Chapter

The Energy as a Determinant Factor in the Ethiopathogeny of Chromosomal Abnormalities. The Unsuspected Bioenergetic Role of Melanin

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Abstract

In the study of chromosomal abnormalities, in genetics, and in medicine in general, attention is rarely paid to the role of energy in the healthy subject and in the sick patient. The research on the chromosomal anomalies that are constantly published, does not mention the energy necessary for the biochemical processes involved in the function, replication and formation of genes, to be carried out in an adequate way. It seems that it is assumed that energy levels are always fine or at least did not have a significant role in the conditions associated with what we call chromosomal anomalies. A characteristic of the cell nucleus that has gone unnoticed is that it contains neither mitochondria nor ATP, much less glucose. Perhaps because of this, some researchers and clinicians come to think that the nucleus of cells does not require energy. The purpose of this work is to draw attention to the importance of energy levels in all the metabolic processes of the cell; and to make known that glucose is not an energy source, as it is only a source of carbon chains; and finally remark that our body, through melanin, can take energy directly from light.

Keywords: melanin, water dissociation, energy, hydrogen, aneuploidy

1. Background

Diseases attributed to chromosomal abnormalities are currently perceived as a defect occurring at the deepest level of mutations in the complex sequence of nucleic acids and causing biochemical, clinical or physical manifestations. The so-called genetic diseases do not have yet a specific treatment, at most only symptomatic; because the problem has proved more complex than anticipated, as gene therapy in its diverse form has not yielded the expected results; therefore alterations in the bases, or in genes, or in chromosomes, or inclusive in histones have been more extensive and complicated than expected.

The chromosome is called the highly organized structures, made up of DNA and proteins, which contains most of the genetic information of a living being. The DNA double helix is bound to proteins called histones. The histones have positively

charged (basic) amino acids to bind the negatively charged (acidic) DNA. The DNA is wrapped around the histone core of eight protein subunits, forming the nucleosome. The nucleosome is clamped by histone H1. About 200 base pairs (bp) of DNA coil around one histone [1].

Methylation of histone or of DNA usually turns a gene off. Acetylation of histone usually turns a gene on. Phosphorylation is not known what that does. The only thing they have in common is that for them to happen properly, they require energy, and in various ways, not just activation energy.

Prokaryotic cells (bacteria) contain their chromosome as circular DNA. Usually, the entire genome is a single circle, but often there are extra circles called plasmids. The DNA is packaged by DNA-binding proteins.

The bacterial DNA is packaged in loops back and forth. The bundled DNA is called the nucleoid. It concentrates the DNA in part of the cell, but it is not separated by a nuclear membrane (as in eukaryotes). The DNA does form loops back and forth to a protein core, attached to the cell wall [2]. By the way, melanin, in prokaryotics, is in the cell wall mainly.

Chromosomes are fundamental part of genetic information, comprising molecular DNA wrapped in a highly complex form by histones that surround the double helix. Damage or even minute changes to the structure of the chromosomes, genes, nucleotides or histones can lead to diverse health problems and health defects. Having too many or too few chromosomes in a cell can be considered as chromosomal abnormality.

Chromosome abnormalities, even to the nucleotide level, may cast light on the nature of mechanisms whereby normal anatomy evolves, and abnormal anatomy arises. Correlating genotype to phenotype is a formidable challenge exercise [3].

The number of chromosomes, as well as every one of the structures that make up them is astonishingly accurate and is repeated every day from the beginning of time. Then, why are the alterations to whether is in genes or chromosomes? And even more, why are chromosomal alterations not isolated or unique? If the energy source is ATP and therefore mitochondria, why does the cell nucleus have none?

2. Introduction

The chromosome is the heart of a central paradox in evolution. How do species in the three kingdoms remain the same over long periods of geological time and generate enough variability to produce new species, sometimes relatively rapid? [4]. Stability versus change is a crucial dichotomy in molecular biology. The events that bring about stability and change in DNA structure involve processes of replication, transcription and recombination; and since beginning of time, similar mechanisms operate in the three living kingdoms.

Free living bacteria need genetic information and energy to synthesize proteins that means energy expenditure for executing vital functions. Most bacteria have a single chromosome with DNA that is about 2 Mbp (mega base pairs) long (1 Mbp = 1,000,000 base pairs), being the DNA content of different species variable from 0.58 to greater than 9 Mbp of DNA, and some bacteria have multiple chromosomes.

3. Energy and chromosomes

Eukaryotic organisms generally have larger chromosomes than bacteria. In humans, the 5000 Mbp of haploid DNA is distributed among 22 autosomes and 2 sex-specific chromosomes. Larger chromosomes mean more energy expenditure in

many ways. Eukaryotic DNA is in a compartment, the nucleus, which is separated by a phospholipid-containing membrane from cytoplasmic ribosomes and protein translation activity. Cell uses energy in many ways, even to keep the shape, the organization, function, compartmentalization, etc. During cell division, the eukaryotic nuclear membrane breaks down once per cell cycle to distribute the 46 diploid chromosomes equally between 2 daughter cells. We must keep in mind, that any change requires energy, so, every step during cell division need energy to happen, and the amount and type of energy must be same as has been since the beginning of time.

Eukaryotic genomes must be condensed by several orders of magnitude to fit in the largest cell organelle: the nucleus. Compaction of genomes is achieved by coiling the DNA around histone proteins to form a chromatin fiber, which is subsequently folded into complex higher order structures such as loops, domains and compartments [5]. The coiling of DNA and subsequent folding requires energy.

Despite the ubiquitous presence of all major architectural features of genomes, there is considerable variability and heterogeneity in genome organization at the single-cell level [6]. Although the position of chromosomes and genes are non-random in the cell population, their patterns of location are variable among individual cells [7]. This variable location probably has relationship with the concept that every melanosome is unique.

The fundamental variability of genome organization is mirrored by stochasticity in the transcription process itself [8]. Active transcription generally occurs in short bursts at irregular intervals [9], requiring energy in several ways. This pattern of punctuated gene transcription is common to all organisms, particularly widespread in mammals [10]. There is a dynamic binding of transcription factors and chromatin motion [11], requiring both energy expenditure.

The stochastic nature of transcription points to structural heterogeneity of the chromatin fiber and of the genome as a whole, thereby energy requirements must be conceptualized with the same characteristics, as a whole (**Figure 1**).

