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Genetics of aging and its impact on human longevity: theories and evidences that helps to prevent age-associated diseases

Genética do envelhecimento e seu impacto sobre a longevidade humana: teorias e evidências para prevenção das doenças do envelhecimento

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ABSTRACT

Biogerontological studies about the factors that affect the human longevity and sucessful aging are highly relevant. Therefore, here this paper I review and coment some questions about currently aging theories, the existence (or not) of "longevity genes" and main genetics mechanisms potentially involved in aging and lifespan. From this review I also will consider the impact environment on genetic and epigenetic factors on human aging, health and longevity.

KEYWORDS: Genetics. Longevity. Aging.

RESUMO

Estudos biogerontológicos sobre fatores que afetam a longevidade humana e o envelhecimento bem sucedido são altamente relevantes. Portanto, aqui eu reviso e comento algumas questões atuais sobre teoria do envelhecimento, a existência (ou não) de "genes da longevidade" e os principais mecanismos genéticos e epigenéticos que potencialmente estão envolvidos no envelhecimento e tempo de vida. A partir desta revisão eu também faço considerações sobre o impacto do ambiente na genética e epigenética que influencia a saúde e longevidade humana.

DESCRITORES: Genética. Longevidade. Envelhecimento.

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INTRODUCTION

Currently, the world presents elevate and growing number of elderly people related to improvements in public health and medicine. Taking the Brasil as reference is estimated that in 2020 the aging population will be more than 26.2 million representing 12.4% of all population.[1,2] However, despite this phenomena to represents an advance of human civilization, the increase of elderly number in the population has an important social impact since elderly people show a fragile phenotype, high prevalence of dysfunctions and chronic diseases that have negative impact on health and social services, as well as in the own elderly quality of life.[3,4]

Although the human being reasonably expect to live longer today than past generations did, until moment the age-related diseases burden has not effectively changed. For this reason, the greater challenge to be obtained in the next years involves the effective maintenance of biological functional state until very late ages. However, decelerate aging process is not an easy task, involving the accumulation and integration of a large number of information produced from biological and psychosocial areas.[4]

For this reason, biogerontological studies about the factors that affect the human longevity and healthy aging are highly relevant. Among these investigations the elucidation of genetics and evolution contribution to human lifespan is an intriguing and complex topic generating three important questions that are not totally solved: Those genetic factors contribute to being healthy and lifespan? We can modulate our genes to decelerate our biological aging by environmental manipulation? How environmental factors act in our genetic altering our aging and lifespan? In this paper I will comment these questions considering the currently aging theories, the existence (or not) of "longevity genes" and main genetics mechanisms potentially involved in aging and lifespan. From this critical review I also will consider the impact of this knowledgment on human health and longevity.

THE SENEMORPHISM AGING THEORY BASED IN GENE-ENVIRONMENTAL INTERACTIONS THAT CHANGE LIFESPAN

In the broadest sense, biological aging is an inevitable process that reflects all the changes that occur over the course of life, being a progressive and intrinsic event that is directly associated with frailty, disease, and death. The continued biological aging changes observed in the individual's anatomy and physiology is consequence of tissue, cellular and molecular alterations.[5,6] Since it cannot be stopped, the slowing the aging process has been a dream since the dawn of civilization, despite this dream to be far from being realized. Several authors have tried to explain aging and longevity phenomena and their ideas originated a whole of aging theories categorized in stochastic and evolutionary theories.

Evolutionary theories of aging predict the existence of certain genes that provide selective advantage early in life with adverse effect on lifespan later in life (antagonistic pleiotropy theory) or longevity insurance genes (disposable soma theory). On the other hand, stochastic theories consider that aging is result of "wear and tear" during lifespan. However, as emphasized by Trindade et al[7] this is a false dichotomy, considering that evolutionary forces, mainly natural selection favors traits resulting in efficient reproduction whether they benefit the individual or the kin. In fact, there are a consistent number of evidences suggesting that when the species are exposed to advantages and disadvantages environmental conditions during before and during reproductive period this consequence to short or extend their lifespan. Recently Trindade and collaborators proposed an integrated new theory named: "aging senemorphism theory". This theory considers that aging patterns encoded by the genome are modulated by environmental factors that change the ontogenetic program and, consequently alter lifespan. For this reason, aging biological patterns could to be accelerated or decelerated and, in consequence can increase or decrease the species longevity.[8] The lifespan modulation occur within a range of a maximum age would be genetically programmed in each species.

