

Metabolic Syndrome: Early Development and Aging

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Abstract

Adult metabolic and heart diseases have their origin early during intrauterine development and childhood. They can be traced to the inherited genome but patterns of cellular gene expression appropriate to the environment during development (epigenetics) also play an important role. This is particularly important during critical periods of time where structural and functional changes known as critical windows. There is a critical window of the pancreas when, if changes in diet occur, the risk of metabolic diseases during adulthood increases.

Aging is defined as a series of morphological and functional changes which take place over time. The term also refers to the deterioration of the biological functions after an organism has attained its maximum reproductive potential. The aging process is altered or accelerated when cardio-metabolic diseases are present but also aging makes organisms more susceptible to such ills. The same genes and proteins that might undergo epigenetic changes that predispose to metabolic diseases in the adult, also participate in the acceleration of aging with metabolic syndrome. Aging predisposes to metabolic syndrome, type-2 diabetes or insulin resistance; however, other predisposing conditions such as obesity, inflammation, changes in the activity of the hypothalamus-hypophysis suprarenal axis and in the activity of the autonomous nervous system, hypertension, also contribute to increase its prevalence.

Keywords: Metabolic syndrome; Early development; Epigenetic changes; Critical windows; Aging; Insulin resistance; Hypertension

Early Development

It is nowadays recognized that adult metabolic and heart diseases, begin early during intrauterine development and childhood. Many of them can be traced to the inherited genome but patterns of cellular gene expression appropriate to the environment during development (epigenetics) also play an important role [1]. Such nongenomic tuning of phenotype through developmental plasticity has adaptive value because it attempts to match an individual's responses to the environment predicted to be experienced. When the responses are mismatched, disease risk increases. Environmental influence on the genome is particularly important during critical periods of time where structural and functional changes during normal organ development known as critical windows [2]. Therefore it is important to consider the early development of an individual for a better understanding of cardio-metabolic diseases.

Epigenetics

The term epigenetics refers to processes which establish and maintain distinct patterns of cellular gene expression appropriate to the environment during development and that are mitotically heritable without changing the underlying gene sequence [1]. The epigenetic processes involving chromatin remodeling have received much attention in the last decade and play important roles in contemporary research in animal physiology. They consist of: A) DNA methylation which comprises the addition of a methyl group to nucleotides, which typically silences gene expression. Mammalian gene promoters contain cytosine-guanosine dinucleotide (CpG) sites which play a pivotal role in the control of gene expression. Methylation of the cytosine residues regulates transcription directly by inhibiting the binding of specific transcription factors, and indirectly by recruiting methyl-CpG-binding proteins and their associated repressive chromatin-remodeling activities. These epigenetic alterations are responsible for modulation of developmentally-regulated and tissue-specific gene expression [3,4]. B) Histone modification which consists of the acetylation mediated by histone deacetylases (HDAC) and/or methylation of chromosome

packaging proteins, C) Noncoding RNA (ncRNAs) activity, involving small RNAs, microRNAs and large RNAs, which has also been shown to play an important role in modulating protein activity *via* regulation of translation, transcription or protein structure. There is increasing evidence for regulatory roles of ncRNAs during development and in response to stress and environmental stimuli. MicroRNAs play a role in many diseases, including diabetes [5,6]. D) Parental effects generally can be defined as the change in offspring phenotype due solely to maternal and/or paternal influence without a concomitant change in offspring DNA sequence [7].

These changes result in life-long alterations in gene expression. Such nongenomic tuning of phenotype through developmental plasticity has adaptive value because it attempts to match an individual's responses to the environment predicted to be experienced. When a mismatch arises the risk of diseases increase as for example when either there are inaccurate nutritional cues from the mother or placenta before birth, or there is a rapid environmental change through improved socioeconomic conditions, these changes would contribute to the increasing prevalence of type-2 diabetes, obesity, and cardiovascular disease [1].