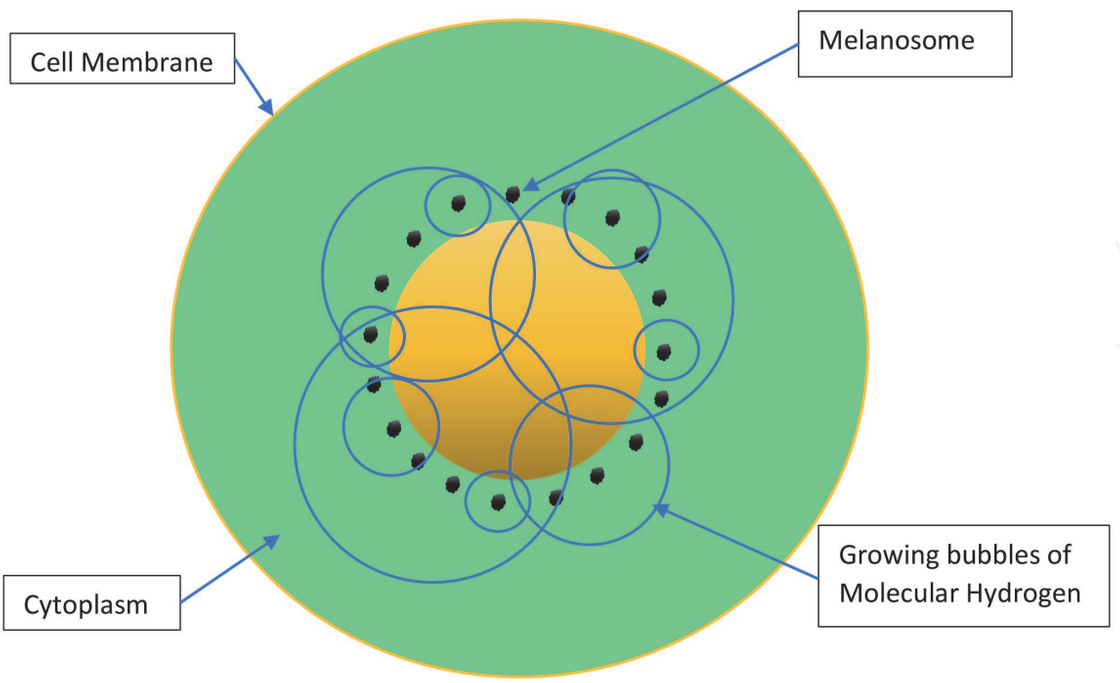

Figure 1.
Diagram to show the organization of melanosomes located in the perinuclear space, forming full envelopment around the cell nucleus. Melanin releases molecular hydrogen (H_2) and molecular oxygen (O_2) symmetrically, in all directions, following the laws of simple diffusion; like growing spheres of energy. These energy bubbles coalescing forming high energy areas inside and outside cell nucleus. These facts explain the energy for the cell nucleus, a zone of high energy expenditure, in absence of ATP and mitochondria.

The large-scale genome structures, such as chromatin compartments, are consistently present in individual cells, but smaller organizational units, such as chromatin domains, are variable between cells [12]. This is congruous with the concept that any melanosome is unique.

The stochasticity observed in gene expression is indeed paralleled by high variability in genome organization [13]. Therefore, although chromatin domains can be observed in individual cells, their boundaries are highly variable. The relative position of individual chromatin domains within compartments varies considerably, and modeling suggest dynamic movement within individual chromatin domains [14], this dynamic movement requires energy.

Looping events are highly variable between cells and are likely to be dynamic (energy expenditure), forming and reforming many times during a single interphase [15]. The cell uses energy in many ways and at the same time, for instance, regulate chromatin loop stability and loop formation, this is a different processes with apparently distinct dynamics that are regulated and impelled when it is necessary with the same energy.

Interestingly, the behavior of the two alleles in the same nucleus is not correlated, which suggests that the variability present is largely intrinsic and not dependent on cell-level variables such as cycle stage [16]. However, energy was not considered as a variable by the authors.

The observations are consistent with a single-cell mapping data showing that individual interactions underlying the formation of chromatin domains and loops are highly variable [17]. By the way, any interaction requires available energy.

Thereby, several observations demonstrate a high degree of heterogeneity in genome organization, suggesting that in individual cells in a population, genomes can assume distinct, albeit related; spatial conformations mediated by short-lived chromatin-chromatin interactions rather than by persistent or pervasive associations. This complex variability does not imply that structural features of chromatin organization are not relevant for gene functions, but rather it suggests that structural heterogeneity may be another layer modulating the stochasticity of gene expression [18]. We must keep in mind that any change requires energy, therefore chromatin organization and gene expression need energy in several, accurate and distinct ways.

Genome organization is a highly complex issue but at the same time is intrinsically flexible and is so strict in terms of energy requirements; furthermore, the two alleles in a cell may be differentially organized which means energy expenditure with a highly accuracy. Genes such as the permanently inactive immunoglobulin loci, as well as the entire inactive X chromosome are located at the nuclear periphery, which are zones of low energy; whereas their active counterparts are found nearer the center of the nucleus [19] that is a high energy zone due to confluence of growing bubbles of molecular hydrogen (H_2) coming from the melanosomes (**Figure 2**) that completely surround the nucleus located mainly in the perinuclear space.

In olfactory neurons, thousands of olfactory receptor (OR) loci that are not expressed are sequestered into a single heterochromatin focus [20]. Thereby, the genome organization and its stochastic nature may be a universal mechanism in establishing differences in the cellular properties of alleles [21], that in turn requires universal energy.

There is little correlation between interactions of the two alleles of the same cell. The allele-specific mapping data demonstrate that the two alleles in a cell generally contact different sets of partners [22]. This contact and relative processes undoubtedly require energy.

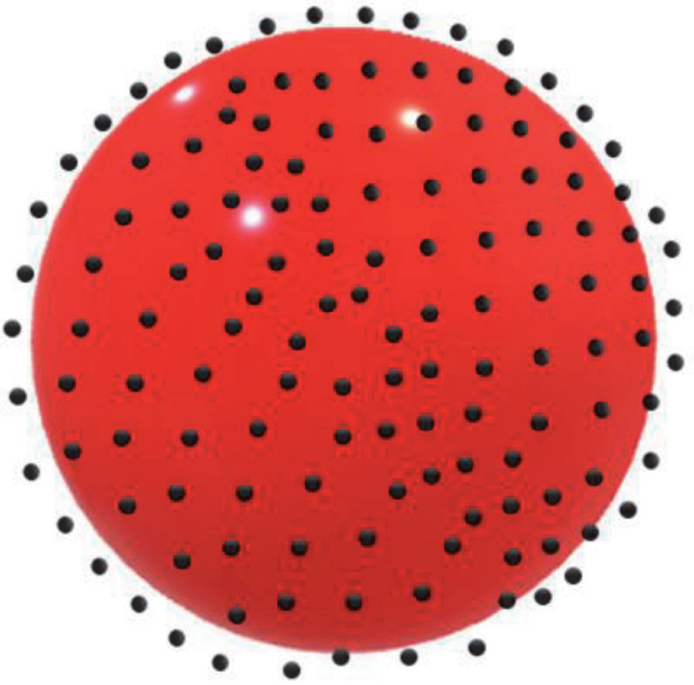

Figure 2.
The main location of melanosomes is in the perinuclear space, covering the entire cell nucleus surface.

