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International Journal of Clinical Research and Reports

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Review Article

Heterochromatin and Heterochromatic Regions

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Received date: May 18, 2024; Accepted date: May 31, 2024; Published date: June 10, 2024

Citation: Abyt Ibraimov, (2024), Heterochromatin and Heterochromatic Regions, *International Journal of Clinical Research and Reports*, 3(3); **DOI:**10.31579/2835-785X/056

Abstract

The terms heterochromatin (HC) and chromosomal heterochromatic regions (HRs) are often used interchangeably. Even specialists do not attach much importance to this, implying that it will not prevent the reader from perceiving the essence of the problem under discussion. However, they understand that HC and HRs are not the same thing: for the former it is the molecular composition that is important, and for the latter the features of HC localization, size and number in the chromosome (variability). What HC and HRs have in common is their molecular composition: both consist of short, highly repetitive nucleotide sequences that cannot code for specific peptides (non-coding DNAs). Nevertheless, a closer look at the problem shows that HC and HRs are not the same thing and should be considered separately. It is important for correct statement of the question, its understanding and interpretation. The matter is that to many it seems that the problem of "excess" non-coding DNAs (ncDNAs) and variability of HRs can be reduced to the molecular biology of HC. However, many years of attempts to understand the biological role of ncDNAs in general, HC and chromosomal HRs in particular exclusively by studying their molecular organization have not yielded the expected results. As a result, those who studied HC as an object of molecular biology stopped understanding the results of studies that investigated the variability of chromosomal HRs, and vice versa. Result: the biological roles of ncDNAs, HC and HRs remain undiscovered. Solution: it is necessary to revise the existing views about HC and HRs.

Keywords: heterochromatin; heterochromatic regions; constitutive heterochromatin; facultative heterochromatin; condensed chromatin; non-coding DNA

Background

The term heterochromatin (HC) was the first to appear and we owe it to E. Heitz [1928-1935], who discovered it in the chromosomes of dividing cells of the moss Pellia epiphyla, Vicia equine bean, and Drosophila due to its most important feature of remaining in a condensed state throughout the cell cycle. Heitz [11] found that the substance making up the bulk of the nucleus—chromatin—consists of two components: 1) euchromatin, which contains genes, and 2) heterochromatin, which does not carry such genetic material. In 1935 [12], in his review "The Structure of Chromosomes and Genes" he came to the following conclusions: "(1) All chromosomes show a longitudinal differentiation into euchromatin and heterochromatin that relates to the genetic properties of each chromosome. (2) The differentiation is specific for each chromosome and is different in the karyogram of each animal and plant species (5). Heterochromatin formation and the degree of chromosomal contraction are genetically determined, and heterochromatin is located at corresponding positions of homologous chromosomes. (6) Chromocenters of interphase nuclei result from equilocal positioning of heterochromatin of different chromosomes. (7) Species can be distinguished by their size and pattern of chromatin distribution. (8) Euchromatin is closely connected to gene activity during interphase; heterochromatin corresponds to genetically inert regions (11). Sex chromosomes are frequently subject to heterochromatin formation" (cited in [48]). By proposing the term euchromatin, Heitz was referring to those parts of the chromosomes that are no longer visible under an optical microscope at the end of the telophase.

Shortly after Heitz's death, Brown [4] suggested the terms "constitutive" and "facultative" heterochromatin, which are still controversial. From his point of view, HC represents the visible expression of repression in chromosomes of gene activity during individual development and evolution. The introduction of the term "facultative" heterochromatin has raised many objections. For example, Prokofyeva-Belgovskaya [52] believed that "the term itself contains an erroneous idea that there are no fundamental differences between euchromatin and heterochromatin and that these differences can be reduced only to the states (condensed and decondensed) in which a given chromosome segment remains for a long time. Heterochromatin and euchromatin are fundamentally different with respect to the molecular organization of DNA. It seems appropriate at present to replace "facultative heterochromatin" with the term "condensed" or "inactivated" euchromatin, which correctly expresses the nature of this structure and its state."

In the last collective monograph devoted to heterochromatin, one of the authors writes:

"There was a time when it could be argued that heterochromatin differed from euchromatin in its behavior but not in its fundamental structure [2;4;8]. That time is now past. Constitutive heterochromatin is indeed composed of DNA sequences with distinctive characteristics. Moreover, there are not two classes of heterochromatin, constitutive and facultative, as is still commonly

claimed. The use of the noun heterochromatin to describe euchromatin that is facultatively inactivated is both misleading and unnecessary. The facultative heterochromatinization of euchromatin, in principle, has more in common with tissue-specific condensation of euchromatin, though it obviously takes place on a more extended scale, both temporally and spatially, within the individual organism and usually to only one sex" [40].