During early embryogenesis, the mammalian genome is 'wiped clean' of most epigenetic modifications, which are progressively re-established during embryonic development. Thus, the epigenome of each mature cellular lineage carries the record of its developmental history. The subsequent trajectory and pattern of development are also

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responsive to environmental influences, and such plasticity is likely to have an epigenetic basis. Epigenetic marks may be transmitted across generations, either directly by persisting through meiosis or indirectly through replication in the next generation of the conditions in which the epigenetic change occurred [8].

A definition of “epigenetic epidemiology” has been proposed and it is important to delineate how this emerging field can provide a basis from which to explore the role of epigenetic mechanisms in “developmental origins of health and disease” (DOHaD) [9].

Epigenetics of metabolic syndrome

There is evidence for the induction of different phenotypes by variations in the early life environment, including nutrition, which in man is associated with a graded risk of metabolic disease [10-13]. That there is a heritable or familial component of susceptibility to chronic non-communicable diseases such as type-2 diabetes, obesity and cardiovascular disease, is well established, but there is increasing evidence that some elements of such heritability are transmitted non-genomically and that the processes whereby environmental influences act during early development to shape disease risk in later life can have effects beyond a single generation [14].

Insulin is a master regulator of metabolic homeostasis and it is secreted from pancreatic beta cells in response to nutrient stimulation. Insulin gene expression begins early in the embryonic development of the pancreas and remains tightly-regulated at multiple levels throughout adult life. Previous studies have established the regulation of insulin activity at the transcriptional, post-transcriptional, translational, secretory, and even post-receptor levels. In mice and humans expression and secretion of insulin are epigenetically controlled by methylation of specific CpG sites in the promoter region of the gene. Additionally, miRNAs play an important role in the production and secretion of this hormone and levels of several miRNA in beta cells are regulated by nutrients such as glucose [4,6].

Maternal lifestyle and epigenetics

Maternal obesity might adversely affect fetal development, producing lasting effects on offspring, including predisposition to obesity and diabetes. Obesity and insulin resistance are closely linked. A growing body of evidence demonstrates that obesity and insulin resistance have a fetal origin in many patients.

Low-grade inflammation accompanies obesity. Maternal obesity induces fetal inflammation, which changes fetal skeletal muscle development by promoting adipogenesis. Obesity activates the JNK signaling pathway. JNK signaling activates JUN, which induces expression of inflammatory-related genes. Recent evidence points to the association between inflammation and epigenetic modification of key genes regulating myogenesis and adipogenesis, providing an additional mechanism for inflammation and altered fetal skeletal muscle development [15].

Stressful conditions and inflammation in the mother increase NF- κ B activity and elevate expression of pro-inflammatory cytokines which increase activation HDAC. Although HDAC inhibitors increase acetylation of histones, a condition associated with increased transcriptional accessibility, multiple reports have shown that HDAC inhibitors possess suppressive effects on immune response gene induction. HDAC inhibitors decreased TNF- α -induced monocyte adhesion *in vitro* and *in vivo* via suppression of the VCAM-1 gene [16,17]. Therefore HDAC inhibitors have been increasingly identified

as possible therapeutic approaches toward many inflammatory conditions, including cardiovascular diseases [18]. Therefore stressful conditions in the mothers might induce epigenetic changes in the offspring leading to increased risk of metabolic disease during adulthood.

Low birth weight and metabolic syndrome

Clinical observations indicate there are long-term health consequences for persons of low birth weight. Neel [19] proposed the first theory to explain this relationship based on the existence of a diabetic genotype known as the “economic or thrifty genotype”. It was based on epidemiologic studies in west North America where a high incidence of type-2 diabetes is observed and it proposed that “diabetic or economic genes” were selected during evolution from stages in which food was scarce. These genes favored that, after energy requirement fulfillment, the surplus substrates would be accumulated as fat to provide energy during long fasting periods until new food would be available. This condition that was beneficial during fasting periods is nowadays a predisposing condition to the development of insulin resistance, type-2 diabetes and obesity.

