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Review Article

Cell thermoregulation hypothesis: its origin, material basis, mechanisms and meaning

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Abstract

The accumulated knowledge about the chromosome structure, redundant DNA and an interphase nucleus inevitably raises, at least, two questions: (1) Why are there so much non-coding DNAs in chromosomes of higher eukaryotes and (2) what is the role of their organization in interphase nucleus on cellular function? These questions in cell biology are attracting increased attention as the genomes of higher eukaryotes are being sequenced. Based on investigations of chromosomal heterochromatin regions variability in human populations, condensed chromatin (CC), interphase nucleus and redundant non-coding DNAs in the genome, an attempt is made to justify the view of possible participation of CC in cell thermoregulation. 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.

Keywords: Cell Thermoregulation; Condensed Chromatin; Q-heterochromatin; C-heterochromatin; Human Body Heat Conductivity; Human Adaptation

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Introduction

A fundamental feature of genome in higher eukaryotes is the presence of two types of euchromatin genetic material: and heterochromatin. Euchromatin, the conservative portion of the genome, contains structural transcribed genes, while heterochromatin, the variable portion of the genome, is predominantly composed of nontranscribed repeated DNA sequences. Heterochromatin is distributed in the chromosomes of all plants, animals and man,

accounting for 10% to 60% of their genome. Heterochromatin regions account for about 15% - 20% of the human genome [1-3].

To-date two types of constitutive heterochromatin are recognized: Q- and C-heterochromatin [4-6]. There are 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*) [7,8]. Heterochromatin and euchromatin occupy different nuclear domains. Heterochromatin is



usually localized in the periphery of the nucleus and is attached to the nuclear membrane. In contrast, euchromatin the active chromatin occupies a more central position. The role of heterochromatin remained a mystery, as its frequent polymorphisms did not appear to have any visible phenotypic effect.

Origin of the cell thermoregulation hypothesis

Despite the fact that chromosomal Qheterochromatin regions (Q-HRs) exist in the genome of three higher primates, their broad quantitative variability is only inherent in human populations [9-24]. By studying the variability of chromosomal Q-HRs in human populations living permanently in different climatogeographic conditions of Eurasia and Africa, we have obtained data indicating their possible selective value in adapting to some extreme conditions. In particular, it turned out that there is a certain regularity in the distribution of the amount of chromosomal Q-HRs in the genome of human populations: changes in the amount of Q-HRs have a tendency to decrease from southern geographical latitudes to northern ones, and from low-altitude to high-altitude ones [11-19]. However, the possible cause of this phenomenon remained to us unclear. Based on investigations of chromosomal O-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 CC in cell thermoregulation. 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 [25,26].

Material bases of cell thermoregulation

The material bases of cell thermoregulation (CT), we believe, are condensed chromatin, localized around the nucleus, chromosomal HRs of nucleoli and chromocenters [25,27,28]. Everything that is known about CC, 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 [29]; (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 [5,30-36];

(3) There are observations of contacts of nucleolus with secondary constriction of human chromosomes 1, 9 and 16, containing the largest C-HRs blocks in the human karyotype [37]. Thus, the CC and chromosomal HRs being the densest formations in the interphase cell must have the appropriate thermal conductivity with all the ensuing consequences.

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.

Apparently, Nature chose a very simple and effective solution: its increased heat conductivity of the nuclear areas where excess heat is produced into temporary structures in the form of CC around the nucleus, chromocenters and nucleoli. The essence of the proposed hypothesis is the assumption that the CC, chromocenters, along with the nucleolus participate in cell 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 condensed chromatin in the cytoplasm.

The question arises: why are three different structures required to remove excess heat from the interphase nucleus: a dense layer of peripheral condensed chromatin around the nucleus, nucleoli and chromocenters? The answer may be the following. A dense layer of condensed chromatin 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, besides similarity in molecular composition (hr DNAs), they are morphologically closely related to peripheral condensed chromatin. 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 [25,27,38].

The assessment of cell thermoregulation on the example of man

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 [39,40]. Virtually, there is nothing new in the idea that the body of the human should possess some heat conductivity. Nevertheless, it has not drawn the attention of nor physicists, neither physiologists for the present as the important physical characteristic of a human body. Apparently, it is connected with known physical heterogeneity (in sense, density) of a human body. Probably that's why; we did not manage to find in the literature not only a special method, but even any attempt to estimate body heat conductivity (BHC) of live organisms.

In thermo physics, measurement of heat conductivity of solid bodies (f.e. metal) is carried out by determination of heat conductivity coefficient by a calorimetric method. Transfer of heat occurs through a metal rod, the ends of which are placed in a calorimeter with the water taken at temperatures T1 and T2 (T1 > T2). It is obvious that direct transfer of a method of measurement of the heat conductivity, applied in thermo physics is unacceptable to a human body both for technical and ethical reasons.