The range of distance by most locus pair is roughly 1-μm radius of constraint typically observed for DNA movement in live cells, and long-range events are rare [23], but as small as they are, such movements require energy.

The interaction of chromatin proteins with their substrate is dynamic, even for the architectural proteins that forms "stable" loops, such as CTCF and cohesin [24]. It takes energy both for chromatin proteins to interact with their substrate, as well as to preserve form.

In transgenic systems in *Drosophilia*, colocalization between promoter and their cognate enhancers is necessary for proper expression in cis and trans [25], which also requires the use of adequate energy. It appears that the movement of enhancer elements, as well as their position relative to promoters, is functionally relevant. Again, any movement, any change; requires energy with no exception.

Cancer-relevant translocations occur more frequently among chromosomes that are in spatial proximity, which suggests that variability in spatial organization strongly determines the repertoire of translocations in a given cell type or tissue [26], which means that normal spatial organization requires normal generation and distribution of energy (from melanin).

In some cases, active loci move less than silenced ones [27], whereas, for other genes, actively transcribing alleles show increased mobility [28]. Energy is involved in both cases, indeed.

Furthermore, haploinsufficiency, mutation and down regulation of the architectural protein CTCF, all of which lead to destabilization of chromatin loops and cause more variability in genome organization, have tumor-promoting effects including deregulation of cancer-relevant gene expression programs, disruption of cell polarity and a decrease in patient survival [29]. Cell polarity and all above-cited processes require energy.

It is a long-lasting observation that a cancer cell has a low voltage, which is congruous with low levels of energy that is also consistent with the observation of extensive heterogeneity in tumors [30].

The generation of a stable output from variable inputs is a complex challenge. The extensive structural heterogeneity in genome organization on the one hand,

and on the other hand, the requirement for establishment and maintenance of stable cells states means that the energy from melanin is a major driver in gene expression and genome function, acting as intrinsic noise present in individual cells.

The purpose of the description of some of the processes that happen at the nucleus was to highlight the very accurate and constant energy they require to happen in a timely manner. The generation and distribution of energy, from melanin, is an exact, that when we alter its anatomy, for example, by sectioning the cell membrane, the process is noticeably disturbed and stopped. Hence, the impossibility of properly studying the vital processes happens constantly in the living cell.

Cell nucleus activity is constant, as it happens incessantly both day and night, and cannot be explained based on the dogma of glucose and ATP as energy sources; because the cell nucleus normally does not contain either.

4. Enzymes require energy (from melanin) to carry out its function

The complexity of chromosomes biology can be represented by the enzymes that explain the untangling enigma are topoisomerases, which break and rejoin DNA molecules; allowing individual strands to pass one through another. These enzymes have, at least; two important roles: they provide a swivel to allow processes such as replication and transcription to proceed unimpeded, and they untangle knots and inter-chromosome links between DNA molecules [31].

The phosphodiester bonds that are broken and reformed per reaction cycles [32] require the presence of available energy, however, cell nucleus has neither ATP nor mitochondria. Furthermore, chromatin (DNA + proteins attached to a chromosome) must be folded many times to fit within a cell nucleus; and the highly accurate processes of folding and unfolding also requires energy.

In all organisms, DNA becomes organized in turns of the double strand over the interwound twists of the Watson-Crick helix, named supercoils or σ which represents the number of super-helical turns divided by the Watson-Crick turns of a double helix. The formation and maintenance of this highly complex organized structure requires energy. Supercoiling influences the Watson-Crick structure and, like the spring, the mechanical energy of super negative coils or opposite to the handedness of the Watson-Crick turns; increases exponentially with quantity [33]. However, this kind of energy (mechanical) does not have the properties of accuracy, direction and force that could explain the extraordinary characteristics and dynamics of folded DNA structures.

In the average eukaryotic nucleus, nuclear DNA is several times more concentrated than bacterial DNA. Eukaryotic DNA is wrapped tightly around nucleosomes, generating solenoidal supercoils that condense DNA 8-fold [34], which means significant energy expenditure.

DNA is a plectonemic helix [31], this is two helical strands entwine around each other (**Figure 3**). Two antiparallel strands of DNA are interwound once for every 10 base pairs. Because of this wound configuration, biochemical transactions that involve strand separation require chromosome movement (spin) about DNA's long axis. The processes of DNA replication, recombination and transcription all require DNA rotation, and during DNA synthesis the rotation speed approaches 6000 rpm. This amazing rotation speed indeed requires energy, as any one of the biochemical transactions involved. The question remains: Where come from the energy for the cell nucleus? There is neither mitochondria nor ATP.

Supercoiled branches are dynamic so that opposing DNA in one supercoiling domain interact more than 100 times more frequently with other proteins in the same domain than it does with other proteins bound to a different domain. These

biochemical processes are astonishing accurate, they do not happen by chance, and those rates of domain interactions requires energy in many ways [35].

In the eukaryotic nucleus, enzymes such as RNA polymerase gain access to DNA, which remains histone bound throughout most biochemical transactions. There are complex interactions that require energy in continuous an adequate form. The way in which multiple proteins interact with coated DNA nucleosomes is not completely understood but it is for sure that requires energy.

When DNA is liberated from cells by breaking the peptidoglycan coat, chromosomes form bundled loops that represent domains. Such preparations (called nucleoids) behave as discrete bodies [36]. Every step above described requires energy, which must be in a very precise location, amount, availability and quality. By the way, energy is defined as everything that produces a change.

Many reactions of the chromosome require the formation of intricate DNA-protein machines to replicate, transcribe or recombine DNA at specific sequences. Thereby, many reactions mean substantive energy expenditure. Chromosome-associated proteins assist in the formation of complexes by shaping DNA that include HU, H-NS, integration host factor (IHF) and factor for inversion stimulation (FIS) [37]. These highly complex and accurate processes need energy in many ways. For instance, proteins tend to dissolve in aqueous media thereby energy is required to keep the shape, not only to carry out their function.