Some years later a complementary theory was proposed. Hales & Barker [20] explained the association of nutrient deficiency and diabetes during adult life, based on the “theory of programming”. They proposed that high insulin-mediated glucose utilization leads to the organic overwork of the pancreas in undernourished individuals during early developmental stages. Substrates in these individuals are destined to be used by the brain, leaving unprotected organs such as muscle, liver and pancreas thus leading to altered metabolism during postnatal life. The individual is programmed to survive in precarious conditions and when these conditions change the adaptations predispose to metabolic disease. This theory is in accordance to epigenetic explanations [21,22].

Examples of genes that are “epigenetically susceptible” being affected by perinatal insults have been reported such as the dual-specificity phosphatase 5 (DUSP5) and insulin-like growth factor (IGF-1). DUSP5 is a nuclear Erk-specific phosphatase which negatively regulates members of the mitogen-activated protein (MAP) kinase superfamily (ERK-1 and ERK-2) and also has as a target the insulin receptor substrate 1, a major component of the insulin signaling pathway. Alterations in histone acetylation and methylation of specific CpG sites of the DUSP5 gene are related to presence of insulin resistance in the adult [23,24].

IGF-1 is of vital importance for growth, normal carbohydrate metabolism in both mice and humans, and mediates many of the anabolic and mitogenic actions of GH in postnatal life. Low IGF-1 levels also contribute to adult insulin resistance [24,25].

Epidemiological Studies Relating Low Birth Weight to Disease Predisposition

Forsdahl [26] in the United Kingdom was the first to report a correlation between a nutritional deficit during childhood and an increased risk to develop diseases during adulthood. Wadsworth [27] reported that blood pressure was inversely correlated with birth weight in men and women born in 1946. In 1987, in Hertfordshire, one of the first retrospective studies was done with subjects born between 1911 y 1930, showing low weight at birth or during their first year of life. The results were published by Barker [28] and he showed a high incidence of hypertensive persons and people dying from cardio-vascular diseases. Hales [20] published that the same subjects also showed

altered glucose intolerance tests or type-2 diabetes. The rate of these conditions decreased in people who had higher body weight at birth. In India Yajnik [29,30] proposed that these diseases are also increased if there is an un-balanced diet during childhood or a change in lifestyle.

The Pima Indians are an isolated community which lives in Arizona and are genetically related to Mexican communities living in the Sierra Madre in Mexico. This community has a high incidence of insulin resistance and type-2 diabetes [31]. In contrast to inhabitants of the Sierra Madre the community in the United States shows obesity due to elevated calorie ingestion and low energy expenditure [31,32]. The early influence of diet during early childhood and genetic factors also play an important role in the development of insulin resistance and type-2 diabetes [33]. Numerous recent epidemiological studies associate early nutrition and low birth weight to an increased risk to develop obesity, diabetes and hypertension during adulthood [34-40].

Critical windows

Multiple studies demonstrate that poor *in utero* growth predicts adult morbidities, such as obesity and insulin resistance. There is growing evidence, primarily from animal studies, that supports the idea that processes put in motion during development that contribute to DOHaD do not necessarily reflect compromised growth or altered birth weight. Throughout the body of work investigating the DOHaD hypothesis, several themes have emerged, particularly the presence of critical periods of vulnerability.

The process of DNA methylation takes place *in utero* and in early postnatal development and is therefore a good candidate for disturbance by environmental interference, and thus provides a potential mechanism for fetal programming. Whereas methylation patterns are generally considered to be established in early postnatal life and persist thereafter, there is evidence from human monozygotic twin studies that methylation patterns can change with aging.

A critical window is a period of important structural and functional changes during normal organ development when exposure to certain environmental changes may originate life-time consequences [2].

Lucas [41] proposed the “programming theory” which describes how a dietary deficiency or imbalance might be kept in the memory of cells or individuals for the rest of a lifetime or even be transmitted to the next generation. This programming consists of a saving phenotype leading to more fat accumulation and a propensity to develop obesity and metabolic diseases and was afterwards named “metabolic or nutritional programming” [42]. In contrast to Lucas, Waterland [43] suggested that more than a “metabolic programming” it is a “metabolic print” leading to a “thrifty or economic phenotype”.

