

It should be noted that DNA copies of exogenous retroviruses – precursors to a certain retrotransposons, as a rule, are localized in the regions of genomes where matrix attachment regions (MAR) are found (Johnson, Levy, 2005; Narwade et al., 2019).

There is a lot of data showing that reproductive barriers can form even between closely related animals, for example, between subspecies of the European rabbit (Carneiro et al., 2014), TE activation during hybridization, leading to reproductivity reduction (Laporte et al., 2019), or genomic rearrangements and the appearance of new species (Auvinet et al., 2018). Now, the importance of these data is as high as ever, because of climate changes, farm animals' transportation to new ecological and geographic regions, as well as genetic erosion of factory breeds. All of the aforementioned factors require an increase in the adaptive potential of animals, that can be achieved by hybridization with closely related wild species (for example, (Cao et al.,

2021)). This is obviously hindered by the high rate of transposons evolution, which is involved in genetic divergence, in particular, of centromeric sequences, contributing to the errors during mitosis and meiosis, and a reduction of hybrid animals' reproduction.

Evolutionary rate of transposons is the best to evaluate using their spectral differences in laboratory strains of mice, created no more than 100 years ago (Nellaker et al., 2012). Transposons-based dendrogram corresponds to the history of genetically defined lines breeding (Figure 11).

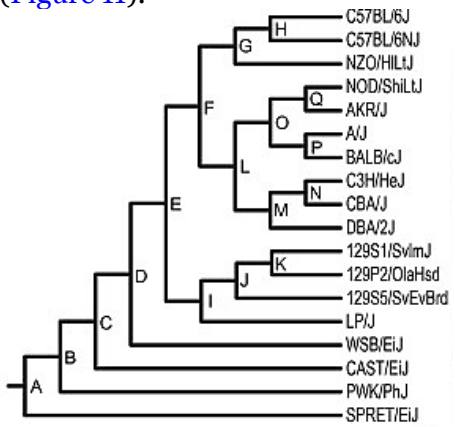


Fig. 11. Dendrogram of genetic relationships between laboratory strains of mice, built on the basis of the presence/absence of homological sites in different retrotransposons (Nellaker et al., 2012)

In our own research, while we were analyzing the metaphase plates of the cell populations from fusion of mouse and mink cells, we found an explanation for the high rate of mink's chhromosome loss in those cell hybridomas. Simply, mink chromosomes were not able to attach to the division spindle (Figure 12).

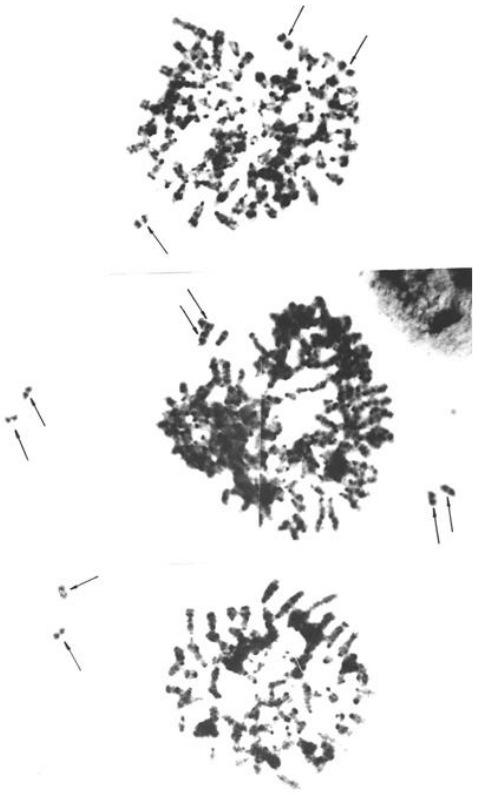


Fig. 12. Metaphase plates of mouse-mink hybridomas. Arrows indicate mink chromosomes located outside the boundaries of the mouse chromosome accumulation (Glazko, 1988)

In early 1980 Michael Bennett had shown, for hybrid plants, that there is a specificity of chromosomal sets interactions with division spindle. Haploid sets in hybrides were clearly separated (Figure 13).

