Cell Thermoregulation: Reality or just a logical Construction?

AI Ibraimov

Laboratory of Human Genetics, National Center of Cardiology and Internal Medicine, Bishkek, Kyrgyzstan

*Corresponding Author: A.I. Ibraimov, Laboratory of Human Genetics, National Center of Cardiology and Internal Medicine, Bishkek, Kyrgyzstan. Email: ibraimov_abyt@mail.ru

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Abstract
The existence of biological thermoregulation at the molecular and organism (physiological organ-based system of thermoregulation) levels is well known. The possibility of thermoregulation at the level of individual cells is discussed. By cell thermoregulation (CT) is meant the elimination of the temperature difference between the nucleus and cytoplasm, when, for one reason or another, the level of thermal energy in the nucleus becomes higher than of the cytoplasm. The CT hypothesis can shed light on some scattered facts and observations, known in different areas of biology and medicine, but without rational explanation. It is assumed that CT originated from the evolution of ncDNAs in the eukaryotic genome, and its material basis is condensed chromatin. Although the CT hypothesis has not yet been directly experimentally confirmed, nevertheless, its existence can be determined by indirect methods at the organism level.

Keywords: Cell thermoregulation; Condensed chromatin; Chromosomal heterochromatin regions; Human body heat conductivity

Introduction
The metabolism of organisms proceeds well only within narrow ranges of internal physical and chemical conditions. Among the physical factors affecting metabolism, the first place is occupied by temperature. Temperature has a fundamental influence in all chemical and biochemical reactions. It influences reaction rates, equilibrium amounts, viscosity, solubility, molecular arrangements and numerous other parameters. Virtually, the life, which is known to science, with rare exceptions, is possible at positive temperature.

Maintaining the relative constancy of the internal temperature (temperature homeostasis) is a necessary condition for normal life and its highest form-mammals-are able to keep a relatively high temperature in the body preserving a very high level of metabolism. Many of the mechanisms that organisms possess serve to maintain this relative internal constancy.

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 [1,2]. 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 [3,4]. The existence of physiological thermoregulation at the level of the whole organism is a well-established fact.

However, the question of whether thermoregulation can also exist at the level of individual cells remains open. This situation may be explained by the fact that the internal sources of thermal energy (thermogenesis) in organisms are well known: cellular metabolism, muscle contraction and active ion transport. Organisms receive energy from the environment in the form of potential energy contained in the chemical bonds of molecules of fats, carbohydrates and proteins. Energy metabolism of cells (formation, transfer and transformation) occurs mainly in mitochondria. Since heat cannot be used by the body as an energy source, some of the energy released during combustion is stored by the formation of ATP. About 80% of the energy used in muscle contraction is lost in the form of heat due to the low efficiency of its transformation, and only 20% is converted into mechanical work. Ion transport takes place on the plasma membrane. As an additional product of the vital activity of cells, thermal energy is not used to perform biologically useful works, and therefore, it should be timely removed outside the cell. Thus, thermal energy is produced in the cytoplasm, and from there it is removed in the interstitial fluid.

Facts and observations

There are facts and observations, seemingly unrelated, but indirectly indicating the possibility of thermoregulation at the cellular level. Some of them are listed below. Let's start with the cell nucleus:

1) At both light and electron microscopy, the nuclear periphery in most cell types is predominantly occupied by heterochromatin in the form of condensed chromatin (CC), 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;
2) Lamina (inner lining of nuclear envelope) in the cells is located between the CC and the inner nuclear membrane. In principle, a lamina could also be located outside the nuclear membrane (on the plasma membrane as the cell wall in plant cells or in prokaryotes) if the lamina task is limited only to strengthening the strength and shape of the nucleus;

3) The biological significance of the chromocenters that form in interphase nuclei is still unclear. Chromocenters in fact vary with cell type and stage of development, both within and between species;

4) There are observations of contacts of nucleolus with HRs of secondary constriction of human chromosomes 1, 9 and 16, which do not contain ribosomal cystrones. The frequency of associations of acrocentric chromosomes with chromosome 1 grows with an increase of the size of its heterochromatin block. Preferential spatial proximity of sex chromosomes HRs to nucleoli in interphase nucleus is a well-established fact;

5) Chromosomal HRs (C- and Q-heterochromatin) passed a long way of evolution, beginning at one-celled eukaryote as C-heterochromatin, completed with the emergence of a new kind of constitutive heterochromatin - Q-heterochromatin - in the ancestors of three higher primates (Homo sapiens, Pan troglodytes, Gorilla gorilla).