Since the earliest stages of evolution, organisms have faced the challenge of sensing and adapting to environmental changes for their survival under compromising conditions such as caloric restriction (CR) or stress. Implicit in these responses are mechanisms developed during evolution that include the targeting of chromatin to allow or prevent expression of fundamental genes and to protect genome integrity. CR is tightly related with the structure, stability and function of the chromatin of specific tissues and that it regulates several processes such as aging [44]. One of the factors by which CR induces changes in the chromatin is the NAD⁺-dependent deacetylases known as sirtuins (SIRT1-7 in mammals). The sirtuins are a family of proteins localized in various subcellular compartments that have been implicated in longevity, metabolic processes and stress resistance. Sirtuins are a highly conserved group of NAD⁺-dependent deacetylases and their

dependence on NAD⁺ suggests that they might be possible mediators of dietary restriction. NADH has been suggested to be more important to nutrient sensing than ATP.

In mammals, SIRT1 deacetylates many key transcription factors and cofactors, such as the tumor suppressor p53, forkhead box class O (FOXO) proteins, peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), and nuclear factor-κB. These specific actions may affect cellular pathways involved in glucose homeostasis. The effects of SIRT appear to be beneficial, as they trigger metabolic changes similar to those observed in CR. Indeed, CR increases the levels of SIRT1 in liver and muscle, which are key insulin-sensitive organs. In light of these observations, SIRTs have been proposed as a possible target for the treatment of metabolic syndrome (MS) [45].

The critical window of the pancreas

A postnatal critical window for the rat pancreas has been demonstrated [11]. The nutritional status during the breastfeeding period which corresponds to the pancreatic critical window, determines the development of glucose intolerance in adulthood and in turn predispose to development of type-2 diabetes [12]. In humans, critical windows also occur but it is difficult to identify them because they begin at earlier stages and continue for longer after birth [46].

The first month of life in the rat determines glucose homeostasis. During this period, rat pups are mother-fed with milk until day 21 when weaning occurs. Blood glucose and insulin levels are elevated in the rat during the suckling period and decrease after weaning [11]. Circulating levels of cortisol could cause the high glucose levels since this hormone induces a reversible loss of glucose sensitivity [11,47]. The insulin tolerance test in 20 day old rats is flat when compared to the adult [11]. Glucagon decreases throughout the first month and from day 6 to day 12 glucagon levels are higher than those of insulin. A decrease in the insulin/glucagon ratio induces glycogenolysis, gluconeogenesis and ketone body synthesis [48,49]. Therefore this neonatal period is characterized by physiologic hyperglycemia and hyperinsulinemia and by insulin resistance.

If the diet is changed during the suckling period in the rat, hyperinsulinemia and hyperglucagonemia are observed [50,51], beta cell secretory function is altered [12,52] and morphological changes within the pancreas are observed [53]. These changes program the pancreatic islet function in adult rats, resulting in the maintenance of hyperinsulinemia in the post-weaning period and eventually leading to the development of obesity in adult life [51,52]. The nutritional status during the breastfeeding period in humans also determines the development of glucose intolerance in adulthood and in turn predispose to development of type-2 diabetes [13]. Furthermore, low birth weight in humans is strongly predictive not only of obesity and diabetes but of hypertension, cardiovascular diseases and insulin resistance [54,55].

An epigenetically regulated gene involved in linking maternal diet to development of disease during adult life of the offspring is the hepatocyte nuclear factor 4-α (HNF-4α). HNF-4α is a transcription factor from the nuclear hormone receptor superfamily, which plays a pivotal role in development of the fetal endocrine pancreas, adult pancreatic function, and, consequently, glucose tolerance. HNF-4α has been linked to the development of type 2-diabetes [56].