Fig. 13. Metaphase plates of burley and wild rye hybrids. After FISH hybridization 7 barley chromosomes (orange) are surrounded by 7 wild rye chromosomes (yellow) (Leitch et al., 1990)

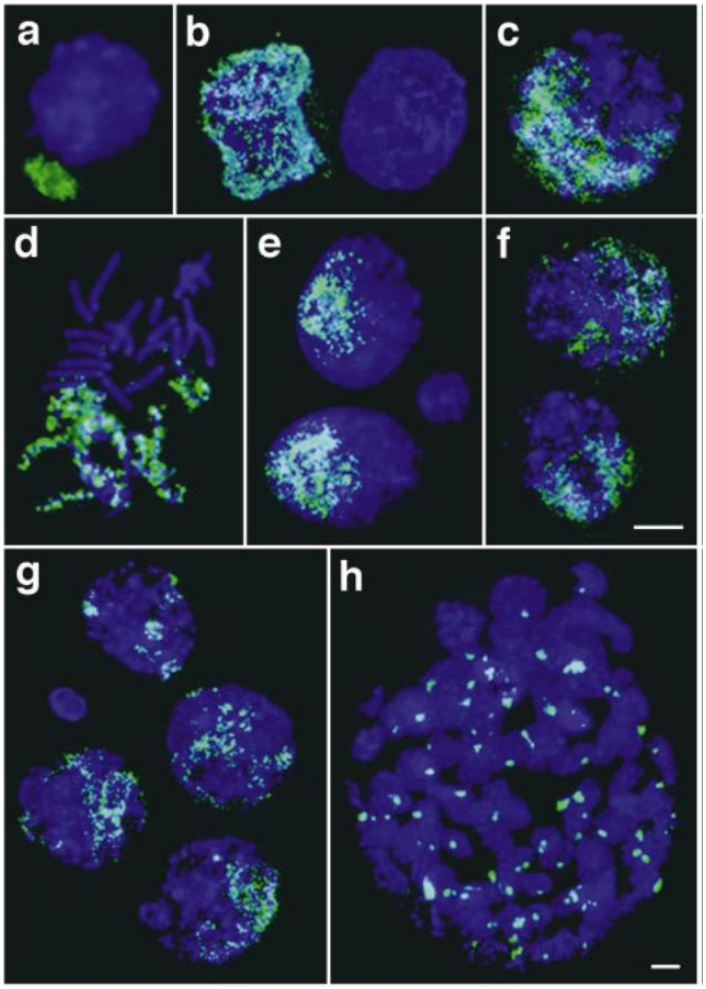


Fig. 14. Distribution of paternal chromatin in early mouse embryos (Mayer et al., 2000)

In plants, similar to mammalian hybrids (Figure 12), one species is losing chromosomal set faster than the other (Polgari et al., 2019).

Interestingly enough, starting from zygotic phase in mammalian cells there is spatial separation between diploid and haploid chromosomal sets (Figures 14, 15).

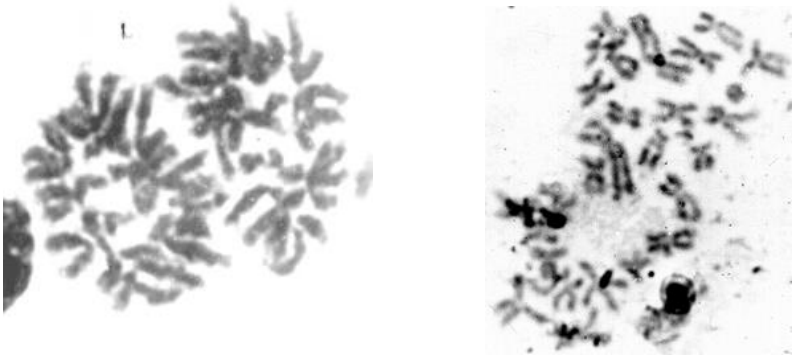


Fig. 15. Separation into haploid chromosomal sets in bone marrow cells of *Mus musculus* end *Microtus oeconomus*

As it was already mentioned, tandem and dispersed repeats are directly involved in the architectonics of the interphase nucleus, providing ectopic contacts between chromosomes and between chromosomal centromeric regions (Figures 16, 17).