In addition, many people are still undecided on the question: HC is a substance or a state. In this regard, Sumner [55] expressed quite clearly and reasonably that "Many years ago, it was argued over whether heterochromatin was a substance or a state. We are now in a position to answer this question, and it is clear that in general, constitutive heterochromatin is a substance in that it contains specific types of DNA and has specific proteins associated with it. On the other hand, facultative heterochromatin is equally clearly a state because its DNA is essentially identical to that of its euchromatic homologue. It is derived from euchromatin, and in rare cases can revert to an active, euchromatic state".

It should be noted that some scientists warned about the danger of the tendency to confuse HCs with chromosomal heterochromatic regions (HRs) as early as in the last century. For example, Beridze [3], the author of the first monograph on satellite DNA, wrote: "In this matter, two aspects should be clearly distinguished: the first is the compaction of satellite chromatin and the formation of a condensed state, known as 'constitutive heterochromatin', the second is a function of the most constitutive heterochromatin, structure, which is a supramolecular formation, functioning as a qualitatively new unit. With the formation of constitutive heterochromatin, some new properties are acquired that are not characteristic of either satDNA or proteins that are part of the constitutive heterochromatin separately, that is, the properties of constitutive heterochromatin are not the sum of the properties of its components. ...The functions of constitutive heterochromatin should be considered separately. At the moment, the question of the functions of heterochromatin is a cytogenetic problem rather than a molecular biological one".

However, despite all this, there is still confusion that there are two types of HC: constitutive and facultative. This fact seriously complicates the already complicated situation when chromosomal HRs are considered only as a large block of HCs visible under the microscope, and their biological role can be elucidated through studies of their molecular organization. This approach makes it particularly difficult to elucidate the causes and consequences of the wide heritable variability of chromosomal HRs for individual and population.

Definitions of HC and HRs.

The known similarities between HCs and HRs in molecular composition, organized by non-transcribed highly repetitive, often satellite sequences, has been and remains the main obstacle in attempts to clearly define these two types of chromatin. The situation became especially confusing when it became known that transcribed genes are also localized in heterochromatin, such as the bobbed gene in the proximal heterochromatin of the X chromosome of Drosophila melanogaster [45]. After the use of complementation analysis, the number of genes in the HRs of the polytene X chromosome increased significantly [54]. These circumstances eventually led to the fact that such chromosome sections were called not HC but chromosomal HRs, meaning that HC in this region is encrusted with few transcribed genes.

According to the first definition, HC is a chromosome segment that does not undergo morphological transformations in telophase unlike euchromatin, remains condensed in interphase, and differs from euchromatin in prophase by more intense staining [11,12]. According to Heitz, the term "heterochromatin" is a purely morphological concept ("Eine rein morphologische Tatsache"), and this term accompanied all further development of cytogenetics, as Pfeiffer [51] aptly put it, "like a shadow from a cloud". It seems to us that this "shadow" has only thickened over the years.

Yunis and Yasmineh [58] gave a more modern definition of HC as "a special type of chromatin that contains mainly satellite DNA". The inaccuracy of this definition is that HC DNA, as now established, may consist not only of satellite sequences but also of other types of highly repetitive DNA [14,42].

It is equally difficult to give an unambiguous definition of chromosomal HRs. Prokofyeva-Belgovskaya [52] specifically investigated this issue and concluded that "the concept of chromosomal HRs corresponds to the concept of euchromatic region, which should be understood as a section of euchromatin in which intercalary heterochromatin regions are encrusted. They represent a heterochromatic region if non-transcribed heterochromatin loci predominate, and an euchromatic region if transcribed heterochromatin loci predominate. ...Since the investigator of different organisms is dealing with heterochromatin, the degree of saturation of which with transcribed genes is unknown, in all these cases it is more correct to operate with the concept of heterochromatic region rather than heterochromatin." John [40] in his very informative review "Heterochromatin" did not use the term chromosomal HRs at all.

Functions of HC and chromosomal HRs.

The precise role of HC and chromosomal HRs long remained a mystery, as its frequent polymorphisms did not appear to have any functional or phenotypic effect. However, the situation is gradually changing and nowadays not much is known about HC and HRs. It is not our task to analyze them in detail. Therefore, we will limit ourselves to their brief enumeration. It is most often stated that HC plays an important role in the organization of nuclear domains. In particular, heterochromatin and euchromatin occupy different nuclear domains. HC is usually localized in the periphery of the nucleus and is attached to the nuclear membrane. In contrast, the active chromatin occupies a more central position. It is generally accepted that the peripheral localization of HC concentrates the active elements towards the center of the nucleus, allowing the active euchromatin to replicate and be transcribed with maximum efficiency. The possible role of HC is also discussed in gene repression (epigenetic regulation): HC appears to be involved in controlling the transcriptability of the genome and genes that are usually located in the euchromatin can, therefore, be silenced when they are placed close to a heterochromatic domain [43]. It has been suggested that centromeric HC is necessary for the cohesion of sister chromatids and that it allows the normal disjunction of mitotic chromosomes. However, all of this does not provide a satisfactory answer to the question of what function HC performs after all, since its role observed so far is only a tiny fraction of the total number of ncDNAs.