To organize this theory, Trindade and collaborators based your ideas mainly in the impact of "diet pattern" in lifespan schedule of several species. Particularly I believe that the senemorphism theory is the most accurate currently aging theory being supported by genetic knowledge produced in the last recent years. About this Moskalev and Pasyukova[19] in their recent publication commented that aging senemorphism theory could be an universal evolutionary aging theory.

Despite the aging senemorphism theory to associate genetics, environmental conditions and apparently stochastic aspects that affect aging process, until moment the theory did not explain in details how the aging process and lifespan can have evolved so differently among the species.

Several authors, when I am included think that existence of genes that evolved to regulates the longevity *per se* is hard to believe, since a large number of species including human being present

an age-specific mortality curve U-shaped. This curve shows that mortality declines with age in the developing cohort before increasing with age.[9] From this observation is assumed that force of selection against mortality is constant across pre-reproductive ages and, the organism that dyes before reproduction is considered a maladaptive.[10]

To identify the two moments of death population-level phenomenon Levitis[11] named ontogenescence the period that which the death rate of each cohort tends to decrease with increasing age between conception and maturity. The ontogenescence period occurs before the increase of mortality risk after the reproductive stage that is known as senescence period. In other words, the dead in ontogenescence period is not desired whereas the dead in the senescence period is expected.

Until recently, always existed a conceptual difficult to explain the lifespan evolution in senescence period whether we consider the classical concepts preconized in the modern evolutionary synthesis theory.[12-18] The difficult to explain the evolution of longevity as a biological trait is related to assumption that in senescence period there is absence of selection forces, as was previously preconized by Medawar in 50 decade.[14] In a genetic sense, as commented by Levitis[11] "the post-reproductive period is like the vacuum of space". This is because there are no forces acting directly on gene expression in this period. In post-reproductive phase, the competition between alleles (variants of a gene) for representation in the next generation no longer exists.

For this reason makes more sense to think that the biological species fixed survival genes to guarantee the reproductive success (from the egg production to reproductive maturation of progeny) in the ontogenescence period, and post-reproductive lifespan would be just a sub-product of this first biological moment. From this view, is possible to consider that biological lifespan is result of fixed survivelance genes selected until reproductive period and not specifically consequence of genes selected to increase the longevity. Here is important to comment that senemorphism theory somehow advances the concept proposed in the antagonist pleiotropic aging theory developed by George Williams in 1957.[15] The pleiotropic theory arguments that aging is caused by the combined effect of many pleiotropic genes that each had a beneficial effect in an animal's youth but also had an adverse side effect in older age. The senemorphism theory did not discard this action, but also consider that environmental exposition on early development can also act positively in ontogenetic program extending lifespan. In the other words, the modulation of survivelance genes by environmental factors resulting in a given lifespan period is according to "senemorphism aging theory".[8]

Therefore, I believe that aging processes and consequently lifespan modulation are sub products of survivelance genes in response to environmental conditions. These genes act mainly until reproductive period affecting post-reproductive lifespan. The differential modulation of survivelance genes in response to environment variation would be to provide plasticity in lifespan schedule of subjects avoiding species extinction due environmental changes. This point explains the large phenotypic differences among species and among populations of the same species living in different environmental conditions, including the human being aging and lifespan.

GENETIC AND EPIGENETIC FACTORS ACTING ON AGING AND LIFESPAN

Evidences from experimental models and human beings suggest that aging and consequently lifespan can be influenced by genetic and epigenetic factors.[20-22] However, before we make specific comments about these genes we will review briefly some molecular aspects related of our genetic background to become more easily the understanding of next considerations (Figure 1).

It is widely known that biological characteristics are genetically determined and fixed in each species due the important DNA molecule properties. Chemically DNA is a double-helix polymer that consists of a 5-carbon sugar (deoxyribose) attached to each other by a phosphate group. The two DNA strains are linked by two nitrogenated bases that are complementary (Adenine and Timine and Citosine and Guanine) linked by hydrogen bridges. A deoxyribose molecule linked with nitrogen consist a DNA unit named nucleotide. Nucleotides sequences are extremely important to all proteins that are synthetized in the cells. In the genes, the ordinate sequence of pair bases determines what will be the amino acid to be incorporated into polypeptide chain synthetized. Other important information to be considered in terms of eukaryotic genetic material is its gene structure. In eukaryotic species the nucleotide sequences are functionally structure in three regions: promotor region, exons and introns. The number of exons and introns are variables according each gene. The promoter region is the local where bioactive molecules (endogenous or exogenous) can bind inducing the gene to starting or stopping the mRNA transcription, as well as to intensify or to decrease the transcription. The molecules that are able to modulate the RNA transcription of one gene are considered "regulatory molecules".