There are other facts and observations not directly related to the cell nucleus, but having, as we believe, some relation to the issue discussed here. So, for example:

1) The mechanism(s) of origin of multicellular organisms has not yet been clarified;

2) There is not idea of the cause(s) of the origin of homoeothermic animals;

3) The biological role of B chromosomes is not clear;

4) It is generally accepted that to maintain temperature homeostasis in the body, along with behavioral and cultural reactions (f.e.: in humans), enough organ-based system of physiological thermoregulation;

5) Genetic mechanisms of human adaptation to such extreme conditions as the high-altitudes and the Far North have not been clarified;

6) The causes for the existence of purely human forms of pathology (obesity, alcoholism, drug addiction and atherosclerosis) have not been established;

7) There is 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 in the population genome have a tendency to decrease from southern geographical latitudes to northern ones and from low-altitude to high-altitude ones. [14-29].

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 [30]. 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’ [31]. 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.

Discussion

We believe that there may be some internal connection between the above disparate facts and observations. Namely, they all, directly or indirectly, are related to cell thermoregulation (CT), by which we mean the elimination of the
temperature difference between the nucleus and the cytoplasm, when the nucleus temperature, for one reason or another, becomes higher than the temperature of the cytoplasm.

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 that 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 envelope. 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. Since the proposed idea is based on cell phenomena, from the author’s point of view, Nature ‘found’ a very simple and effective solution: it increased its heat conductivity through compression of the internal layer of the nuclear membrane by CC and lamina [5-11].

How can the above facts and observations be related to the proposed cell thermoregulation? The fact that the nuclear periphery is occupied by heterochromatin in the form of a layer of CC and lamina and they are connected to nuclear membrane with one of the nucleoli has long been known. The location of heterochromatin on the periphery of the nucleus is usually associated with its genetic inertness, believing that the active biochemical processes occur closer to the center of the nucleus. The basis for this statement is such an example as the detection of human chromosomes 19 and 20, known with an extremely small number of HRs, which are often found in the center of interphase cells. We believe that the genetic inertness of chromosomal HRs may not be the only reason for their localization and compaction on the periphery of the nucleus.

It seems highly probable to us 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 too liquid to perform their function normally. Of course, to remove excess heat from the nucleus cell membrane layer would be ideal because of their thickness. However, 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.

Despite the fact that chromocenters and B chromosomes were discovered more than a hundred years ago, their biological meaning is still not clear. It is highly likely that in order to protect the nuclear membrane from the harmful effects of high temperature emanating from the nucleus, chromocenters are formed, and in some cases, Nature uses the services of B chromosomes. The essence of the hypothesis is the assumption that the chromocenters and B chromosomes, along with the nucleolus 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 nucleus [9-11].

The observations that human chromosomes 1, 9 and 16, which do not contain ribosomal cystrones, but have a big HRs blocks and contacts with nucleolus still have no explanation [32]. In the same situation there is a preferential spatial proximity of sex chromosomes HRs to nucleoli in interphase nuclei [33]. Our position on this issue we have repeatedly discussed the essence of which is that the redundant ncDNAs in the form of chromosomal HRs has no phenotypic expression and bears no specific function because HRs in CC participate in thermoregulation at the level of individual cells.

CC, being the most densely packed material, apparently has the greatest heat conductivity in the interphase cell [7]. We have devoted special researches to possible mechanisms of origin of multicellular organisms, homeothermic animals, circulatory systems in multicellular organisms and their supposed connection with cell thermoregulation. [34, 9-12].

Question about CT probably has one more hypothetical aspect, namely, why the nucleus for removing excess heat come running to the help of chromocenters and nucleoli? It seems to us highly probable that these means are used, in addition to the removal of thermal energy, to protect the physical properties of the nuclear envelope. So, for example, if the heat was taken evenly around the entire circumference of the nucleus, then, perhaps, there would be a real danger of damage to the entire nuclear envelope. If that was the case, so then it would be safer to take the excess heat outside the nucleus locally using the chromocenters and the nucleolus, and then to the interstitial fluid via cytoskeleton filaments.

