Received: December 2, 2021
Revision received: January 1, 2022
Accepted: January 2, 2022
www.cribmb.com
DOI : 10.33702/crbmb.2022.4.1.1

Review Article

Chromosomal heterochromatin regions: cell division or cell thermoregulation?

Abyt Ibraimov, Stalbek Akhunbaev, Orozali Uzakov

International Higher School of Medicine, Intergelpo str, 1F, Bishkek, Kyrgyzstan

ABSTRACT
Despite the over 90-year history of studying the heterochromatin part of the genome of higher eukaryotes, its biological role remains unclear. Our ignorance of the true role of heterochromatin has left the field open for a variety of hypotheses ranging from the idea that it is "selfish DNA" simply perpetuating itself to ascribing to it an important function in development and evolution. Currently, most researchers believe, that chromosomal heterochromatin regions (HRs) are responsible for accurate chromosome segregation in cell division. Our experience shows that chromosomal HRs is more likely to be associated with cell thermoregulation (CT) than the guiding correct chromosome segregation during mitosis. Based on investigations of chromosomal HRs variability in human populations, as well as on the analysis of existing literary data on the condensed chromatin (CC) in the genome, an attempt is made to justify the view of possible participation of HRs in CT. CC, being the densest domains in a cell, apparently conducts heat between the cytoplasm and nucleus when there is a difference in temperature between them. The essence of the proposed hypothesis is the assumption that the CC, nucleolus, along with the chromocenters participate in CT. Namely, they are involved in the removal of excess heat from the "hot" areas of the interphase nucleus through a dense layer of peripheral CC in the cytoplasm. We believe that such a complex process as mitosis and meiosis cannot rely on the chromosomal HRs, which differ from euchromatin in their high variability in evolution and in individual development.

Key words: heterochromatin regions; cell thermoregulation; cell division; cell nucleus; nucleolus; chromocentres**.**

Citation: Abyt Ibraimov. (2022). Chromosomal heterochromatin regions: cell division or cell thermoregulation? Current Research in Biochemistry and Molecular Biology, 4(1),1-8 . http://dx.doi.org/10.33702/crbmb.2022.4.1.1

Author for correspondence: *Abyt Ibraimov, International Higher School of Medicine, Intergelpo str, 1F, Bishkek, Kyrgyzstan.*

Email: ibraimov_abyt@mail.ru

INTRODUCTION

A fundamental feature of chromosomes in higher eukaryotes, including man, is the presence of two evolutionally consolidated types of genetic material: euchromatin and heterochromatin. Euchromatin, the conservative portion of the genome, contains transcribed structural genes, while heterochromatin, the variable portion of the genome, is predominantly composed of non-transcribed repeated DNA sequences.

Heterochromatin is universally distributed in the chromosomes of all the eukaryotes - plants, animals and man, accounting for 10% to 60% of their genome. Heterochromatin regions (HRs) account for about 15% - 20% of the human genome [1-4]. Chromosomal HRs does not change during ontogenesis and are inherited in a regular manner as discrete traits.

To-date two types of constitutive heterochromatin are recognized: Q– and C–heterochromatin [5]. There are several significant differences between them: C-heterochromatin is found in the chromosomes of all the higher eukaryotes, while Q-heterochromatin - only in man (*Homo sapiens*), the chimpanzee (*Pan troglodytes*) and gorilla (*Gorilla gorilla*) [6,7]. C-heterochromatin regions (C-HRs) are known to be invariably present in all the chromosomes of man, varying mainly in size and location (inversion).

Basic features of chromosomal HRs upon which all hypotheses about their role are based, are the following: they consist, basically, of highly repeated sequences of DNA; HRs occupy quite certain loci of chromosomes having rather great values, namely: areas of centromeres and telomeres, and areas of nucleolar organizers, bearing rRNA genes; replication lability; wide intraspecific variability and, on the other hand, evolutionary fixedness of chromosomal HRs in higher eukaryote genome.

However, the role – if any – that heterochromatin plays is still essentially unknown. This is also reflected in variety of hypothesis, none of them backed up by solid evidence, concerning the possible effects of heterochromatin. These range from the idea that heterochromatin has no function, consisting of "selfish DNA, to the assumption that it has an important role in development and evolution.