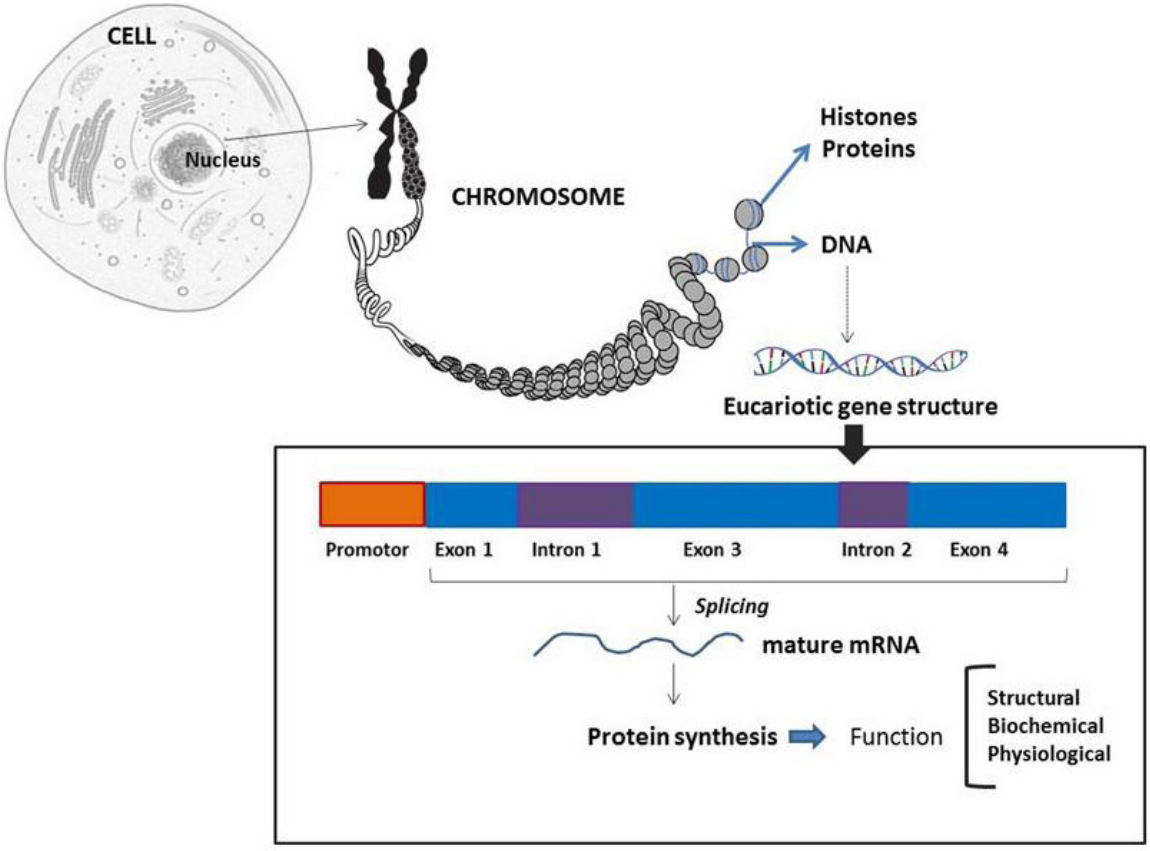

Figure 1. General schem showing the eucariotic genetic material structure. Eucariotic genes are into Nucleus organized in chromosomes. Each chromosome are constituted by one DNA molecule associated with histones and non-histones proteins. Genes are DNA segments that are able to produce or not several types of RNAs. Eucariotic gene has three important regions constituted by DNA segments: promotor,exons and introns regions. Regulatory molecules as steroids hormones endogenously produced or bioactive molecules present in foods, such as resveratrol are abe to binding in promotor region influencing the transcription, and consequently the protein synthesis, cell metabolism and body physiology. Exons are DNA segments that will produce a mature mensager RNA whereas introns transcript segments that will be excluded of mRNA when this molecule leave from the nucleus to cytoplasm. The process that exclude introns of some gene are named splicing. The aging biology can be influenced by genetic variations that alter some gene causing alteration in some cell function. These genetic variations (named polymorphism when are present > 1% of population) are transmited from parents to next generation. The aging biology can also be influenced by regulatory molecules that change the transcriptional pattern of some gene. For example, resveratrol is able to induce transcription of Sirtuin 1, that is a protein associated with cell longevity. The differential regulation of genes triggered by dietary patterns, physical activity and stress is not transmissible to next generation. Both DNA and histone proteins can suffer some types of chemical reaction, such as methylation or acetylation that turn on or turn off genes, and these process can also to alter the cell function. These chemical alterations are known as "epigenetic modifications". Recent studies suggest that epigenetic patterns present in parents genes can be transmissed by next generation.