Hyperglycemia and hyperinsulinemia modify vascular responses [57]. MS rats which have hyperglycemia and hyperinsulinemia, hypertriglyceridemia and central obesity have increased vascular contraction to KCl and norepinephrine and decreased vasorelaxation

when compared to control responses [58]. Insulin resistance is strongly associated to acute coronary syndrome in young people and limits endothelium dependent coronary vasodilation [59,60]. Hyperinsulinemia and insulin resistance are also present in rats which develop MS [61]. Changes in aortic vaso-reactivity during the postnatal pancreatic critical window, where insulin and glucose, are elevated have been studied and compared to those in control and MS rats [62].

Is there a critical window for hypertension?

It is nowadays recognized that adult heart diseases, coronary artery disease and essential hypertension begin in childhood, after studies of autopsies in which cardiovascular and renal modifications can be observed since the first decades of life. Therefore, risk factors can be identified from early development on and preventive measures can be taken from very early [63].

There is a tight correlation between adult blood pressure measured in children and their values when adulthood is reached [34]. Age, height, body mass, initial blood pressure levels and a family history of hypertension determine changes in blood pressure in children. Diet and levels of electrolytes also play a significant role in regulation of blood pressure in childhood. Cardiac output, left ventricular mass, renal blood flow and autonomic nervous system activity in children and young people correlate to increased blood pressure and future hypertension [64].

During the fetal stage, one of the mechanisms employed by the body to compensate a nutritional deficit is to protect vital organs shifting blood flow to favor important organs and diminishing blood flow to other regions [39]. The rennin-angiotensin system (RAS) is altered in low birth weight subjects [65]. Vessel structure is also modified having a reduced elasticity [36,66]. Cardiac myocytes which are completely differentiated before birth are also altered being bigger and less numerous [39].

Vascular dysfunction is present in many types of hypertension and in MS caused mainly by a decreased production or bioavailability of nitric oxide. In mammals, the production of nitric oxide is catalyzed by 3 isoforms of nitric oxide synthase (NOS) encoded by separate genes on 3 different chromosomes: neuronal NOS (NOS1), inducible NOS (iNOS) (NOS2), and endothelial NOS (eNOS) (NOS3). These NOS isoforms differ in their regulation and cell-specific distribution. The latter isoform, eNOS, is constitutively expressed and responsible for the majority of nitric oxide produced by the vascular endothelium. Both eNOS and iNOS are examples of epigenetically regulated genes in which DNA methylation and histone posttranslational modifications determine the expression in cells at specific conditions. Additionally, the expression of these enzymes is regulated by transcriptional, posttranscriptional and posttranslational mechanisms [17].

Histone deacetylases, particularly HDAC3 and HDAC7, are necessary for vascular normal development and they regulate genetic expression in diseases where transcription factor NF- κ B is implicated [17].

The RAS also participates in many types of hypertension. Environmental and maternal factors regulate the expression of some of the components of this system through epigenetic modifications and therefore favor the development of hypertension [67].

A high-salt diet limited to the prenatal period is not sufficient to program hypertension in adult offspring. However, this narrower critical period is sufficient to imprint a lasting hyper-responsiveness to stress, in adult female offspring. These data indicate that excessive

maternal salt intake during pregnancy can adversely affect the cardiovascular health of adult offspring [68].

Aging

Aging is defined as a series of morphological and functional changes which take place over time. The term also refers to the deterioration of the biological functions after an organism has attained its maximum reproductive potential. We do not know yet whether organisms start to grow old from the moment of conception or from maturity, or if aging constitutes a process of evolution or involution. Stress response genes and nutrient sensors regulate energy directed to cell protection and maintenance; when food is plentiful and stress levels are low, genes support growth and reproduction, in contrast harsh conditions favor a shift in gene activity towards cell protection and maintenance extending lifespan. Important genes in extending lifespan include kinase mammalian target of rapamycin (mTOR), AMP-activated protein kinase (AMPK), sirtuins and insulin/IGF-1 signaling. These genes integrate longevity pathways and metabolic signals in a complex interplay in which lifespan appears to be strictly dependent on substrate and energy bioavailability [69].