The search for a possible biological role for chromosomal HRs continues to be the subject of intense research. Now there is no longer any doubt that chromosomal HRs plays more than one role in the life of eukaryotes. Therefore, they are credited with many functions. Some of these possible roles seem so logically obvious that they are not even questionable, despite the lack of experimental evidence necessary in such cases.

However, in our opinion there is one point that causes us serious doubts. We are talking about an almost generally accepted point of view that pericentromeric constitutive heterochromatin plays a decisive role in cell division, in particular, during the divergence of metaphase chromosomes at the cell poles during mitosis and meiosis. Almost all authors discussing the possible biological role of pericentromeric heterochromatin note precisely this role of chromosomal HRs.

Back in the last century, it was suggested that since the centromere is the most important structural element of the chromosome, which binds to the spindle filaments in mitosis, the hrDNAs contained in it should play an important role in the organization of the mitotic spindle microtubules, with all the ensuing consequences for cell division [8,9]. This idea continues to exist and has hardly become generally accepted in recent years. Below a just a few examples.

Thus, Verdaasdonk and Bloom [10] argue that 'Centromeres do play a conserved function in guiding correct chromosome segregation during mitosis, suggesting an epigenetic basis for centromere identity'. 'The constitutive heterochromatin maintained by H3K9me3 is pivotal for genomic integrity by preventing abnormal chromosome segregation, recombination, and DNA replication' [11]. Saksouk et al., [12] write that 'Pericentromeres consist of repetitive tandem satellite repeats and are crucial chromosomal elements that are responsible for accurate chromosome segregation in mitosis'. 'Centromeres and telomeres, composed of constitutive heterochromatin, are two essential features of all eukaryotic chromosomes. The centromeres interact with spindle microtubules to ensure segregation of sister chromatids during mitosis and of homologous chromosomes in meiosis. They evolve rapidly, and undergo transcription. Defects in centromere function can lead to aneuploidy and chromosomal instability. [13].

Chromosomal heterochromatin regions: cell division or cell thermoregulation?

Our experience in studying the possible biological role of chromosomal HRs using the example of human populations shows that HRs is more likely associated with cell thermoregulation (CT) than the guiding correct chromosome segregation during mitosis [14-23]. This assumption is supported by the following facts: a) there is a wide quantitative and qualitative polymorphism of chromosomal HRs in the population of animals and plants; b) the divergence of homologous chromosomes in anaphase begins from the end of the chromosome arms [24], and not from the centromeric regions, as previously assumed; c) the divergence of homologues at the poles from the equator of the dividing cell (both in speed and in the pattern of divergence) does not depend on the amount of pericentromeric constitutive heterochromatin; d) in three species of higher primates, in the pericentromeric region of chromosomes, in addition to C-heterochromatin, there is another type of constitutive heterochromatin - Q-heterochromatin. Unlike C-heterochromatin, which is present without exception on all chromosomes in humans, this constitutive heterochromatin: i) may be completely absent in the karyotype in a significant part of individuals in the human population without visible phenotypic manifestations, and ii) in humans, it can occur only on seven autosomes (3, 4, 13-15, 21 and 22) and on the Y chromosome. However, as is known, these three higher primates do not differ from other mammals in the mechanisms of mitosis and meiosis; e) there is no evidence of a fundamental difference between pericentromeric heterochromatin and other chromosomal HRs, which would indicate an exclusive affinity to cell division.

Now let's try to substantiate our objections. Speaking about the wide polymorphism of chromosomal HRs in the population genome and the supposed role of constitutive heterochromatin in cell division, we first of all imply that such a complex process as mitosis and meiosis cannot rely on HRs that differ from euchromatin precisely by its high variability in evolution and in individual development. It is well established that the divergence of homologues in anaphase begins from the end of the chromosome arms, and not from the centromeric regions, as previously assumed [24]. It is also known that the pericentromeric regions of homologous chromosomes very often differ significantly in the sizes of C- and Q-heterochromatin. However, there is no evidence of an effect of the size of C- or Q-HRs on the divergence of homologous chromosomes during mitosis or meiosis. Our objections regarding the role of the centromeric heterochromatin for accurate chromosome segregation on the example of the human karyotype are reduced to the following considerations: a) since some chromosomes (autosomes 1, 9 and 16 and the Y chromosome) in the population almost always differ in size by C-HRs, and by Q-HRs even more, it is difficult to imagine why they do not affect the divergences of these homologues at all. Why should it not be expected that homologues with large blocks of constitutive heterochromatin will diverge somewhat later than chromosomes with small HRs, or autosomes with large heterochromatin will pull along a homologue with a smaller HR size? As is known, the well-studied example of non-divergence of homologues in meiosis is Down syndrome. Thus, no one has yet shown that this type of aneuploidy is somehow related to the size of C- and Q-HRs in the karyotype of parents of patients with Down syndrome; b) in three species of higher primates in the pericentromeric regions of chromosomes, in addition to C-heterochromatin, there is another type of constitutive heterochromatin - Q-heterochromatin, and nevertheless, this important circumstance did not effect on mitosis and meiosis in these primates.