In the organism, steroids hormones such as testosterone and estradiol are considered regulatory molecules that are able to bind in promoter region of several genes of target cells. On the other hand, these molecules can also to be obtained from environment, especially diet. A good example is resveratrol, a polyphenol found in red grape products, such as red wine.[23,24] Functionally, resveratrol is a fungicide molecule that some plant species produced as chemical defense against microorganisms. A large number of studies showed that resveratrol is able to modulate several genes, including genes that synthetize proteins that are associated with cell lifespan extension such as Sirtuins.[25] In addition, it is important to comment that there are others regulatory pathways of cell function that was not comment here.

Variations in nitrogen bases in some DNA sequence of some gene are named mutations, and can be originated by nitrogenated bases substitution, addition or deletion. Frequent mutations (> 1% frequency) in the species genome are named "genetic polymorphisms". Specifically punctual mutations are named single nucleotide polymorphisms (SNP). Human beings genome have 1.42 million of SNP distributed throughout DNA, with estimative that 60.000 SNPS can provide some type of protein modification that can alter the cell function.[26] The SNPs variations located in some point of some gene are named "alleles". Considering that each person is compound by genetic material from mother and from father, each person has two alleles named "genotypes".

Considering that SNPs transmission is made by parents and obeys the genetic population assumptions a large number of studies have being performed to evaluate the potential association between some genes and human longevity, especially investigating extreme long-live centenarians. These studies are based in the Hardy Weinberg principle that is a referential core of synthetic evolutionary theory. The Hardy Weinberg principle states that allele and genotype frequencies, in some large population with random matting will remain constant from generation to generation in the absence of evolutionary influences, such as natural selection. In these terms, if the allelic and genotype frequencies of some SNP are similar between young adults and long-lived elderlies living in the same population, this SNP is not considered to be associated with longevity.[22] At contrary, changing on allele or genotype frequencies between young adults and oldest-old elderlies can indicate potential influence of the SNP studied with longevity. For example, when a candidate longevity gene X with two alleles A and B is studied in some human population, researchers select long-lived subjects (preferentially nonagenarians and centenarians) and a young control group with same ethnic characteristics. After genotyping of groups by molecular assays (the most common is the polymerase chain reaction, PCR analysis), the allele and genotype frequencies are compared between two samples. Significant differences in allele or genotype distribution indicate that gene X is associated with longevity because the genotype or allele found in higher frequency in the long-lived subjects suggest some biological advantage that confer greater longevity.[22]

Though it seems easy to perform this research, studies using this methodological approach not necessarily produce consistent results due the presence of several intervenient endogenous an exogenous variables. For this reason, some studies described association between one SNP polymorphism and longevity whereas other studies report did not find same results.

An investigation performed by my research team focused this problem when studied a genetic polymorphism located in the angiotensin converting enzyme gene (ACE). ACE is a key component of renin angiotensin system (RAS) that has an important role in blood pressure homeostasis by generating the vasoconstrictor peptide angiotensin II. The ACE gene is located on chromosome 17q23 and present many polymorphisms. Among these polymorphisms, the 287–base pair Alu insertion/deletion (I/D) polymorphism in intron 16 is the most studied producing three genotypes: DD, II and ID. The DD phenotype involves high ACE serum concentrations that observed in II and DD carriers. A meta-analysis performed by Garantachea et al.[26] I/D ACE polymorphism that included 10,484 controls and 1803 centenarians suggested that DD genotype confer a modest but significant advantage to reach exceptional longevity. However, when my research team analyzed the association between I/D ACE polymorphism and age over 60 in two populations ethnically differentiate (gaucha and Japanese immigration populations living in Brazilian Southern Region) we found high number of DD genotype just in the gaucha mixed population.[27] These controversy results were obtained despite the elderly of two populations living in the same macro environmental conditions, and the methodological approach to perform the study and to inclusion subjects to be same. Probably differences of ACE polymorphism association can be influenced by some hide genetic and environmental factors and this limitation become the genetic associations with human longevity very hard to be conducted.

An important intervenient variable that until few years ago was not considered in the longevity studies is the occurrence of epigenetic modifications that can change the development program affecting human lifespan. But, in fact what is epigenetic modification and why these events have so crucial impact on human aging and longevity?