Indeed, cytoskeletal filaments can reach from one end of the cell to the other, spanning tens or even hundreds of micrometers. It is known that ‘plectin and other plakins can interact with protein complexes that connect the cytoskeleton to the nuclear interior. These complexes consist of SUN proteins of the inner nuclear membrane and KASH proteins (also called nesprins) of the outer nuclear membrane. SUN and KASH proteins bind to each other within the lumen of the nuclear envelope, forming a bridge that connects the nuclear and cytoplasmic cytoskeletons. Inside the nucleus, the SUN proteins bind to the nuclear lamina or chromosomes, whereas in the cytoplasm, KASH proteins can bind directly to actin filaments and indirectly to microtubules and intermediate filaments through association with motor proteins and plakins, respectively. This linkage serves to mechanically couple the nucleus to the cytoskeleton and is involved in many cellular functions, including chromosome movements inside the nucleus during meiosis, nuclear and centrosome positioning, nuclear migration, and global cytoskeletal organization’ [35]. We believe that the excess thermal energy is removed outside the nucleus to the interstitial fluid, mainly by cytoskeleton, and not by diffusion and convection, as is commonly believed [30].

It is possible that chromosomal segments (G, Q and R bands) as heterochromatinin regions (HRs) also participate in CT. It has been demonstrated that chromosomal G, Q and R bands are absent in plants and are always present in chromosomes of higher vertebrates (reptiles, birds and mammals). In case of invertebrates, fishes and amphibians, it is difficult to reveal
the G, Q and R bands. In some insect’s part of the chromosomal segments is equivalent to C bands, and G, Q and R bands apparently are absent. The banding technique (differential staining of chromosomes) used most successfully in plants corresponds to C banding, and the resulting darkly stained bands probably also represent C-heterochromatin. Chromosomal bands, which we find with differential staining techniques, are best exhibited in warm-blooded vertebrates (birds and mammals), then in amphibians and reptiles, and worst of all in insects and plants [5-7].

The banding technique used most successfully in plants corresponds to C banding, and the resulting darkly stained bands probably also represent C-heterochromatin [36]. Difficulties of revealing variable segments in plants, insects, other invertebrates, fishes and amphibians are frequently explained by methodological difficulties. But we believe that it is not connected to the reproducibility of techniques of differential staining and reflects a true state of affairs, namely, the density of chromosomal bands in birds and mammals [37].

We assume that the chromosome segments of the higher eukaryotes have undergone their own evolution in the direction: C-heterochromatin → G+ and Q+ bands → Q-heterochromatin as response of the CT for denser packaging of ncDNAs (for the increase of the heat-conducting effect of CC between the nucleus and cytoplasm). For example, at a later stage of evolution of the mammals in Africa in the ancestors of three higher primates (Homo sapiens, Pan troglodytes, Gorilla gorilla) besides C-heterochromatin, a new type of constitutive heterochromatin, Q-heterochromatin, appeared [38, 39]. Obviously, this is related to the increase of the metabolism intensity in their organism, and, accordingly, the further improvement of the intracellular thermoregulation. In this case the Q-heterochromatin is not only a new type of constitutive heterochromatin, but possibly an additional ‘center of condensation and attraction’ for more dense packaging of adjacent inactive chromatin, thus, increasing the heat conducting effect of CC in the interphase cell of three higher primates.

The elucidation of the relationship between temperature and base composition of DNA of animals can now be better understood due to the fact that it has been discovered that temperature actually changes the genome of higher organisms. Bernardi and Bernardi (1986) [40] have made an extensive study of the base composition of the DNA of poikilothermic (fishes, amphibians and reptiles) and of homeothermic (birds and mammals) vertebrates. Both the ncDNAs and the sequences that code for proteins turned out to be much richer in guanine cytosine in homeothermic than in poikilothermic animals. To test whether this canalization of DNA evolution could be ascribed to the action of temperature they compared the base composition of related species of fishes living in cold (20-25 °C) and in warm (37-40 °C) water. Again guanine-cytosine rich DNA appeared in the fishes inhabiting warmer water. They concluded that the temperature appeared to be a main factor in the canalization of the evolution of DNA. Thus, it is possible to expect that in higher vertebrates, such as birds and mammals, thermoregulation ensuring constancy of cell temperature canalizes the change of nucleotide sequences of DNA.