The following studies also support our objection. Thus, Sumner [1991] thoroughly investigated mammalian chromosomes from prophase to telophase using scanning electron microscopy. Two important findings have emerged from this study. The first is that prophase chromosomes do not become split into pairs of chromatids until late prophase or early metaphase. The second finding is that the centromeric heterochromatin does not split in two at the same time as the rest of the chromosome, but remains undivided until anaphase. Vig [25] has reviewed evidence that at anaphase the sister chromatids of different chromosomes do not separate simultaneously, but that their order of separation is related to the amount of centromeric heterochromatin that they possess. Fadloun et al., [26] write that 'The centromere ultrastructurally, takes the form of a distinct primary constriction on the condensed metaphase chromosome of higher eukaryotes. The constricted region comprises a different chromatin structure consisting of DNA and protein complexes (the kinetochores) to which microtubules bind to effect proper chromosome movements. The DNA sequence in the centromere is not conserved between organisms, yet the centromere displays similar features across evolution such as the presence of repetitive elements that include the alpha satellite in humans, the minor satellite in mice, the AATAT and TTCTC satellites in Drosophila (Cleveland et al., 2003). Consequently, the sequence requirements, if any, for a functional centromere are not established. [26].

And what is offered in return?

We believe that the biological role of chromosomal HRs mainly lies in their participation in thermoregulation at the cellular level. Based on investigations of chromosomal HRs variability in human populations, as well as on the analysis of existing literary data on the condensed chromatin (CC) in the genome, justified the view of possible participation of CC in cell thermoregulation (CT). CC, being the densest domains in a cell, apparently conducts heat between the cytoplasm and nucleus when there is a difference in temperature between them. The assumed heat conductivity effect of CC is stipulated by its principal features: a condensed state during the interphase, association with the lamina and the inner nuclear membrane, replication at the end of the S period of a cell cycle, formation of the nucleolus and chromocenters, genetic inertness, and wide variability in the quantitative contents both within and between species [14, 15].

The material bases of CT, we believe, are CC, localized around the nucleus, chromosomal HRs of nucleoli and chromocenters. Everything that is known about chromosomal HRs, an interphase nucleus and non-coding DNAs does not contradict the idea of a possible heat conductivity role of CC between cytoplasm and nucleus in a cell, including the following: (1) Non-coding DNAs of most eukaryotic organisms is complexed with proteins in highly compact structures designated as CC. Heterochromatins are a particular case of the differential packaging of the chromosome [27]; (2) The nuclear periphery in most cell types is predominantly occupied by heterochromatin, which is closely associated with the lamina and the inner

nuclear membrane, and nucleoli are surrounded by dense chromatin, which in addition connects the nuclear membrane with one of the nucleoli [1-4, 28-33]; (3) There are observations of contacts of nucleolus with secondary constriction of chromosomes 1, 9 and 16, containing the largest C-HRs blocks in the human karyotype [34]. Constitutive heterochromatin of Y chromosome and heterochromatinized X-chromosome in mammals interphase nuclei are associated with the nucleolus body [58]. Thus, the CC and chromosomal HRs being the densest formations in the interphase cell must have the appropriate heat conductivity with all the ensuing consequences.