To answer this question is important to comment an very important study performed by Dr. David Barker during 90 decade that originated the theory initially named "fetal origins hypothesis" and currently named "developmental origins of health and disease". This hypothesis considers that the fetal environment and early infant health program permanently the body´s metabolism and grow affecting the risk of chronic diseases development in adult and elderly states, mainly metabolic and cardiovascular morbidities.[28]

This theory emerged from epidemiological investigations performed by Dr. Barker wit birth weight data collected in the early 1900's in the south east of England and the follow-up of mortality data of these children until latter ages. The results suggested that adult disease has fetal origin associated with under nutrition in middle to late gestation. The results found by Dr. Baker were further reproduced in other populations and controlled studies using animal experimental model also support the "developmental origins" theory.[28]

The results obtained from experimental models confirmed that perturbations of the maternal environment involve an abnormal intrauterine milieu for the developing fetus. The altered fuel supply from mother to fetus induces alterations in the development of the fetal endocrine pancreas and adaptations of the fetal metabolism to survive and finish the development in the altered intrauterine resulting in intrauterine growth retardation. Maternal diabetes or some specific genetic factors also can trigger these alterations. Therefore, intrauterine growth restriction may permanently alter the endocrine-metabolic status of the fetus, driving an insulin resistance state that can promote survival at the short term. However, this extreme situation that permits fetus survivelance facilitates the development of type 2 diabetes mellitus and metabolic syndrome in adult life. The risk of diabetes and metabolic syndrome development in adult state can also to be increased when the intrauterine nutrient restriction is followed by a postnatal obesogenic environment.[29]

Complementary investigations also demonstrated that besides prenatal under nutrition other factors can cause fetal developing alterations that can increase the risk of chronic diseases from adult period. Hypoxia, exposure to toxins and other intrauterine insults are among the factors that can change the fetal programing and to increase the risk of diabetes type 2, obesity, insulin resistance, hypertension and ischemic heart disease.

From these results emerged an important question: as environmental factors, such as nutrition can trigger changes in fetal development program, that last consequence is to increase the risk of disease and early death in the late stage of life?

Recent investigations have strongly suggested that environment factors can act on gene regulation, such as commented before as well as by epigenetic processes triggering changes in developmental programming.[29,30] For this reason is necessary to understand what is the epigenetic phenomenon that occurs in the genome of eukaryotes, including human beings. Observe again the Figure 1 that shows the genetic material organization. As can see, each DNA molecule is structurally associated with proteins named histones. During the cellular interphase DNA plus histones are in a relaxing state to permit the access of RNA polymerase and other molecules including non-histones protein related to transcriptional processes. However, when cell is under division, the material genetics needs to be protected and the DNA plus histones are compressed forming a structure known as chromosome. Therefore, human beings have 46 chromosomes, and each one is formed by one DNA molecule associated with histones proteins.

Epigenetic changes involve chemical modifications on DNA molecule, or in histones molecules or also in the production of some special class of RNA-associated silencing.[30] These RNA are also named noncoding RNA or RNA interference (iRNAs). Any epigenetic processes have as main function switch gene on or off and determine which proteins will be transcribed. Evidences showed that epigenetic events are part of normal cellular processes and occur according to different cell tissues and/or in different ontogenetic developmental periods. For example, one important epigenetic event that occurs in all mammals females, including women is the chromosome X inactivation.[29,30]

In other words, epigenetic mechanism are biologically important because are able to silencing genes that not need to be expressed in some cells. In addition, permit a high genetic plasticity in response to environment conditions. This plasticity related to genetic silencing is so crucial, which probably explains partially why genetic twins are not phenotypically identical.[30]

In biochemical and molecular terms the DNA methylation involves a methyl group binding to DNA. However, the methyl-DNA binding occurs in regions rich in cytosine-guanine sequences named CpG sites. These sites in DNA genome are methylated by action of three specific enzymes called DNA methyltransferases (DNMTs). Inserting methyl groups changes the gene DNA structure not permitting its transcription even when in the presence of regulatory molecules that before methylation process was able to activate this gene. Therefore, methylated genes are typically turned off, and if some unusual event leads to gene loss its methylation, this gene can be abnormally activated and cause biological disturbs or diseases such as cancer. This phenomenon is known as hypomethylation. On the other hand, the occurrence of methylation of genes that need remain active leads a state called hypermethylation. The hypermethylation is not beneficial and also has being associated with some types cancer due silencing of tumor-suppressor

genes as p53 gene. During embryogenesis the DNA methylation is used to differentiate which gene copy is inherited from the father and which gene copy is inherited from the mother. This phenomenon is named genomic imprinting.[30,31]