Since the literature does not have a special method for measuring human BHC, we could only use the method of trial and error to find the areas of the body, which at least allow to roughly estimating the transfer of thermal energy from environment into body and from one body part to another. For example, hand is



selected from ethical and technical considerations [39,40].

The principle of the method is very simple. To evaluate human BHC it is necessary to: a) create a temperature gradient between a certain part of the human body and the environment. To this end, the left hand is immersed in a water bath, where the water temperature is set at 9 °C higher than the temperature of the left palm of the individual under study; b) for 20 minutes, the temperature of the right palm is measured every minute (the transition of thermal energy from one part of the body to another) using a non-contact thermometer used in medicine; c) the time of onset of the temperature maximum on the right palm (rate of transition of thermal energy) shall be recorded.

BHC estimation of individuals should be conducted indoors at a temperature of $20 \,^{\circ}\text{C}$ – $22 \,^{\circ}\text{C}$. Measuring the left palm temperature was necessary for preparation of 'hot' water. 'Hot' water was prepared by adding of number nine to the thermometer reading. For instance, if an individual's palm temperature was 31.0° C, then 'hot' water temperature for his hand should be 40.0° C. Certainly, no fundamental constant of a human body is at the back of this number. But it is also undesirable to increase the temperature of 'hot' water more than 9 °C. In that case, we could face with denaturation of proteins in cells of individuals whose temperatures of palms are close to that of armpit.

The examinee plunges slowly his left hand up to the wrist in water bath (volume ~ 6.0 liter), which maintains water temperatures at a given mode until the end of the experiment. Throughout the whole thermal load, the right palm temperatures were minutely measured. Measuring the right palm temperature was necessary for determining the amount and rate of thermal energy passed from the wrist of left hand to the wrist of right hand. The assessment of the BHC is carried out as follows: if the temperature peak occurred within the first 5 minutes, it is assumed that such an individual has a high heat-conducting body; from 6 to 10 minutes 6 middle from 11 minutes and above as a low heat-conducting body [40].

Thus, to indirectly assess the rate of transition of thermal energy from the nucleus to the cytoplasm in humans, we use the method of assessing the BHC at the level of the whole organism. For practical purposes, to assess the level of human BHC may be not necessarily measure the rate of transition of thermal energy from the nucleus to the cytoplasm in its cells [28,39-41].

Main results

Thereby, as a whole our results show that: a) individuals in a population differ from each other on the level of 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 differ on the average by higher BHC than population of high altitude ones; e) natives of low latitudes differ on the average by higher BHC than populations of high latitudes; f) weight, height, types of body constitution (nomothetic, asthenic and hypersthenic), pulse rate and level of arterial pressure do not effect on the variability of BHC in population [39,40,42,43].

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 low geographical latitudes to high ones, and from low-altitude to high-altitude ones [9-27,40-47].

Human uniqueness in addition to all his known characteristics is that he is the only who managed to populate the whole Earth surface including such extreme areas as Far North and high altitudes remaining single tropic biological species. Moreover, all this took place in a short period of time (around 30,000 - 50,000 years), an unprecedented fact in life evolution [48].

Unlike many animal species, man is unstable to live in an extreme cold environment. He is basically a tropical homoeothermic. Naturally, all three effector thermo regulating systems mobilize: heat production, heat loss and thermoregulatory behavior. Though being important, they cannot be effective at long-term perspective. We suppose that H. sapiens, besides those inherent in all mammals possesses an additional but very fine and simple mechanism of thermoregulation. In the present case, in order to preserve temperature homeostasis under different environmental conditions, in addition to physiological, behavioral and biochemical mechanisms such as wide intra population variability by BHC was used [25,26,28,39,41,45]

On the whole, we see efforts for maintaining temperature homeostasis under conditions different from climate of the Eastern Africa as individual with follows: 1) an less chromosomal Q-HRs in the high latitudes effectively maintain more temperature homeostasis in organism because of low BHC, permitting to preserve additional amount of produced heat in organism longer and slow down the body cooling rate from external cold;

2) an individual with high BHC in the high latitudes, constantly loosing additional amount of metabolic heat through conduction which is necessary for organism in terms of cold climate and exposing to relatively fast cooling because of cold, has to produce larger amount of heat and/or consume more high calorie food for heat production, which is not always simple; 3) an individual with low BHC in the low latitudes (where environment temperature is higher than body temperature) besides his own internal heat production receives additional heat from environment by means of conduction, which, as it is known, is not used in useful physiological work. That is why these individuals' bodies overheat faster and they have to return heat surplus (through sweating, polypnoe, forced rest, behavioral reactions and etc.) to environment at the cost of significant decrease of physical and mental activities that finally negatively influences on their adaptation to hot climate; 4) an individual with big amount of Q-HRs in genome in the South having body with high thermal conductivity perhaps adapts better to high temperature of environment, more effectively leveling temperature differences in different parts of the body and faster directing surplus heat flow from organism to environment, including the way of heat radiation.