How do we imagine the mechanisms of cell thermoregulation? Chromosomes have both internal (repair, recombination, rearrangement, modification, restriction) and external (replication, transcription, packaging, organized movement) molecular activities, which are accompanied, inter alia, by some heat output. If for any reasons the temperature in a nucleus begins to exceed than in cytoplasm there is a need for dissipation of surplus heat outside the nucleus. To do this the nucleus has two options: increasing its volume or increasing the heat conductivity of the nuclear membrane. The first option is limited for obvious reasons. The second option is the more promising one should the heat conductivity of the nuclear membrane be increased somehow. Since the nuclear envelope consists of double-membraned extension of the rough endoplasmic reticulum, the nuclear membrane cannot essentially change its structure. But it is necessary to remove the surplus heat from the nucleus somehow.

Certainly, CT hypotheses should be checked on the cell level. But till present no one had the opportunity to evaluate CT at the level of individual cells. Nevertheless, we have checked this hypothesis on the level of human organism assuming that CT is the basis for heat conductivity of whole cell part of body [16,35]. As a whole our results show that: a) individuals in a population differ from each other on the level of body heat conductivity (BHC); b) on the average BHC of males is higher than that of females; c) individuals differ in BHC from different age groups, on the average human BHC level is steadily changed decreasing with age; d) natives of low altitude regions of southern latitude differ on the average by higher BHC than population of high mountains and northern latitude; e) weight, height, types of body constitution (normosthenic, asthenic and hypersthenic), pulse rate and level of arterial pressure do not effect on the variability of BHC in population [16,36,37].

It is interesting that these results meet the data obtained during investigation of quantitative variability of chromosomal Q-HRs in human population, namely: a) individuals in a population differ from each other in the number of chromosomal Q-HRs in the genome; b) as a rule, amount of chromosomal Q-HRs in male is higher than in female one on the population level, since the male chromosome Y has the largest Q-HR block in the human karyotype ; c) different age groups have different amount chromosomal Q-HRs: the greatest number of Q-HRs is characteristic of neonates, while the lowest – of elderly subjects; d) a consistent interpopulation differences in the quantitative amount of chromosomal Q-HRs in their genome were established. These differences proved to be related to features of the ecological environment of the place of permanent residence, and not to their racial and ethnic composition. The amount of chromosomal Q-HRs in the population genome tend to decrease from southern geographical latitudes to northern ones, and from low-altitude to high-altitude ones [17, 18, 38-55].

Lack of interest on the possibility of the existence of thermoregulation at the level of nucleus has quite objective reasons. Recognized internal sources of heat in the body are localized in the cytoplasm (mitochondria). Apparently, it is taken for granted that if the temperature of the cytoplasm rises above the optimal level for the organism, it should be freely displayed in the interstitial fluid, at least because of the microscopic size of the cells. The cell nucleus is not usually considered as one of the internal heat sources, despite the fact that very active biochemical processes take place there (repair, recombination, rearrangement, modification, restriction, replication, transcription etc. of DNA). And, finally, there is no known mechanism for a cell to actively dissipate excessive thermal energy. It is considered that diffusion and possibly convection are the primary means to passively remove the heat generated inside the cell [56]. This explanation is strongly objected to. Matter of fact, 'Inside the cell the molecules are mostly associated with polymeric structures (cytoskeletal polymers or membranes) and thus exist in very heterogeneous, solid state environments that alter their behavior dramatically compared to free molecules in test tubes' [57]. As such, highly localized heat sources are expected to create a subcellular temperature gradient. In other words, the interacting molecules in the cell do not float freely, as in a test tube with a water solution. Therefore, diffusion and convection cannot be the primary means to remove the heat generated inside the cell. Consequently, it is necessary to look for other additional mechanisms for removing surplus heat from the cell, and especially from its largest organelle - the nucleus.

There are still no direct data on the temperature of different parts of the cell nucleus, measured *in vivo*. Nevertheless, it is difficult to expect that the temperature in the nucleus will be the same in all its parts. It is obvious that the biochemical activity in the nucleoli or chromocenters will be higher than in the rest of the nucleus. In addition, the nucleus is not a heterogeneous mass and a deeply structured organelle (for more details see [19, 22, 23]).

The nucleus, in contrast to the cytoplasm, cannot conduct heat directly in the extracellular space, from where the heat is taken by the circulating flow of sap, lymph and blood. Thus, the nucleus can conduct heat only in the cytoplasm. The role of the circulatory systems (CS) has not been discussed here in maintaining temperature homeostasis of the cells. The thing is the CS cannot influence directly the temperature inside the cells, as they are linked with the CS indirectly through the intercellular space. The only exception may be endothelial cells lining the inner surface of blood vessels. Thus, the CS influence on inner cellular temperature homeostasis is limited. That is why it seems that the problem of maintaining the inner cellular temperature homeostasis is solved by cells themselves, and we call it the cell thermoregulation [5,6,34-36].