A number of hypotheses have been raised about the possible role of chromosomal HRs. Basic features of 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, namely: areas of centromeres and telomeres, and areas of nucleolar organizers, bearing rRNA genes; wide variability and, on the other hand, evolutionary fixedness of chromosomal HRs in higher eukaryote genome.

A number of authors [13,46,39] assume, that chromosomal HRs can not to have any function, that is they have something in common with known point of view of Brown [4], that for HRs "importance of doing nothing". Such view was reasoned in particular by wide quantitative variability of HRs without any phenotype manifestations. John [40] suggested that "there is then a very real possibility that heterochromatin per se has no function in either development or evolution" and "the inertness of constitutive heterochromatin in terms of its transcriptional inability, is a consequence of its distinctive DNA structure".

Gershenson [15] first showed that near chromosomal HRs the crossing-over usually not occurs. Their possible participation was considered in the formation of the interphase nuclei specific pattern by maintaining of a certain spatial position of chromosomes relatively to each other and the nuclear membrane [5,16,17,41,47,53,56]. As well the "bodyguard hypothesis" [14] has been proposed, assuming that HRs are used by a cell as a protective body to guard euchromatin by forming a layer "shield", distributed on the outer surface of the nucleus.

Darlington [6] first attributed to chromosomal HRs the important role in the evolution, namely, the speciation through formation of viable translocations.

There are data that species are not indifferent to increase or decrease in quantity of heterochromatin. The main result of these studies is that changes of HRs in different species have apparently adaptive nature, providing them with quick adaptation to changing environmental conditions [8,10,44].

Some authors suggest that the function of chromosomal HRs is attached to the processes of cell division. Thus, the ability of chromosomal HRs by non-homologous conjugation can determine behavior of chromosomes prior to their pairing and formation of synaptonemal complex [57,58]. Prokofyeva-Belgovskaya [52] believes, that: "Changes in the heterochromatin content of chromosomal heterochromatin regions in species are adaptive. They apparently ensure adaptation to changes in environment more rapidly as compared to the process of mutation. In order to survive and leave descendants in a new environment, the organism utilizes different mechanisms, and this does not always require the participation of genes. Quantitative changes in heterochromatin could be of great importance". For our part, we believe that the main function of chromosomal HRs is their participation in maintaining temperature homeostasis at the level of individual cells (cell thermoregulation) [28,35].

Evolution of HC and chromosomal HRs.

There have been no special studies on the origin and evolution of HC and chromosomal HRs. Nevertheless, it is possible to make a number of speculations on this topic. Obviously, HC were the first to arise in the genome of eukaryotes during evolution. Apparently, they represented regions of DNA clusters with short repetitive nucleotide sequences, presumably introduced by viruses. Over time, in some eukaryotic lineages, they proved capable of multiple expansion and became predominant over coding DNA ("excess" DNA). In some cases, such "excess" ncDNAs have come to occupy extended regions of chromosomes, which we call HC. In higher eukaryotes, some HC formed complex forms of supramolecular organization known as chromosomal HRs and were called C-heterochromatin. At the last stages of animal evolution another remarkable event occurred: a new type of constitutive heterochromatin, Q-heterochromatin, appeared in the genome of the common ancestors of the three higher primates (Homo sapiens, Pan troglodytes and Gorilla gorilla). It turned out that this type of HC shows wide variability only in human populations [49,50].

HC vs chromosomal HRs

What we mean when we say that incorrect interpretation of the terms HC and chromosomal HRs has led to serious misunderstandings in perception of research results obtained by molecular biologists and cytogeneticists, and this circumstance prevents the elucidation of their biological role. This can best be demonstrated on the example of perception of the data obtained by studying the variability of chromosomal HRs in human populations. Those who study the molecular organization of chromosomal HRs in order to elucidate their biological role do not perceive the significance of the data obtained by cytogeneticists indicating that:

a) there is wide quantitative and morphological variability of chromosomal HRs at the population level;

b) the number of chromosomal Q-HRs in the genome of populations depends on the ecological conditions of the places of their permanent residence: the number of Q-HRs in permanent residents of low geographical latitudes is significantly higher than in natives of high latitudes and high altitudes;