Both genome-wide and specific methylation profile/patterns change with age, and this may be genetically controlled. A generalized decrease in DNA methylation with age has been reported in mice and in cell lines, although this decrease may be tissue and/or gene specific. Decreased methylation may be accompanied by reactivation of previously silenced genes [70,71].

SIRT6 is a major neural histone deacetylase with important potential implications for common human diseases. Remarkably, SIRT6 deficiency causes dramatically increased acetylation of histones H3K9 and H3K56, despite the presence of several other histone deacetylases in the brain, including SIRT1 and SIRT2.

Schwer [72] link neural SIRT6 to GH/IGF1 signaling, a pathway conserved across phyla that affects lifespan, metabolism, cancer, and neurodegeneration and propose that SIRT6 functions as a central regulator of somatic growth and plays an important role in preventing obesity by modulating neural chromatin structure and gene activity.

IGF-1 mediated signalling is determining for longevity. Abnormalities in the insulin signaling pathway generate age-related diseases and increased mortality, whereas the GH/IGF-1 axis could potentially modulate longevity in many species. Moreover in humans, an age-related decline in IGF-1 levels occurs, and at old age, low IGF-1 levels are associated with frailty, poor nutrition and cognitive decline and an increased risk of death [73,74].

The aging process is altered or accelerated when metabolic and cardiovascular diseases are present and the risk of diseases increases with age. Many predisposing conditions which increase in prevalence during aging, such as obesity, insulin resistance, inflammation, changes in the activity of the hypothalamus-hypophysis suprarenal axis, stress and hypertension also contribute to increase prevalence of MS. Aging and the development of insulin resistance seem to be accelerated in the MS [75-77].

Aging and metabolic syndrome

The mechanisms that account for precocious aging in MS are incompletely known, but it is becoming clear that longevity genes might be involved. Experiments with overactivation or disruption of key lifespan determinant pathways, such as silent information regulator SIRT1, p66Shc, and mTOR, lead to development of features of the MS in

mice. Additional pathways are involved in linking nutrient availability and longevity, certainly including insulin and IGF-1 signaling, as well as FOXO transcription factors [78]. The same genes and proteins participating in the accelerated aging in MS are the possible blanks undergoing epigenetic changes during early development.

Although there is considerable disagreement on the underlying MS pathophysiology, clinical and experimental data support a link between SIRT1 and MS. Interestingly, the only clinical variable related to SIRT1 beyond MS components was age, which is physiologically related to SIRT1 function as a life-span determinant gene [45].

Aging and obesity

Obesity and aging are two overlapping and mounting public health problems. The prevalence of obesity has been related to the increasing prevalence of MS, which is growing progressively even among older age groups. Indeed, Insulin resistance observed with aging may be more related to adiposity than aging *per se* [79]. Obesity is strongly correlated with insulin resistance, although not all obese patients have insulin resistance, nor does insulin resistance always result in obesity [80]. Obesity is linked to an increased production of inflammatory adipokines that may alter insulin sensitivity and muscle mass [81].

Central, or visceral, adiposity has been particularly associated with insulin resistance and MS, but the mechanisms responsible for this association are unclear [82]. Obesity leads to insulin resistance through the increased liberation of free fatty acids. Fatty acids interfere with glucose transporter translocation through alterations in protein kinase C λ activity. They also down-regulate insulin receptor substrate 2 (IRS2) and increase the expression of the lipogenic transcription factor SREBP-1c [82].

Insufficient intracellular fat oxidation is an important contributor to aging-related insulin resistance, while the precise underlying mechanism is unclear. AMPK is an important regulator of intracellular fat oxidation and plays a key role in high-glucose and high-fat induced glucose intolerance [83].