Apparently Nature chose a very simple and effective solution: it increased heat conductivity of the nuclear areas where excess heat is produced into temporary structures in the form of CC around the nucleus, nucleoli and chromocenters. The essence of the proposed hypothesis is the assumption that the CC, nucleolus, along with the chromocenters participate in cell nucleus thermoregulation. Namely, they are involved in the removal of excess heat from the "hot" areas of the interphase nucleus through a dense layer of peripheral CC in the cytoplasm.

Features of the elimination of excess heat from the cell nucleus

We still do not know exactly the mechanisms for removing excess heat from the cell. It is also not known whether the mechanisms of heat elimination of the cytoplasm differ from the nucleus. One can only assume that they should be different. Perhaps the main difference of the cytoplasm is that excess heat is diffused from it without the formation of special “heat-removing” structures, such as CC, nucleolus and chromocenters as in the nucleus. If the excess heat in the cytoplasm is actively eliminated into the intercellular space, then for this it uses the cytoskeleton, since all the organelles that produce excess heat are somehow attached to it [19,22].

However, such a mechanism of heat removal may not be acceptable, and even dangerous, to the nucleus. Firstly, the elimination of all excess thermal energy uniformly throughout the nuclear envelope can damage its unique physicochemical property as a bio membrane under the influence of high temperature. The fact is that, unlike nuclear envelope, the surface area of the cell membrane is very large and does not correspond to the volume of the cytoplasm due to the many protrusions emerging into the intercellular space, including cilium. Compared to the cell membrane, the surface area of the nuclear envelope is small and corresponds to the volume of the nucleus. Secondly, the most active biochemically parts of the nucleus where it is expected that the highest heat production, we believe, are organized into special temporary structures in the form of nucleoli and chromocenters to remove excess thermal energy [19,22].

The question arises: why are three different structures required to eliminate excess heat from the interphase nucleus: a dense layer of peripheral CC around the nucleus, nucleoli and chromocenters? The answer may be the following. A dense layer of CC lining the inner surface of the nuclear envelope removes heat into the cytoplasm not only from the entire interphase nucleus, but also from the nucleoli and chromocenters, because they have physical contact with inner nuclear membrane.

It seems highly probable that the localization and compaction of chromosomal HRs at the periphery of the nucleus is due to two reasons: a) the need for CT to effectively remove excess heat from the nucleus; and b) the risk of damage to the fine structure of the cell membrane from the effects of high temperature emanating from the biochemically highly active interphase nucleus. The first reason, apparently, does not need any additional argument, since the CC layer located on the periphery of the nucleus is the densest and, accordingly, the most heat-conducting structure in the interphase cell with all the ensuing consequences for cell thermoregulation. The second reason is related to the features of cellular membrane. As is known, membranes are very sensible to fluctuations in a temperature: at a low temperature they become too hard, and at high temperature too liquid to perform their function normally.

Apparently, the high vulnerability of cell membranes to temperature fluctuations seems to have 'forced' Nature to use chromosomal HRs, lamina, nucleolus, chromocenters and cytoskeleton to protect them. The layer of lamina is located between the CC and nuclear envelope. Why? It is accepted to consider that the lamina just beneath the inner nuclear membrane functions to give a nucleus its strength and shape. But, in principle, lamina could be located outside the nuclear envelope, as a cell wall on the plasma membrane in plant cells or in prokaryotes, if the task of lamina is limited only to strengthening the strength and shape of the nucleus. Perhaps in the localization of lamina just beneath the inner nuclear membrane lies a deep biological meaning - to protect the nuclear envelope from the dangerous effects of high temperature emanating from the biochemically active nucleus.