In addition to the histones, eukaryotic chromosomes contain regulatory proteins that are much less abundant. One class of proteins, the high mobility group (HMG) family of DNA-binding proteins, bends DNA much like bacterial proteins IHF and FIS [38].

Any chemical process requires activation energy to happen, but the amount and type of energy must be accurate in location, quantity and quality, otherwise it does not happen, or at least will occurs differently, or perhaps happens in excess, and there would be significant variations in quantity and nature of the reaction products, which is non-compatible with the highly accuracy of life's biochemical processes.

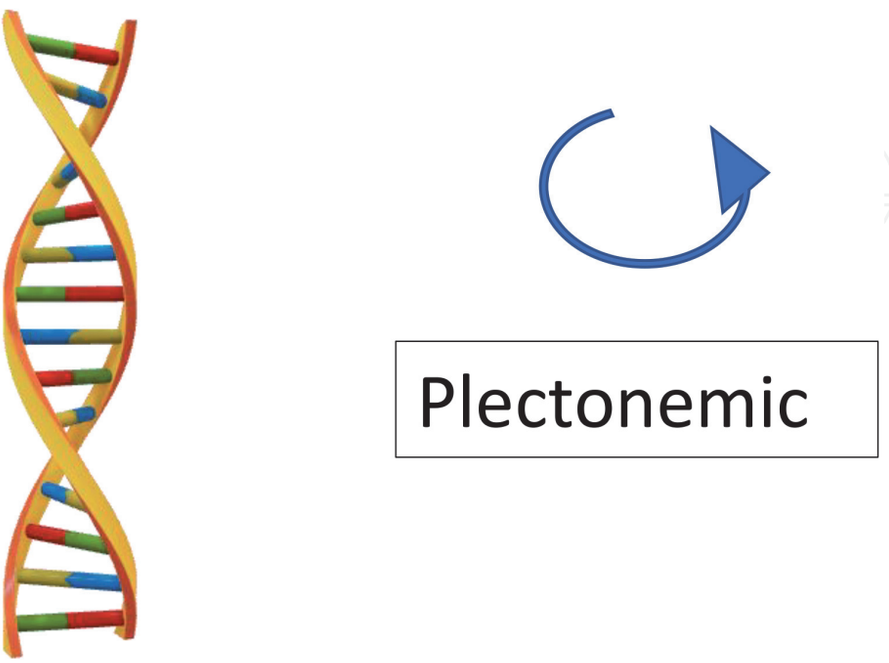

Figure 3.
DNA is plectonemic [31] and keeping chromosomes untangled requires a special class of enzymes called topoisomerases, however, both chromosomes and enzymes requires energy to function properly.

5. Genetic therapies failures

Those who are engaged in the understanding and therapy of genetic disorders are aware that common single-nucleotide polymorphisms may be strongly associated with an outcome (based on highly significant *P* values) and yet have very modest effect sizes (based on the odds ratios) thereby, it have been recognized that if there are differences in the genetic characteristics associated with the initiation of a disease versus its progression (presumably representing the outcomes of different biological pathways), we may have to tailor therapies (and their timing) to address these different stages of disease, for instance, antisense oligonucleotides [39].

Thus, pharmacologic targets based on abnormal genes may have clinical relevance for treating the progression of these conditions as well. However, the failure of clinical trials based on this kind of therapy apparently rational is the rule. Perhaps, measuring the effectiveness of this therapeutic approach by measuring the rates of progression of genetic diseases may not only fail but also mislead us from recognizing potential benefits at early stages of the disease [40].

It is possible to use the genetic endophenotypes [41], of these individuals conduct clinical trials that can address the inhibition of disease initiation and/or slow the disease progression prior to the development of overt systemic symptoms and advanced somatic findings.

Since 1949, Linus Pauling published about molecular diseases [42] and chromosomes are constituted by molecules. However, in biology, nothing has sense except at light of evolution, and chromosomes cannot explain the origin of life, thereby what's behind the chromosomes? What gave rise to genes? What causes atoms to sort in a certain way and conform to complex organic molecules? We think the mysterious force behind these questions all is energy.

But it is not any kind of energy, it is a very special energy that is precise, adequate, constant and which is constantly available. Such an astonishingly accurate type of energy, as nature wastes nothing, it cannot come from the oxidation of glucose or from the hydrolysis of ATP in ADP.

We believe that the energy that directs the formation of the molecules that make up the chromosomes, as well as their proper functioning and even their replication is the energy that comes from sunlight, but must be transformed into chemical energy by dissociating water molecule to make it wearable, such as chlorophyll in plants. Our discovery of melanin's unsuspected intrinsic ability to transform sunlight into chemical energy, by dissociating the molecule from water, such as chlorophyll in plants, will mark a before and after in biology, and even more so in the biology of chromosomes.

6. Chromosomal abnormalities in the oocytes

The oocyte is a relatively simple example that allows us to observe important chromosomal anomalies, such as aneuploidy. The oocyte has been and is highly studied because female fertility declines dramatically depending on age [43]. Arrested human embryos are more likely to have abnormal chromosomes than developing embryos from women of advanced maternal age [44]. Most arrested embryos have multiple chromosome anomalies, indicating that the factors causing aneuploidy may also affect embryo development. The detailed relationship between embryo development and aneuploidy is not known.

Chromosomal anomalies could occur in any chromosome, and the proportion of anomalies in the most common 5 chromosomes (13, 18, 21, X and Y) accounted for

only 25% of total abnormal chromosomes [45]. High aneuploid rates in human blastocysts were also reported in a recent study with 15,169 samples, overall in patients of 42–45 years old [46].

More euploid embryos can develop to blastocysts than aneuploid embryos. Arrested embryos are more likely to have abnormal chromosomes than developing embryos. High proportions of human embryos were aneuploid and the aneuploid rate increased with advanced maternal age. Interestingly, no significant difference was found in the developmental potential of embryos between younger patients and older patients.

In terms of monosomy and trisomy, no significant differences were found in the chromosomal distribution between blastocysts and arrested embryos. More arrested embryos had multiple chromosomal abnormalities than blastocysts. Errors occurred randomly in chromosomes, and there was no obvious difference between blastocysts and arrested embryos.