The example from the modern sport life can better illustrate our understanding of BHC role. More and more countries situated at low latitudes have started taking part in the world sport movement. The most notable in this process is that, natives of this region achieve great success in sports, requiring (in addition to other factors) effective heat-loss (football, professional boxing and marathon race). While sportsmen from high latitudes prevail in water and winter sports and also in mountaineering [10,12-14,19,22]. Since southerners' bodies, as we think, have relatively high heat conductivity [39] it is not surprising, that they are successful in sports, which require effective heat-loss. Indeed, a sportsman with high heat conductivity cannot make much progress in water sports due



to the fact that their body cools rapidly. However, this sportsman can be more successful in sports which require effective heat-loss.

Since wide quantitative variability of chromosomal Q-HRs was detected only in human population but alimentary obesity, alcoholism and drug addiction relate to the group of "purely human being pathology" we thought that it would be quite logically to study peculiarities of BHC of such diseased individuals. It was established that among patients, drug addicts had the highest BHC, then alcoholics and individuals suffer from obesity [42,43,49,50].

We assume that one and the same dose of alcohol taken by persons with different BHC may result in different consequences. So, in the individual with low BHC the alcoholic intoxication begins after he takes a relatively large amount of alcohol for one drink because of lower leveling of temperature in different parts of body that finally leads to stronger intoxication with a hang-over syndrome than with persons with normal or high BHC. It is due to the longer time needed for heating the whole body that is necessary for having a sense of thermal comfort in the whole organism. Drug addiction also appears due to the desire to have a sense of thermal comfort as soon as possible, but this time this "pleasure" is a result of a "drug overcooling" of the body that have subsequent emotional, or other experiences. Individuals with lesser amount of Q-HRs in genome are more prone to develop alimentary obesity. In individuals with low BHC even if they take normal amount of food, fat will be stored in more amount than in persons with high BHC [49].

It is known that with age the number of women in a population begins to prevail over men. It is possible that a certain advantage of women is explained by their relative resistance, as compared with men, to cold and stress, hunger and even loss of blood because they have less heat conductivity body. In order to be convinced of the relative resistance of women to cold and stress, we shall given several known examples: a) pearl divers in Korea are exclusively women -"ama" [51]; b) women succeed best in swimming across the cold water of La Manche [51]; c) during the period of the Leningrad blockade during the World War II about 80% of the women survived despite the fact that being in the rear they had a lesser access to food; d) at the reproductive age women, without detriment to their health lose every month from 120 to 300 ml of blood during menses and about 300-500 ml of blood even during normal labor.

Place of cell thermoregulation in maintaining of temperature homeostasis

A change in environmental temperature is one of the most common stresses experienced by a wide range of organisms from bacteria to plants and animals. Organisms respond to temperature stress at the molecular and organism level. The response of prokaryotic and eukaryotic systems to heat-shock stress has been investigated widely in a large number of organisms and model cell systems. The expression of heat-shock proteins is a universal response found in all living cells [52,53]. All organisms from prokaryotes to plants and higher eukaryotes respond to cold shock in comparatively similar manner. Generally, cells respond to cold stress by expression of a small group of proteins, the so termed cold shock proteins [54-56]. The existence of thermoregulation at the level of the whole organism is a well-established fact. Based on the study of the distribution of chromosomal Q-HRs in different human populations, in the norm and pathology the hypothesis of the possibility of the existence of thermoregulation at the level of individual cells is proposed. The essence of the hypothesis of cell thermoregulation is to reduce the temperature difference between the nucleus and the cytoplasm, when the nucleus temperature becomes higher than the temperature of the



cytoplasm [25,28,41]. 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. 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 [25,26]. As we suppose, during his evolution man, possibly owing to chromosomal Q-HRs, had an additional and very flexible tool to ensure more effective thermoregulation, allowing him to master almost all the ovkumene [27,33,41]. H. sapiens is not only devoid of a more or less large anatomic structure, but also has no protein or enzyme that has no analogue in the animal world. The fundamental structural characteristic of man is the presence of chromosomal O-HRs in its genome which he has inherited together with the chimpanzee and the gorilla - from one common ancestor. Apparently, the physiological thermoregulation functions relatively independently from CT as evolutionally new adaptive system. From our point of view. CT can be the missing link. which should fill the "gap" between the thermoregulation systems, functioning at the molecular level and the whole organism. It is likely that we faced with physiological problem which is a new and alien for classical courses of physiology.

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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.

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