We believe that in the removal of heat surplus from a nucleus a nucleolus is actively involved. Thus, some of the chromosomes have nucleolar organizer regions (NORs), which contain ribosomal cystrones. In humans, NORs are localized on acrocentric chromosomes (13-15, 21 and 22). The observations that human chromosomes 1, 9 and 16, which do not contain ribosomal cystrones, but have a big C-HRs blocks and contacts with nucleolus still have no explanation. In the same situation there is a preferential spatial proximity of sex chromosomes HRs to nucleoli in interphase nuclei. As it is known, NORs, together with chromosomal HRs form the nucleolus bodies. Since chromosomal HRs are in the body and around the nucleolus, there is nothing surprising in the assumption that they due to its high density can promote removal of excess heat from the nucleolus and further to CC around the nucleus.

We have already discussed the possible role of nucleoli and chromocenters in CT [19, 22]. Very short, chromocenters and nucleoli transfer excess heat from the "hot" sections of the interphase nucleus because: a) one of the fundamental properties of their components - chromosomal HRs - is the ability to conjugate to each other, forming the densest regions; b) nuclear staining reveals foci of the nucleus known as chromocenters corresponding to regions with dense and compact DNA domains; c) the vital genes whose products are needed in large quantities are most often localized closer to the chromosomal HRs and the latter serve as a solid surface a temporary fixation of the polymer chain under synthesis on the insoluble polymer carrier. In other words, the appearance of dense layers of CC creates a physical basis for the removal of excess heat from the «hot» areas of the interphase nucleus. In principle, nucleoli are also chromocenters, but more specialized in the sense that they organize a dense layer of CC from chromosomal HRs of acrocentrics, where NORs and ribosomal genes are located [14,15,23].

Acknowledgements
I apologize to that author whose work is not cited or is cited only through reviews. The reason for this is only the space limitations of the publication.

REFERENCES

[1] Arrighi FE, Hsu TC. (1971). Localization of heterochromatin in human chromosomes. Cytogenetics, 10: 81-86.
[2] Bostock CJ, Sumner AT. (1978). The Eukaryotic Chromosomes. Amsterdam, North-Holland.
[3] Caspersson T, Zech L, Johansson C. (1970). Differential binding of alkilating fluorochromes in human chromosomes. Exp Cell Res, 60: 315-319.
[4] Micloš GLG, John B. (1979). Heterochromatin and satellite DNA in man: properties and prospects. Am J Hum Genet, 31: 264-280.
[5] Paris Conference, 1971, and Supplement 1975. Standartization in human cytogenetics. Birth Defects: Original Article Series, XI, 1-84. The National Foundation, New York.
[6] Pearson PL. (1973). The uniqueness of the human karyotype. In: Chromosome identification techniques and application in biology and medicine. Caspersson T. and Zech L. (eds). New York, London. Academic Press, p. 145.
[7] Pearson PL. (1977). Pattern of bands, polymorphism and evolution of primates. In: Molecular structure of human chromosomes. Yunis J.J. (Ed). Acad. Press. p. 267.
[8] Walker PMB. (1971). Origin of satellite DNA. Nature, 229: 306-308.
[9] Craig-Holmes AP. Shaw MW. (1971). Polymorphism of human constitutive heterochromatin. Science, 174: 702-704.
[10] Verdaasdonk J, Bloom K. (2011) Centromeres: unique chromatin structures that drive chromosome segregation. Nat Rev Mol Cell Biol, 12: 320–332. https://doi.org/10.1038/nrm3107.