Histone modifications also lead to epigenetic events since these proteins are primary components of chromatin. When histones are modified after they are translated into protein, these molecules can influence how chromatin is arranged, which, in turn, can to influence directly the gene transcription. When the chromatin is not compacted the gene is active and can be transcript. Conversely, when chromatin is condensed creating the transcription will not occur. The histone modification leading that cause gene silencing occurs by also methylation reaction or by acetylation reaction. A histone binding with either acetyl or methyl group binding causes an epigenetic modification inactivating genes. These chemical groups binding with some specific amino acids present in the histone proteins. The acetylation is the type of epigenetic change that is also responsible to X chromosome inactivation in females.[31]

RNA interferences are one type of RNA molecules that no codify proteins and that can affect gene expression because trigger heterochromatin formation by histone modifications and DNA methylation. These inactive regions in genetic material are generically named heterochromatin. Nowadays, there are a large number of evidences that some genetic syndromes are related to altered epigenetic patterns causing severe body dysfunctions.

A recent review performed by Brunet and Berger [21] discussed the impact of epigenetic mechanisms on aging regulation. The authors commented that aging is associated with profound epigenetic changes resulting in alteration of genes, biochemical pathways and the occurrence of body dysfunction that predisposes the organism to chronical diseases. On the other hand, the epigenetic changes also could to explain the remarkable aging plasticity found in members of the same species, probably due differential responses of organism to environmental challenges. The good news is related with fact that epigenetic modifications can be reversible and theoretically can be delay or reverses the main diseases of aging.[32]

For this reason, some authors as Capri and collaborators are considered that searching for genes of human longevity reached the end.[32] These authors commented that: "the identification of longevity-related genes does not explain the mechanisms of healthy aging and longevity, but it opens a huge amount of questions on epigenetic contribution, gene regulation and the interactions with essential genomes, i.e. mitochondrial DNA and microbiota. To fully disentangle what appears to be an endless quest, all the components of the complexity of human longevity genetics are taken into account."

In fact, I agree with these authors since the whole of these results support the idea that some aging processes are strongly affected by early development in response to environmental conditions and that our lifespan is just a sub product of these events plus a little luck to avoid non-predicable and catastrophic situations that are out of our control.

In these terms, Figure 2 presents a summary of main genetic contribution in aging processes considering three genetic categories in their relation with environmental challenges. The first category includes structural genes that present less phenotype plasticity. When these genes are altered mainly in early development can cause malformations, high mortality or disturbs that increase the chance to accumulate body dysfunctions aging related. In this category I include genes with present mutations that accelerate aging process like Werner syndrome, Bloom's syndrome, and Hutchinson-Gilford Progeria Syndrome (HGPS). Recent studies have revealed alterations in a several cellular and molecular pathways directly involved with maintenance of genomic integrity as occur in HGPS disease where the LMNA gene that codes for lamin-A and lamin-C proteins, which are structural components of the nuclear lamina are genetically altered.[33] This is a structural protein but that present pleiotropic functional effects since participates of nuclear organization, chromatin dynamics, regulation of gene expression and epigenetics processes. In the case of these accelerate aging diseases the environmental contribution is very low.

The second category grouped regulatory and/or structural genes that are moderately responsive to environmental modifications. Presence of SNPs can increase or decrease risk of several chronic diseases, but generally environmental variables can modulate both, risk or protective conditions that act on disease development. In these group I include genes are transiently activated by endogenous and exogenous factors. This group include genes are regulate by steroid hormones that maintain secondary sexual characteristics and genes that are regulated by exogenous molecules as found in several plant foods as polyphenols and vitamins. When these factors are absent or in very low concentrations the gene regulation is not so effective. For this reason, the nutrigenomics postulated that healthy dietary patterns must be maintained on a basis if they are to protect us from chronical diseases.