Aneuploidy could lead to reduced implantation and high miscarriage rates, but little is known about its mechanisms. Embryos usually arrest at various developmental stages for diverse reasons, such as culture conditions, patients' age and ovarian stimulation protocols. It is not known whether aneuploidy can directly influence embryo development. More euploid embryos developed to blastocyst than aneuploid embryos. These observations suggest that aneuploidy can affect embryo development in an unknown way or that the poorly understood factors that spoil euploidy also affects embryo development, for instance, energy impairment.

It was also observed that not only more arrested embryos were aneuploid, but also more chromosomes had errors in the arrested embryos than in blastocysts. It seems as a generalized failure. Many studies have been conducted to reveal the mechanisms of aneuploid origination in embryos from patients of advanced maternal age. It has been reported that maternal aging can dramatically influence the meiotic spindle assembly process in mammals [47] leading to spindle disorganization and chromosome segregation errors, which in turn cause aneuploid formation. Furthermore, the deterioration of sister chromatid cohesion and failure of the spindle assembly checkpoint in the oocytes are also crucial reasons for aneuploid formation [48], which mean a generalized failure. An aneuploid formation involves failure in many steps, which strongly suggest energy impairment.

The central problem in chromosome replication is generating two high-fidelity DNA copies and distributing them precisely to compartments that become the daughter cells. As cells grow, the mass of protein and membrane increases to a critical point that triggers the initiation of replication. Two replisomes are associated in a 'factory' that moves to the cell centre during chromosomal elongation. As DNA strands are pulled to the centre, replicated sister chromosomes migrate toward opposite cell poles. Completion of DNA synthesis occurs as the DNA that is pulled into the factory reaches the terminus. At this point, chromosomes are tangled together (catenated), and all physical connections must be removed to allow final separation. When physical separation is complete, cell wall synthesis forms two daughter cells.

In eukaryotic replication, initiation steps are not as fully understood as they are in *E. coli*. Initiation occurs at ***ars*** sites, so-called because they are autonomously replicating sequences. Initiation is controlled by a group of proteins called ORC (origin replication complex). Typically, a chromosome has many ORC-binding sites, and bidirectional semi-discontinuous forks move out from several ***ars*** sites on each chromosome until they converge with other forks. Eukaryotic replication also occurs in 'factories', and most of the chromosome is replicated in a semiconservative and semi-discontinuous mode, as in *E. coli*. The eukaryotic replication fork behaves very similarly to that found in *E. coli*.

Because replication is semi-discontinuous, the sister chromosomes are replication isomers. As replication proceeds, positive supercoils build up in front of the fork, and the daughter chromosomes become entangled behind the fork. One segment of a eukaryotic chromosome that is different from prokaryotic chromosomes is the tip of the chromosome, the telomere, which is replicated by a special DNA-polymerase called telomerase, which is related to the reverse transcriptase of retroviruses [49]. Telomerase synthesizes a simple repeat sequence that is added on to every chromosome using an RNA template that is part of the enzyme. In most organisms, telomerase is not expressed after cell differentiation, and consequently the telomere sequences shorten with age, eventually causing cell senescence and death. Following DNA replication in eukaryotes, which occurs in a part of the growth cycle called the S phase, cells move through a mechanical cycle called mitosis to distribute the replicated chromosomes to each daughter cell [50].

Mitosis proceeds through four stages. The first is the prophase in which, after replication, each chromosome becomes condensed. Stage 2 is metaphase, where two changes occur: each pair of replicated chromosomes moves to the cell centre and then the nuclear membrane begins to dissolve. In stage 3, anaphase, one centromere of each pair of chromosomes is attached to a set of fibers called the spindle, and molecular motors pull one of each chromosome pair to opposite cell poles. In stage 4, telophase, the nuclear membrane is reformed, and daughter cells are separated by the synthesis of a new septum [51].

The above brief description of a highly complex and accurate but at the same time poorly understood processes that lack a description about the role of energy generation and distribution, as it is usual in textbooks and research articles.

The organisms can adapt to widely varying growth states, from aerobic growth on rich nutrients to anaerobic growth in minimal salts and a single carbon and nitrogen source. One key to efficient growth is control of gene expression at the level of RNA transcription. The process of making of an RNA complement to a DNA gene is called transcription. The replication and transcription processes are not exempt from the use of energy in every one of its stages.

Because transcription and replication occur simultaneously, two situations arise where transcription machinery and replication machinery collide.

In eukaryotic chromosomes, the RNA polymerase responsible for transcribing most genes is remarkably similar at the structural level to the *E. coli* RNA polymerase. However, regulatory mechanisms are different. Eukaryotic genes have a region called the promoter which is where RNA polymerase binds and starts transcription. However, polymerase binding and its ability to initiate transcription is influenced by sites called transcription enhancers that can be upstream or downstream of the promoter (relative to the direction of transcription). Enhancers act over very large distances, and so DNA looping is required to bring enhancers into contact with RNA polymerase at promoters. In addition to enhancers, there are proteins called co-activators that must bind to RNA polymerase to stimulate transcription.

It is fascinating how mechanisms related to transcription and replication are described, but as usual, the role of energy is not mentioned at all.

Recombination is a critical repair pathway in mammalian chromosomes as well. Proteins that carry out biochemical reactions like the *E. coli* RecABC system have been identified. A protein called p53 coordinates the activity of many DNA repair proteins. Repair enzymes are stored at chromosome telomeres, and after a signal from p53, these proteins migrate to sites of DNA damage to restore chromosome function. Mutations in DNA repair genes have discovered to be responsible for several human genetic syndromes that result in premature ageing and high spontaneous rates of cancer. It is interesting how this highly complex machinery has been

studied and patiently arranged; however, the role of generation and distribution of energy is fully relegated.

In eukaryotes, transposons (usually called retrotransposons because of their similarity to retroviruses and their dependence on reverse transcriptase for replication) make up a large fraction of total chromosomal DNA. In human cells, sequences called short interspersed nuclear elements (SINEs), which are about 300 bp long are present in about 106 copies and represent 5% of the mass of DNA in a haploid genome. One SINE, called AluI, is present on average once every 5000 bp in every human chromosome. There are also long interspersed nuclear elements (LINEs) of about 6 kb that are present in about 105 copies and represent 15% of the haploid chromosomal mass. What function, if any, these sequences provide for the host organism is questionable, but many genetic mutations have been attributed to gene disruption caused by recent transposon insertion. Cell uses energy in many ways, for instance in the careful arrangement of 6 kb, 5000 or 300 bp; besides to keep the form and to carry on their astonishing accurate function.