c) the number of Q-HRs has adaptive significance when the human adapting to the extreme climate of the Far North or high mountains;

d) the number of Q-HRs in individuals belonging to different age groups is different: children have more Q-HRs than people from older age groups. However, it has been established that the number of Q-HRs does not change with age and remains constant throughout a human's life. The predominance of individuals in the population with less Q-heterochromatin in the genome may be due to the fact that they have some selective advantage and may live to older ages. Presumably, they are more resistant to cold and its harmful effects;

e) the number of Q-HRs in the genome has relations to the development of such purely human forms of pathologies as obesity, alcoholism, drug addiction and high-altitude pulmonary edema;

f) chromosomal HRs forming the basis of the condensed chromatin are involved in thermoregulation at the level of individual cells (cell thermoregulation);

g) individuals in a population differ in the level of body heat conductivity depending on the number of HRs in its karyotype [18-35].

In turn, those who study HC at the level of individuals and populations cannot realize how few functions ncDNAs perform, despite the fact that they occupy 98% of the DNA in the human genome. They are particularly surprised that the roles ascribed to them, such as the organization of nuclear domains and regulation of gene activity, are in fact only a tiny fraction of the total number of ncDNAs.

Objections to the generally accepted assertion that the packaging of genetic material and the regulation of gene expression is considered the most important role of chromatin are as follows: 1) The HC component of chromatin has come a long way of evolution, which started from small regions that do not encode repetitive DNA and ended with the formation of a higher form of chromatin organization, such as chromosomal HRs. At the same time, euchromatin did not undergo significant changes; 2) Chromosomal HRs, in turn, also underwent significant evolutionary changes in higher eukaryotes, which started from C-bands in plants, insects, invertebrates, fishes and amphibians ended with the emergence of a new type of constitutive heterochromatin - chromosomal Q-HRs - in the genome of three higher primates. However, we do not know that, in along with the evolution of HC in higher eukaryotes, the mechanisms of their cellular metabolism have changed significantly. In addition, the dense packaging of heterochromatin has long been thought to form the basis for chromatin properties such as transcriptional repression and inaccessibility of DNA to various factors. However, the results of the special studies presented in vivo show that both hetero - and euchromatin are localized at the periphery of the interphase nucleus, leaving its center without chromatin [1].

For our part, we believe that such fundamental structures as nucleosomes, cell nucleus, mitotic chromosomes, chromosome bands, biological sex, species, the Cambrian Explosion, circulatory system, multicellular and homoeothermic organisms, including modern humans, could not have arisen only due to accumulation and favorable mutation of structural genes, but are the result of long evolution of ncDNAs [35-38].

Results and solution

In fact, one can understand molecular biologists who do not accept the assertions that, for example, chromosomal HRs are related to adaptation, the occurrence of some forms of human pathologies, or cellular thermoregulation. After all, for them, if no RNA is transcribed from DNA with subsequent translation, then we should not expect any specific effects or functions from it. Nevertheless, some ncDNAs turned out to be able to organize complex supramolecular structures, such as nucleosomes, cell nucleus, mitotic chromosomes, chromosome bands, condensed chromatin and HRs, capable of performing different functions.

Based on the above, it can be defined that HC is obligate, non-variable regions consisting of short, highly repetitive ncDNAs that mainly form mitotic chromosome bodies and organizes a dense layer of condensed chromatin around the cell nucleus. Chromosomal HRs are the highest level of supramolecular organization of HC, which form structures capable of performing novel functions and effects. They participate in the formation of condensed chromatin, nucleoli, chromocenters, and other membranelles nucleus bodies. Unlike HC, chromosomal HRs are prone to wide variability. As a distant analog could be given the example of coal, graphite, diamond and graphene, which having the same chemical composition differ significantly in their physical properties due to the different organization of the constituent elements.

Thus, despite enormous efforts aimed at elucidating the biological role of ncDNAs in general, HC and HRs in particular, we are still far from our goal.

There are many reasons for this, and they are well known. The issue discussed here is only part of the problem. Contradictory assessments of the results of studies conducted at the molecular and chromosomal levels have led to a slowdown, if not complete cessation of works devoted to the study of the molecular organization and variability of HRs. For example, the last article devoted to human chromosomal Q-HRs was published in 2006 [7]. This circumstance, of course, does not contribute to the solution of the problem. The way out of the current situation seems to be in recognizing that the surrounding world is large and the methods of studying it can be diverse. In other words, molecular biology alone cannot solve the problem; you need some guiding biological idea.

Acknowledgments

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.

Conflicts of interest: none.

Funding: Funding has not been received for the study.

Statement of Consent/Ethical approval: Not required.

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