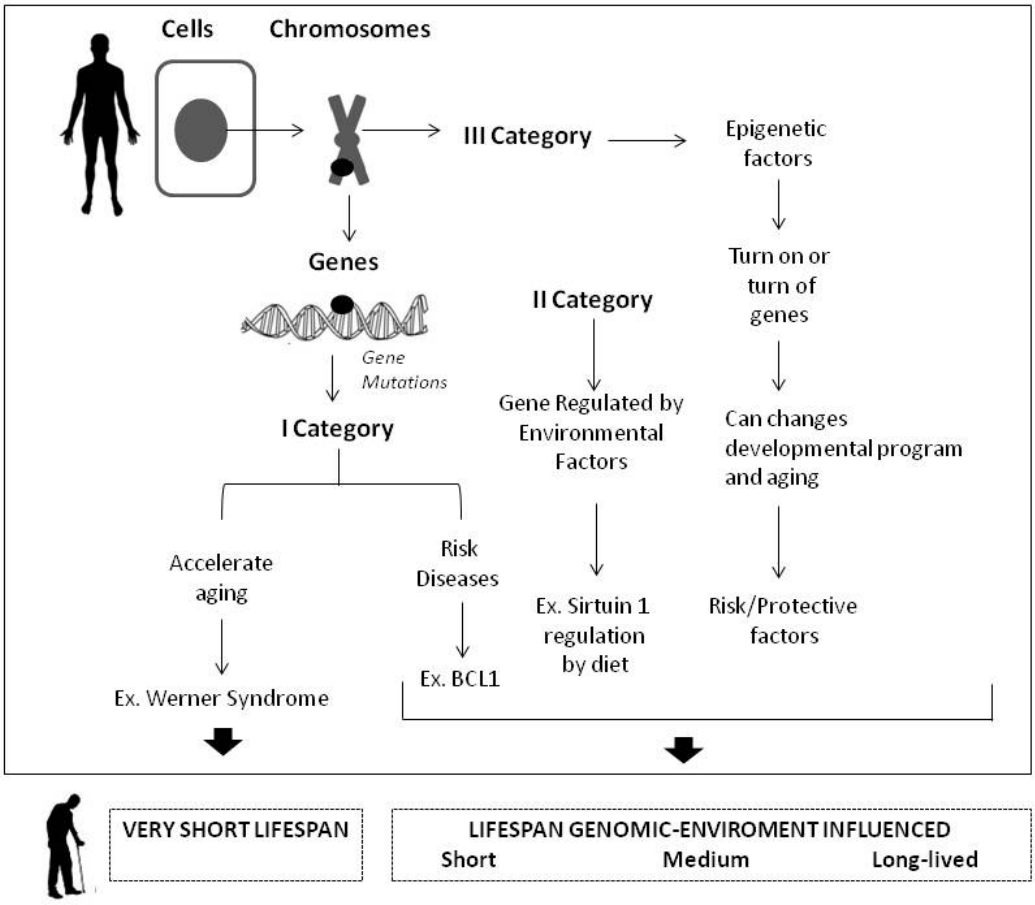

Figure 2. Schematic representation of three genes categories that can influence the aging patterns, health and human lifespan. Category I is constituted by genetic mutations that causes pathological aging acceleration such as Werner syndrome. Category II is constitute by regulatory and structural gene that are responsible to endogenous and exogenous molecules such as hormones and chemical molecules presenting in foods, respectively. During the developmental stages some genes need to be functional (turn on). However, in other biological moments these genes need to be turn off to maintain body homeostasis. The phenomena that turn on and turn off genes is know as epigenetic process. The category III includes alterations in epigenetic patterns that can increase (or decrease) risk of several chronic diseases. Both genes of category II and III are are highly sensible to dietary patterns, physical activity, emotional and physical stressors.

Particularly, I dedicated a large part of my research to identify and to evaluate the action of genes with SNPs included in this second category including studies of T102C SNP of 5-HT2A serotonin receptor; Apolipoprotein E SNP and Ala16Val SNP located in the superoxide dismutase manganese dependent enzyme gene (SOD2 or MnSOD).[34-41]

Specially Ala16Val-SOD2 gene that is produces an antioxidant enzyme that acts into mitochondria has being focus of my studies. SOD2 represents the major defense against reactive oxygen species (ROS) within the mitochondria, a cellular compartment where there is a continuous production of superoxide anion by the electron transport chain. The SOD2 enzyme catalyzes the dismutation of superoxide anion into hydrogen peroxide, which in turn is converted into water by glutathione peroxidase.[42] The control of superoxide anion and hydrogen peroxide concentrations is considered crucial to the cell because at low concentrations ROS can function as intracellular signaling molecules related to homeostatic regulation, whilst at high levels they can cause cellular damage.[43,44]

This Ala16Val-SOD2 SNP (rs4880) occurs in the target sequence of the SOD2 enzyme, where a valine to alanine substitution causes a SOD2 conformational change from beta-sheet to alpha helix, compromising the ability to neutralize O2- radicals. The α-helix SOD2 protein form produced by the A allele is related to a 30-40% increase in enzyme activity, whereas the V allele is related to reduced SOD2 enzyme efficiency.[45] Therefore, this polymorphism causes basal metabolic SOD2 imbalance and the results have suggested that overall superoxide anion scavenging efficiency in the cell is reduced but rather than this being related to

enzymatic activity, it is due to defects in its transport into the mitochondria.[46] The Ala variant is able to traverse both mitochondrial membranes quickly in order to enter the matrix, whilst most of the Val16 variant remain imbedded within the inner membrane.[46] This manifests itself as an imbalance in superoxide anion and hydrogen peroxide levels in mitochondria and several studies have described an association between an A-allele and AA-genotype with several types of cancer, such as breast and prostate cancer.[47-49]