Our long-term studies of the wide variability of chromosomal HRs in human populations living in different climatogeographic conditions of Eurasia and Africa, in the norm and pathology suggest that they seem to be directly involved in CT. This is evidenced by experimental studies on the relationship between the number of chromosomal Q-HRs in the genome and the level of human body conductivity [12,13]. This hypothesis is confirmed by data on a statistically significant relationship between the human body heat conductivity (BHC) and his ability to adapt to extreme climatic conditions of the Far North of Siberia and the Pamir and Tien Shan high altitudes [41,13]. Connections
between the level of BHC and vulnerability of man to the purely human forms of pathology (obesity, alcoholism, drug abuse, and atherosclerosis) is further confirmation of the reality of CT, the phenotypic manifestation of which is the level of the BHC of the individual in a population [42-44].

**Concluding remarks**

From the above may be the impression that our assumption about the existence of thermoregulation at the level of individual cells is the result of purely logical conclusions. Without denying this, we still believe that there are indeed facts and observations whose existence requires a rational explanation. The most important of them is the heat that forms as a result of the functioning of the nucleus, which must somehow be removed outside it. The combination of data obtained using the technique of nanothermometer show that the heat in the cell is not distributed evenly. For example, in the cytoplasm the ribosome and mitochondria, and nucleoli in the nucleus, show the highest temperature [45-51]. These data will have a rational explanation within the hypothesis of CT.

It is supposed that any serious scientific hypothesis can be verified. But what conceivable experimental and natural system can be offered to verify the foregoing idea? It might be reassuring if someone managed to show *in vivo* the following: at the change of temperature by 1°C above or below 37 °C, the speed of transfer of heat from the nucleus to the cytoplasm in a human cell depends, for example, on the amount of chromosomal HRs in the genome of the given individual.

In some sense Nature seems to have done us a favor and conducted part of work for us so that we can understand its ‘intention’. How else would it be possible to explain the following: (1) In the process of evolution of ncDNAs in the genome of higher eukaryotes appeared as repeated sequences, part of which formed CC in the interphase nucleus. In plants C-heterochromatin was formed high repetitive DNAs. In chromosomes of higher vertebrates, in addition to C-heterochromatin, G+ and Q+ bands appeared which also represent repetitive DNAs. (2) Chromosomal bands, which we find with differential staining techniques, are best exhibited in warm-blooded vertebrates (birds and mammals), then in amphibians and reptiles, and worst of all in insects and plants. (3) The internal temperature conditions in animals are more stable than in plants. Amphibians and reptiles have a body temperature which is partly below the ambient one. Some reptiles, such as the iguana, already show a body temperature that is maintained above that of the environment. Birds and mammals control temperature homeostasis within very narrow limits. (4) Thermoregulation in birds and mammals is mainly achieved by the acceleration of the metabolism, which leads to a rise in heat production in cells. Birds and mammals developed organ-based control of thermoregulation that regulates their body temperature. They have a neural ‘thermostat’ situated in the hypothalamic region of the brain. (5) The order Carnivora is quite a unique group among mammals as regards CC features. Identification of chromosomal HRs in them by means of C-technique is extremely difficult. And in some representatives of the genus *Felix* the existing techniques of differential staining of chromosomes fail to identify even centromere heterochromatin [52-54]. Apparently, their known mode of life requires lower body heat conductivity.

In humans, CT seems to involve most of the components of the genome (CC around the nucleus, nucleoli, chromocenters, B chromosomes, HRs of chromosomes 1, 9, 16, all acrocentrics and sex chromosomes, G+ and Q+ bands), as well as some cellular structures (lamina, cytoskeleton and nuclear envelope). As is known, changes caused by temperature at the level of the body, individual organs or tissues, such as poikilothermic animals, in general, reversible, which cannot be said about the cell nucleus (f.e.: errors in repair, recombination, rearrangement, replication,
transcription etc.). This is not unexpected, because the purpose of temperature homeostasis, it is primarily to ensure the normal operation of cells.

In essence the idea proposed here is reduced to the evolution of the genome structure and the physiology of the whole organism in higher eukaryotes going in parallel to counteract changes of temperature in the ambient environment for more effective preservation of constancy of temperature of the internal cell environment. The outcomes of such a parallel evolution were: (1) the appearance of different kinds of condensed chromatin (C- and Q-heterochromatin, G+ and Q+ bands, sex chromatin body; B-chromosomes, inactivation one of the X chromosome in mammals) at a cell level and (2) formation at an organism level of a complex organ-based physiological system of thermoregulation.

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