[11] Chen Fei, Hong Kan, Vince Castranova. (2011). Methylation of Lysine 9 of Histone H3: Role of Heterochromatin Modulation and Tumorigenesis. In Handbook of Epigenetics The New Molecular and Medical Genetics, p.149-157.
[12] Saksouk N, Simboeck E, Déjardin J. (2015). Constitutive heterochromatin formation and transcription in mammals. Epigenetics & Chromatin 8, 3. https://doi.org/10.1186/1756-8935-8-3).
[13] Anitha Ayyappan, Ismail Tanseen, Mahesh Mundalil Vasu. (2020).Centromere and telomere dynamics in humans. in Genome Plasticity in Health and Disease, p.157 -178. https://doi.org/10.1016/B978-0-12-817819-5.00010-3.
[14] Ibraimov AI. (2003). Condensed chromatin and cell thermoregulation. Complexus, 1: 164-170.
[15] Ibraimov AI. (2004). The origin of condensed chromatin, cell thermoregulation and multicellularity. Complexus, 2: 23-34.
[16] Ibraimov AI, Tabaldiev SK. (2007). Condensed chromatin, cell thermoregulation and human body heat conductivity. J Hum Ecol, 21(1): 1-22.
[17] Ibraimov AI. (2015). Heterochromatin: The visible with many invisible effects. Global Journal of Medical Research (C), Volume 15, Issue 3, Version 1.0, pp. 7-32.
[18] Ibraimov AI. (2017). Cell Thermoregulation: Problems, Advances and Perspectives. J Mol Biol Res, 7(1): 58-79. doi:10.5539/jmbr.v7n1p58
[19] Ibraimov AI. (2019b). Chromocenters and cell thermoregulation. J Biol Med Res, Vol.2 No.3:19.
[20] Ibraimov AI. (2021). Why should non-coding DNA be considered as primary material in the evolution of eukaryotes? Current Research in Cytology and Histology, 2(1): 10-16.
[21] Ibraimov AI. (2019). Cell thermoregulation and origin of homeothermic animals. Current Research in Biochemistry and Molecular Biology, 1(1): 10-13.
[22] Ibraimov AI. (2020). Cell thermoregulation: How is excess heat eliminated? Current Research in Cytology and Histology, 1(1): 14-21.
[23] Ibraimov AI. (2020). Chromosomal Q-heterochromatin in the Human Genome. Cambridge Scholars Publishing.
[24] Sumner AT. (1991). Scanning electron microscopy of mammalian chromosomes from prophase to telophase. Chromosoma, 100 (6): 410-418.
[25] Vig BK. (1987). Sequence of centromeric separation: a possible role for repetitive DNA. Mutagenesis, 2: 155-159.
[26] Fadloun Anas, André Eid, Maria-Elena Torres-Padilla. (2013). Mechanisms and Dynamics of Heterochromatin Formation During Mammalian Development: Closed Paths and Open Questions. Epigenetics and Development, 104: 1-45.
[27] Cleveland DW, Y Mao, KF Sullivan. (2003). Centromeres and kinetochores: from epigenetics to mitotic checkpoint signaling. Cell, 112 (4): 407-421.
[28] Comings DE. (1968). The rational for ordered arrangement of chromatin in the interphase nucleus. Am J Hum Genet, 20: 440.
[29] Ferreira J, Paolella G, Ramos C, Lamond AI. (1997). Spatial organization of large-scale chromatin domains in the nucleus: A magnified view of single chromosome territories. J Cell Biol, 139: 1597–1610.
[30] Belmont AS, Zhai Y, Thilenius A. (1993). Lamin B distribution and association with peripheral chromatin revealed by optical sectioning and electron microscopy tomography. J Cell Biol, 123: 1671–1685.
[31] Marshall WF, Dernburg AF, Harmon DA, Agard DA, Sedat JW. (1996). Specific interactions of chromatin with the nuclear envelope: Positional determination within the nucleus in Drosophila melanogaster. Mol Biol Cell, 7: 825–842.
[32] Paddy MR, Belmont AS, Saumweber H, Agard DA, Sedat JW. (1990). Interphase nuclear envelope lamins from a discontinuous network that interacts with only a fraction of the chromatin in the nuclear periphery. Cell, 62: 89–106.
[33] Sadoni N, Langer S, Fauth C, Bernardi G, Cremer T, Turner BM, Zink, D. (1999). Nuclear organization of mammalian genomes: Polar chromosome territories build up functionally distinct higher order compartments. J Cell Biol, 146: 1211–1226.
[33] Verma RS. (Ed). (1988). Heterochromatin. Molecular and Structural Aspects. Cambridge Univ. Press. Cambridge, New York, Sydney.
[34] van Holde KE. (1989). Chromatin. New York, Springer.
[35] Ibraimov AI. et al. (2014). Human Chromosomal Q-heterochromatin Polymorphism and Its Relation to Body Heat Conductivity. Int J Genet, 6(1): 142-148.
[36] Ibraimov AI. et al. (2010). Variability of Human Body Heat Conductivity in Population. I. Methodological and Theoretical Approaches. J Hum Ecol, 32(1): 1-22.
[37] Ibraimov AI. et al. (2010). Variability of Human Body Heat Conductivity in Population. II. Diseases of Civilization. J Hum Ecol, 32(2): 69-78.