The published studies on this subject, despite how detailed they are, do not analyze two variables: energy levels and the presence of toxic molecules such as pesticides, herbicides, fertilizers, metals, plastics, solvents, industrial waste, anesthetic agents, etc.

Since embryological development to adulthood, melanin is so important, that it is present in every stage from the oocyte [52] to the mature adult organism.

7. Creatine kinase and ATP

Creatine kinase (CK), also known as creatine phosphokinase (COK) or phosphocreatine kinase, is an enzyme expressed by various tissues and cell types. CK catalyzes the conversion of creatine and uses adenosine triphosphate (ATP) to generate phosphocreatine (PCr) and adenosine diphosphate (ADP). This CK enzyme reaction is reversible and thus ATP can be generated from PCr and ADP.

Creatine kinase in the blood may be high in health and disease, for instance, exercise increases the outflow of creatine kinase to the blood stream for up to a week. Serum creatine kinase (CK) levels are reported to be around 70% higher in healthy black people, as compared with white people (median value 88 IU/L in white versus 149 IU/L in black people). Serum CK in healthy people is thought to occur from a proportional leak from normal tissues [53]. Creatine kinase (CK) activity in serum is widely used to diagnose tissue damage including myocardial infarction and skeletal muscle myopathy, but it is unknown why serum CK activity is higher in apparently healthy black people of sub-Saharan African descent [54], perhaps because more melanin means more available energy to impel both synthesis and function of creatine kinase.

There is no evidence of muscle damage in black people as cause for the high serum CK activity, and the BB, MB and MM isoenzymes in serum are proportionally higher, but have a normal distribution [55]. Serum CK in healthy subjects is supposedly to be derived from normal tissue "leaking" CK to lymphatic vessels and into the blood stream, proportionate to the intracellular CK concentration. Therefore, it was proposed that the black population subgroup has a generalized high CK activity in tissues, which means more energy expenditure.

CK activity in different types of tissues with high and fluctuating energy demands is higher in black people than in white people, independent of age. Normal tissue loses a small fraction of cytosolic CK into the interstitial space, as was shown in ^{31}P nuclear magnetic resonance spectroscopy studies [56]. In physiological and

pathological states, release from tissue is proportional to tissue CK activity. Interstitial CK is subsequently transported through lymphatic vessels into the blood stream.

The unexplained high serum CK in healthy black people, with a normal isoenzyme distribution might be associated with a generalized high CK activity in tissues of this population subgroup. CK is the central regulatory enzyme of energy metabolism. The enzyme catalyzes the reversible transfer of the phosphoryl group (P) between creatine and ADP. CK supposedly fuels highly energy demanding processes such as cardiovascular contractility, sodium pumping and trophic responses, at a faster rate than glycolysis and oxidative phosphorylation together [57], however, the source of energy to CK system is poorly understood.

8. Glucose and ATP are not source of energy

The current dogma is that glucose is the universal precursor of any organic matter in plants and animals, human included. Glucose only provides highly specific carbon chains with which our body can synthesize and thereby replenishes organic molecules that wear out over the course of the day. The shape of carbon chains, of what we call glucose, seems to be very specific to the astonishing accurate metabolic processes of the human body and in general of all living beings, as they all contain glucose in their body. Glucose is arguably the ideal substrate or at least main substrate that fits appropriately into the sequence of highly complex and very specific metabolic processes of living beings. Thereby glucose is the universal provider of biomass, but no energy. If glucose were source of energy, diabetic patients should fly.

On the other hand, the ATP considered (wrongly) as the universal currency of energy exchange; it is a theory with significant contradictions. Although the theory was proposed more than 60 years ago, by Mitchell [58], who never worked on mitochondria, only on bacteria; in his chemiosmotic theory tried to establish the metabolic pathways about bioenergetics, which describes (theoretically) how living organisms acquire and transform energy in order to perform biological work. ATP is supposedly formed from adenosine diphosphate and inorganic phosphate. The overall reaction is catalyzed by ATP synthase, an enzyme that creates the energy storage molecule adenosine triphosphate (ATP), which is opposed to the law of thermodynamic that said that energy cannot be stored.

Mechanisms responsible for communication between spatially separated intracellular ATP consumption and ATP production process, and their precise coupling over a broad range of cellular functional activity has remained a longstanding enigma [59]. Optimal operation of the cellular bioenergetic system requires that energy-rich phosphoryl are produced and delivered to energy-consuming sites at the rate corresponding to the ATPase velocity, and that products of ATP hydrolysis, namely ADP, Pi and H^+, are removed in order to avoid kinetic and thermodynamic hindrances [60].

Cytoplasmic streaming, positioning of mitochondria and their movement in response to changes in energy utilization, along with formation of enzymatic complexes, have all been shown to contribute towards facilitating intracellular energetic communication [61]. However, such topological arrangements apparently are insufficient on their own to fulfill all cellular energetic needs [62]. Thereafter, a new theory of spatially arranged intracellular enzymatic networks, catalyzed by creatine kinase, adenylate kinase, carbonic anhydrase and glycolytic enzymes, in supporting high-energy phosphoryl transfer and signal communication between ATP-generating and ATP-consuming/ATP-sensing processes has implemented [63].

Fritz Lipman, the author of the energy concept through adenylate wire concept, was among the first to notice the analogy between the energy-carrying adenine nucleotide system and the electrical circuit. Indeed, basic principles of energy transfer, in terms of the rate and efficiency, apply equally to both industrial and metabolic networks [64]. In nature, the amount of energy tends to be constant in any system.

The localization of mitochondria in close proximity to cellular energy-utilizing processes, and their movement in response to activation of ATP-utilizing reactions [65], suggest that the distance of energy transfer is critical for adequate energy supply. It is hard to accept that mitochondria are in close proximity to cellular energy-utilizing processes, for instance, cell nucleus has neither mitochondria nor ATP, in spite to be the largest organelle with a high energy consumption; furthermore, energy transfer by diffusional exchange of adenine nucleotides is kinetically and thermodynamically inefficient since it requires a significant concentration gradient [66] and would result in ATPase inhibition by end products (Pi, ADP and H^+), inability to sustain the high free energy of ATP hydrolysis (ΔGATP) at sites of ATP utilization, and ultimately energy dissipation (–ΔH) during transmission [67]. The difference between ΔG1(ATP) and ΔG2(ATP), signifying energy loss (–ΔH), would increase at higher rates of ATP turnover, and the drop of ΔG2(ATP) below a threshold would impair cellular functions [68].