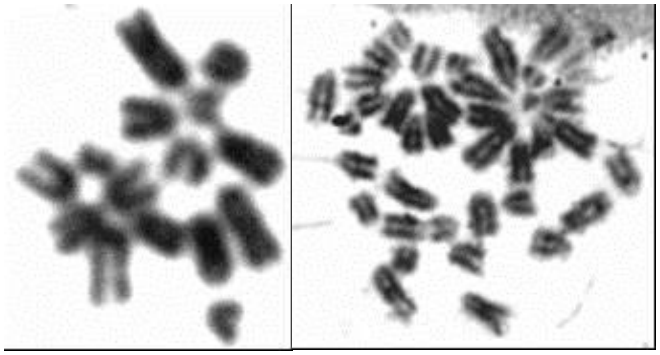


Fig. 16. Centromeric contacts between non-homologous chromosomes in the cell population of G1 embryonic stem cells from embryonic fibroblasts BALB/c mice strain

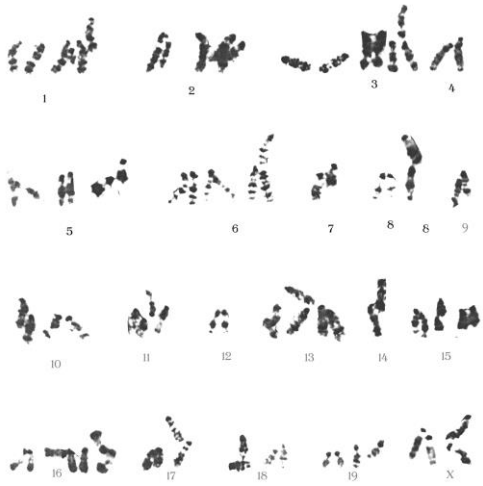


Fig. 17. Ectopic contacts between homologous chromosomes in metaphase plates of the FC3H8 line – embryonic fibroblasts of the laboratory line of C3H mice. The numbers indicate the numbers of the chromosomes entering into associations. Associations of both two and three homologous chromosomes are shown

It is interesting to note that in the cells of the bone marrow of highly inbred laboratory mice strain there is non-homologous chromosomes clustering in centromeric regions (Figure 18A). Such clustering can become Robertsonian translocations when mice are injected with the inducer of single-strand breaks adriamycin (Figure 18B).

A B

Fig. 18. A. Centromeres clustering of non-homologous chromosomes in bone marrow cells of BALB/c laboratory mice; B. Robertsonian translocations formation in mice of the same strain after administration of the inducer of single-strand breaks adriamycin. The arrow indicates the Robertsonian translocation between chromosomes 1; 8

In our previous studies, we compared genomic elements flanked by inverted repeats of microsatellites, in particular with core motif AGC, in Holstein cattle infected with bovine leukemia retrovirus and infection-free animals. We found that infected animals had higher density of retrotransposons and their recombination products as compared to infection-free animals (Glazko et al., 2018). This result suggests that individual differences in retroviral infection resistance could be related, to some extent, with genomic 'resistance' to mobile genetic elements insertions and deletions.

Actually this hypothesis was confirmed with data, accumulated during the aftermath of COVID-19 pandemic. COVID-10 did induce retrotransposons expression in lung and intestine cells. The authors of those studies suggest that retrontransposons activation lead to genomic instability and enhance genes expression, in particularly, reverse transcriptase gene. Therefore people with high basal rate of transposons activity, such as elderly and cancer patients, may have higher risk of additional retrotransposons' activation. Long-term epigenetic inheritance of retrotransposons' activity is now proven. Chimeric transcripts of transposons' RNA and SARS-CoV-2 RNA were also recently found, suggesting potential insertions viral fragments in human genome. Most frequently, chimeric RNA was composed from leading and terminal fragments of SARS-CoV-2 genome. Those findings demonstrate that coronavirus invades human cells and interacts with transposons, leading to more severe disease trajectory in vulnerable patients (Cohen, 2021).

4. Conclusion

Interphase nucleus architectonic and its dynamic have leading role in changing and regulating gene expression programs. In particular, it is achieved through chromatin packaging and positioning, regulating nucleotide sequences methylation and demethylation. Chromatin's architectonic is changing by employing two leading elements: ectopic inter-chromosomal contacts as well as telomeres and centromeres. The major part of centromeres and telomeres consist of tandem repeats and retrotransposons. Around half of mammalian genomes, is made out of transposons (mostly retrotransposons) and their recombination products. These elements have high evolutionary rate and even individual variability is influencing phenotypic variability and reproductive rate of plants and animals. Different interactions of *caryoskeleton's elements, such as SINEs and LINEs, with heterochromatin and euchromatin genomic domains, their movements inside the nucleus' space, could be related with gene clusters expressed at different levels.* It is expected that low genomic 'resistance' toward exogenous retroviruses and retrotranspositions is

controlled by natural selection and significantly influence population genetic dynamic in generations and the appearance of new forms.

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