[38] Buckton KE. et al. (1976). C- and Q-band polymorphisms in the chromosomes of three human populations. Ann Hum Genet, 40: 90-112.
[39] Al-Nassar KE, Palmer CG, Connealy PM, Pao-Lo Yu. (1981). The genetic structure of the Kuwaiti population. II. The distribution of Q-band chromosomal heteromorphisms. Hum Genet, 57: 423-427.
[40] Lubs HA, et al. (1977). Racial differences in the frequency of Q- and C-chromosomal heteromorphism. Nature, 268: 631-632.
[41] Ibraimov AI, Mirrakhimov MM. (1982). Human chromosomal polymorphism. III. Chromosomal Q-polymorphism in Mongoloids of Northern Asia. Hum Genet, 62: 252-257.
[42] Ibraimov AI, Mirrakhimov MM. (1982). Human chromosomal polymorphism. IV. Qpolymorphism in Russians living in Kirghizia. Hum Genet, 62: 258-260.
[43] Ibraimov AI, Mirrakhimov MM. (1982). Human chromosomal polymorphism. V. Chromosomal Q-polymorphism in African populations. Hum Genet, 62: 261-265.
[44] Ibraimov AI, Mirrakhimov MM. (1985). Q-band polymorphism in the autosomes and the Y chromosome in human populations. In: "Progress and Topics in Cytogenetics. The Y chromosome. Part A. Basic characteristics of Y chromosome". A. A. Sandberg (Ed). Alan R. Liss, Inc., New York. USA, pp. 213-287.
[45] Ibraimov AI, Tabaldiev SK. (2007). Condensed chromatin, cell thermoregulation and human body heat conductivity. J Hum Ecol, 21(1): 1-22.
[46] Ibraimov AI, Karagulova GO. (2006). Chromosomal Q-heterochromatin regions in individuals of various age groups. Int J Hum Genet, 6(3): 219-228.
[47] Ibraimov AI. et al. (1982). Human chromosomal polymorphism. I. Chromosomal Qpolymorphism in Mongoloid populations of Central Asia. Hum Genet, 60: 1-7.
[48] Ibraimov AI. et al. (1986). Human chromosomal polymorphism. IX. Further data on the possible selective value of chromosomal Q-heterochromatin material. Hum Genet, 73: 151-156.
[49] Ibraimov AI. et al. (1990). Chromosomal Q-heterochromatin regions in native highlanders of Pamir and Tien-Shan and in newcomers. Cytobios, 63: 71-82.
[50] Ibraimov, A. I., et al. (1991). Chromosomal Q-heterochromatin regions in the indigenous population of the Northern part of West Siberia and in new migrants. Cytobios, 67, 95-100.
[51] Ibraimov AI, Karagulova GO, Kim EY. (1997). Chromosomal Q-heterochromatin regions in indigenous populations of the Northern India. Ind J Hum Genet, 3: 77-81.
[52] Ibraimov AI. et al. (2013). Chromosomal Q-heterochromatin polymorphisms in 3 ethnic groups (Kazakhs, Russians and Uygurs) of Kazakhstan. Int J Genet, 5(1): 121-124.
[53] Kalz L. et al. (2005). Polymorphism of Q-band heterochromatin; qualitative and quantitative analyses of features in 3 ethnic groups (Europeans, Indians, and Turks). Int J Hum Genet, 5(2): 153-163.
[54] Décsey K, Bellovits O, Bujdoso GM. (2006). Human chromosomal polymorphism in Hungarian sample. Int J Hum Genet, 6(3): 177-183.
[55] Stanyon R. et al., (1988). Population cytogenetics of Albanians in the province of Cosenza (Italy): frequency of Q and C band variants. Int J Anthropol, 3(1): 14-29.
[56] Hochachka PW. (2003). Intracellular Convection, Homeostasis and Metabolic Regulation. J Exp Biol, 206: 2001-2009.
[57] Albrecht-Buehler G. (1990). In defense of "nonmolecular" cell biology. Inter Rev Cytol, 120: 191-241.
[58] Seuanez H, Robinson J, Martin DE, Short RV. (1976). Fluorescent (F) bodies in the spermatozoa of man and great apes. Cytogent Cell Genet, 17: 317–326.
[59] Schmid M, Vogel W, Krone W. (1975). Attraction between centric heterochromatin of human chromosomes. Cytogenet Cell Genet, 15: 66-80.