Part of intracellular energy transfer proceeds in the narrow mitochondrial inner membrane infoldings, known as cristae. The cristae arrangement increases, by several folds, the capacity of mitochondrial ATP production without occupying additional intracellular space. However, it creates difficulties in ATP export from the mitochondrial intra-cristae space, as diffusional flux requires a significant concentration gradient. Accordingly, ATP accumulation in the mitochondrial intracristae space would inhibit export of ATP from the mitochondrial matrix by locking the adenine nucleotide translocator [69].

The disruption of the adenylate kinase gene impedes ATP export from mitochondria [70]. Taken together, this would indicate that in the absence of facilitating mechanisms, cell architecture and diffusional hindrances would obstruct free movement of molecules, impeding efficient intracellular communication.

In searching how cells overcome diffusional limitations for substrate development [71] several theories have been implemented. However, is difficult to explain the displacement of the local ATP/ADP equilibrium to other cellular sites to maintain energetic homeostasis [72]. Understanding of creatine kinase function was specially limited when the cell is considered as a homogenous system where enzymes are in equilibrium, and metabolites have uniform distributions and concentrations [73], without forgetting the energy, which also remains constant.

Past observations following deletion of brain B-CK indicate that this isoform is fundamental to processes that involve habituation, spatial learning and seizure susceptibility [74]; however, these effects can be explained by the effect on thermoregulation of mitochondria and CK, more than an energy source effect. The reduction in cellular B-CK activity by dominant negative gene expression abrogates thrombin-mediated, energy-dependent signal transduction during cytoskeletal reorganization [75]; which are varied effects that are difficult to explain from a purely biochemical point of view, except if we take into account the fundamental role of energy.

The muscle exercise performance correlates with adenylate kinase activity, suggesting that this enzyme is an integral part of cellular energetic homeostasis [76], but explainable by its effect on thermic regulation that is astonishingly accurate; more than some effect on generation and distribution of energy from melanin.

It is possible that the main function of mitochondria and ATP is temperature control, as intracellular chemical reactions require (constantly) not only the exact reactants, the exact energy, but also the exact temperature (**Figure 4**).

ATP is thermodynamically unstable and electrochemically stable. When ATP is hydrolyzed to ADP energy is absorbed, and when the ADP is scaled to ATP the energy is released. The characteristics of these reactions are compatible with temperature regulation, as they happen quickly and constantly, as each ATP molecule in the body requires reconstitution every 20 s.

It is pertinent to emphasize that ATP hydrolysis and reconstitution also requires, like any other chemical process of the body or cell, energy at each and every stage of the reaction. The unsuspected intrinsic property of melanin to transform sunlight into chemical energy by dissociating the molecule from water, such as chlorophyll in plants; allows to rethink cell biology in a new way completely different, and chromosomes are not exception.

Thereby, the precise coupling of spatially separated intracellular ATP-producing and ATP-consuming processes is a formidable challenge, and even more so in an organelle that lacks mitochondria and ATP as is the nucleus of the eukaryotic cell.

The role of adenine nucleotides as a supposedly key link between spatially separated energy transducing processes, still it is a theory after almost 80 years that was proposed by Lipmann in 1941. The adenylate wire theory has many contradictions, such as the distance of energy transfer is critical for adequate energy supply, it requires a significant concentration gradient, could be ATPase inhibition by end products; the ΔG_{ATP} is difficult to maintain in the adequate levels at sites of ATP utilization; and finally energy dissipation ($-\Delta H$) during transmission.

The difference between $\Delta G_{1(ATP)}$ and $\Delta G_{2(ATP)}$, signifying energy loss ($-\Delta H$), would increase at higher rates of ATP turnover, and the drop of $\Delta G_{2(ATP)}$ below a threshold would impair cellular functions [68]. Therefore, energy management is very complicated and difficult to explain and understand whether we start from glucose and ATP as an energy source. But if we divide from now on the energy (light/melanin/water) of the mass (glucose), things will change for the sake of the health of the sick.

Supposedly, part of intracellular energy transfer proceeds in the narrow mitochondrial inner membrane infoldings, known as cristae. The cristae arrangement increases, by several folds, the capacity of mitochondrial ATP production without occupying additional intracellular space. However, it creates difficulties in ATP export from the mitochondrial intracristae space, as diffusional flux requires a significant concentration gradient. Therefore, ATP accumulation in the mitochondrial intracristae space would inhibit export of ATP from the mitochondrial matrix by locking the adenine nucleotide translocator [77]. It is very difficult just to explain

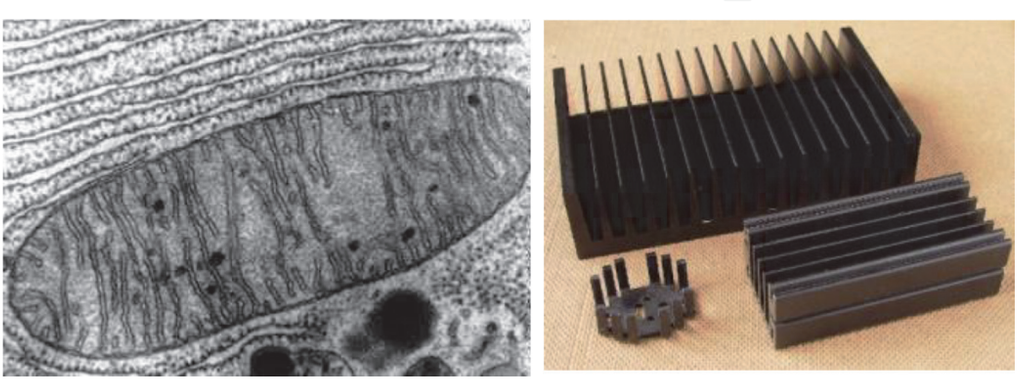

Figure 4.
The morphology of mitochondria (left) is similar to heat sinks (right) used in electronic devices and some light sources.

the generation and distribution of energy from glucose and ATP. And just as you cannot take more energy than a molecule or system has, it is also not possible to explain the inexplicable because it's simply not possible.

The normal cell architecture and the diffusional hindrances seems to be designated to obstruct free movement of molecules, impeding efficient intracellular communication, the generation and distribution of energy from glucose and/or ATP. On the one hand, if energy management were so difficult, life would be a miracle and not an evolution, and on the other hand, if glucose were a source of energy, diabetics would fly.