On the other hand, other investigations have described an association between a V-allele and VV-genotype with metabolic morbidities such as hypercholesterolemia,[50] obesity,[51] cardiovascular dysfunction and diabetes complications.[52] However, these Ala16Val-SOD2 SNP derived outcomes are influenced by environmental factors such as dietary antioxidant intake and exercise.[53,54] Potential pharmacogenetic and toxicogenetic effects of Ala16Val-SOD2 polymorphism from *in vitro* protocols has being described for my research team in the last five years.[55-59]

Finally the last category includes the epigenetic genes. As commented by Kanherkar et al.[60] the exposition to several enviromnetal factors such as pharmaceutical and toxic chemicals, diet, stress, exercise, and other environmental factors can produce positive or negative epigenetic modifications with lasting effects on development, metabolism and health. These can impact the body so profoundly as to permanently alter the epigenetic profile of an individual. [60]

Therefore, environmental disturbs can be change the normal epigenetic landscape causing extensive modification in the expression of structural and regulatory genes. In this way, the impact of epigenetic genes is strong and can trigger modification in lifespan extension.[61] Due high impact on organism biology, I name the epigenetic genes as hyper-pleiotropic genes. Probably these genes are also the first line of survivelance genes that are impact on post-reproductive longevity.

LONGEVITY GENES OR SURVIVELANCE GENES? LESSONS FROM GENETIC STUDIES APPLIED TO SLOWING THE AGING AND HEALTH MAINTENANCE

I have devoted my academic life to research involving biology and genetics of aging and longevity. And for more intricate and complex that it is the biogerontology area, the available evidences until moment allows suggest that human longevity represents a subproduct of survivailence mecanisms "no existing real longevity genes". For this reason aging and consequently the human lifespan are highly modulated by environmental conditions presented an amazing phenotypic variation. Moreover, it makes sense to think that there are genes that fit to some environmental conditions to ensure the survival of the species. In these terms, these genes can help to increase the lifespan when the environment is not so favorable and to decrease lifespan when the environment was favorable enough to ensure survival the next generation. Within this evolutionary perspective, when we become very sedentary and obese we are "telling our genes" that environmental conditions are favorable, and we are no longer needed to help the next generation (our children) to survive!

The discovery that epigenetic modulation in the early development may alter the risk of chronic diseases in adults and elderly added new elements to understand the issue of aging and longevity. Pembrey et al[61] reviewed questions about transgeracional responses to early-life experience and commeting that "mammalian experiments provide clear evidence of male line transgenerational effects on health and development from paternal or ancestral early-life exposures such as diet or stress. Thus, variation, or changes, in the parental/ancestral environment may influence phenotypic variation for better or worse in the next generation(s), and so contribute to common, non-communicable disease risk including sex differences".

In these terms, it seems like the environmental conditions of the parents can modulate diferentially the epigenetic patterns of their children increasing or decreasing the risk of aging acceleration processes that trigger chronic diseases, and that these alterated epigenetic patterns can continue to be transmitted to the next generations. Therefore, probably epigenetic patterns are the key to explain "human and aging lifespan" and cultural differences related with longevity of several humans societies, taking as example Mediteranean and some Asian populations that historically mainly dietary healthy patterns. Populational investigations performed by me and Dr. Euler Esteves Ribeiro in riverine populations living in Amazon rainforest region also indicate that, despite the low acess to health services Amazonian elderly present several good indicators of health and longevity. Among these indicators, additional investigation performed by us and researches from Espanha and Japão showed that Amazonian elderly have a habitual physical activity related with daily activities[62] and consume a diet richest in fish and fruits, such as guaraná powder[63] that present a large number of positive biological effects.[64-70]

CONCLUSION

From the evidences, perhaps the main novelty that emerged and consolidated in these last 10 years in the biogerontology research involving genetic and epigenetics questions is concerns the question that when young adults take care of their health, they are not only increasing the chance of living more time free of diseases and dysfunctions, but also increasing the chance of their children having a long and healthy life. For this reason, the vanguard idea advocated a long time by Prof.Yukio Moriguchi that we should take care of our health through our diet and moderate physical activity from an early age is now the most current and accepted throughout the world.

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