The field of how cells overcome diffusional limitations for substrate movement in the highly structured intracellular milieu is full of theories. Concepts as displacement of equilibrium, near-equilibrium network, sharp concentration waveform, incoming flux wave, flux transfers chains, instantaneous transmission, vectorial ligand conduction, chains of sequential rapid equilibrating reactions, facilitated high-energy phosphoryl transfer are theories initially developed by Peter Mitchel and have gradually been added by other researchers with biochemical "patches" trying to make them believable [78]. But it is not possible to extract energy from where there is none.

Interestingly, there is theory named "walking without moving" that means that ligands do not move the entire length of the pathway, as molecules arriving at the distal sites of this sequence represent the equivalent rather than the specific molecule generated at the origination site [79]; explanation is not simple and more than complex tangled mechanisms are being argued. For instance, it is said that flux wave propagation along rapid equilibrating chemical and biological reaction can proceed much faster than diffusion of reactants [80], but only gases move faster in aqueous solution than the electrolytes contained in it.

And now that we know that melanin releases molecular hydrogen and molecular oxygen continuously, we will have to include these gases in the schemes of intracellular biochemical reactions.

The purpose of this work is not the exhaustive analysis of all the contradictions of the intracellular biochemical pathways described to date in the literature, we only explain some demonstrative examples of the excessive complexity that has been reached trying to explain the prevailing theories and dogmas.

9. Light transduction by melanin and chlorophyll

Photosynthesis, a major bioenergetic process, is the metabolic pathway used by plants in which solar energy is used to synthesize glucose from carbon dioxide and water. This reaction takes place in the chloroplast. After glucose is synthesized, the plant cell can undergo photophosphorylation to produce ATP [81]. To date, it was not known that humans or mammals in general could carry out a transduction of luminous energy to chemical energy from dissociation of water, such as plants (**Figure 5**). However, the study of the minuscule vessels of the optic nerve in humans (**Figure 6**) and their reaction to the presence of melanin came to reveal the unsuspected intricate property of melanin to dissociate and reform the molecule of water [82].

The task ahead is to integrate the unsuspected bioenergy role of melanin into today's biochemical tangle. It is to be hoped that the requirement of philosophers that science has to be simple will be fulfilled. To the definition of life as a self-sustaining chemical system that eventually enters into Darwinian development, we can now add: life is a self-sustaining physical-chemical system capable of evolving.

Chlorophyll:

$2H_2O \longrightarrow 2H_2 + O_2$

Melanin:

$2H_2O \longrightarrow 2H_2 + O_2 \longrightarrow 2H_2O + 4e^-$

Figure 5.
Water dissociation is irreversible in chlorophyll; however, in melanin it is reversible.

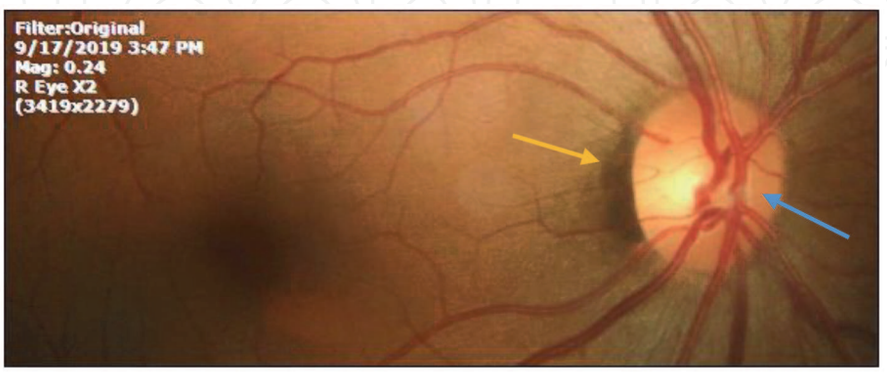

Figure 6.
The optic nerve (blue arrow) and melanin (yellow arrow) are always together with a very interesting crosstalk.

10. Conclusion

In biology, nothing makes sense except in the light of evolution. The origin of life could not be explained from glucose, genes or chromosomes. Nor has it been able to be explained from the ATP. But it is that ATP is not a source of energy, the functions of ATP are different, and you will have to discern them, perhaps it is for temperature control and control of inorganic phosphorus levels.

Therefore, the origin of life could not be explained from the energy of the ATP either. But things change when we understand the unsuspected bioenergy role of melanin in biology. Melanin is the most stable substance known, 160 million years of age. A source of energy so stable and accurate at the same time, allows to order the ideas as to the origin of life, because then we would have, at the beginning of time: melanin, the energy emanating from melanin, then glucose, then more complex molecules such as amino acids, lipids, nucleic acids, etc.

Then the order of the origin of life would look like this: melanin, melanin energy, glucose, amino acids, lipids, proteins (histones), nucleic acids (genes) and so on. Therefore, before the genes was melanin and the energy that comes from it.

Usually, when we talk about genetic alterations, we usually think that before the genes there is nothing, evolutionarily speaking, but now we must be aware that, before the genes is the origin of life, which is explained by the melanin and the energy that emanates of her.

Therefore, chromosomal abnormalities at the chromosome level, at the gene level, at the order level of nucleic acids or even histones can be explained by alterations in the generation and distribution of energy that comes from melanin, which does not glucose or ATP.

In any system, when failure is widespread, we must first think about energy. And in the case of chromosomal abnormalities the alterations are diffuse, are not punctual or limited to a single gene or even a single chromosome. And even

alterations extended to anatomical malformations, which is consistent with widespread failure; and now that we know that the main energy source of the cell, tissues, organs, systems or the human body as a whole comes from melanin, then the alterations observed at the various levels of organization, correspond to a generalized failure, typical alterations in energy generation and distribution.

Our discovery about the intrinsic property of melanin to dissociate the molecule from water is a disruptive finding that breaks into a thousand pieces the sacrosanct role of glucose as an energy source and at the same time opens new paths that will allow us to advance in knowledge of the intricate mysteries of life.

We must rewrite cell biology completely, re-thinking organelle functions based on the discovery that eukaryote cells are able to directly take energy from light. In this chapter, we will give some examples of how the relevant role of energy in the cell nucleus and in the dynamic of chromosomes has been systematically relegated in the study of the biology of chromosomes.

Explaining something completely different from established dogmas is not simple, it is necessary to explain step by step the interpretation errors of glucose-based metabolism as an energy source; there are concepts that the reader will have to unlearn and implement other constructs not only with what he will read here, but in other sources of information, so that he structures a totally different picture from what is known. We aspire to be a first approach with a discovery that will mark a before and after in the study, in the case of this chapter; of the chromosomal abnormalities.

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