It is well known that CR, in many ways opposite to obesity, increases lifespan. Pathways activated by CR include insulin/IGF-1 pathway affecting the downstream phosphatidylinositol 3-kinase/AKT/PDK kinase cascade, mTOR, AMPK and sirtuins [69]. When obesity is present, these pathways are regulated in the opposite direction accelerating aging.

Aging, inflammation and metabolic syndrome

Inflammation is a key factor in the progressive loss of lean tissue and impaired immune function observed in aging. Low-grade inflammation in adipose tissue contributes to insulin resistance and type-2 diabetes [84]. This conclusion is predominantly drawn from studies demonstrating associations between elevated (but 'normal range') levels of circulating acute phase inflammatory markers, typified by C-reactive protein (CRP), interleukin-6 and indices of insulin resistance and the development of type-2 diabetes. There is a debate as to whether these associations are independent of body fatness or, rather, an epiphenomenon of central obesity, an important source of inflammatory cytokines [85].

In addition to producing more inflammatory cytokines, adipocytes from old mice induce a higher inflammatory response in other cells. Sphingolipid ceramide is higher in old than in young adipocytes. Reducing ceramide levels or inhibiting NF- κ B activation decreases cytokine production, whereas the addition of ceramide increases

cytokine production in young adipocytes to a comparable level to that seen in old adipocytes, suggesting that ceramide-induced activation of NF- κ B plays a key role in inflammation [84].

There are predisposing factors for the chronic inflammation that occurs during aging. These include increased oxidative stress, a decrease in ovarian function, a decrease in stress-induced glucocorticoid sensitivity of pro-inflammatory cytokine production in men, and an increased incidence of asymptomatic bacteriuria [86].

An elderly immune system becomes more and more predisposed to chronic inflammatory reactions and is less able to respond to acute and massive challenges by new antigens. A young immune system has to cope quickly and efficiently with acute immunological challenges to assure survival and the reaching of reproductive age. Such reaction capability gradually burns out because of lifelong antigenic attrition. Moreover, lifelong antigenic challenges and the increasing antigenic burden determine a condition of chronic inflammation, with increased lymphocyte activation and proinflammatory cytokines [86].

Polymorphisms in the promoter regions of pro- and anti-inflammatory cytokine genes influence the level of cytokine production and the aging process. Nutrients with anti-inflammatory properties, such as vitamin E and n-3 polyunsaturated fatty acid, may reduce the level of chronic inflammation and thereby ameliorate tissue and functional loss during aging. New evidence suggests that, for the latter nutrient, gene-nutrient interactions occur that alter the effectiveness of dietary therapy [87].

Aging, central nervous and stress responses and their influence on metabolic syndrome

During aging there is a decreased response to stress-induced glucocorticoid sensitivity. Aging has been associated with immunological changes that resemble those observed following chronic stress or glucocorticoid (GC) treatment. Immunosenescence could be associated with changes of peripheral GC levels [88].

Leptin, in addition to regulating appetite and energy expenditure, also regulates corticotropin function [89]. Weight gain increases feedback to the brain (via hyperleptinemia), which in turn results in hypothalamus-pituitary-adrenal axis (HPA-axis) and sympathetic nervous system overdrive, impaired insulin secretion and insulin resistance [90]. HPA-axis overdrive would account for metabolic abnormalities such as central adiposity, hyperglycemia, dyslipidemia, and hypertension, which are well known clinical aspects of the MS [90].

The HPA axis could be stimulated by central factors followed by discrete, periodical elevations of cortisol secretion during normal conditions. A prolonged period of HPA axis stimulation is followed by a continuous degradation of the regulatory mechanisms. The final stage is sustained cortisol secretion with low morning values [91,92].

Stress responsiveness is decreased during aging. The unavoidable chronic overexposure to stressors determines a highly pathogenic sustained activation of the stress-response system, leading to a progressively reduced capacity to recover from stress-induced modifications [86]. Glucocorticoids, the adrenal steroid hormones secreted during stress, may account for this relationship [93].

Stress is a potent modulator of immune function, which in youth can be compensated for by the presence of an optimal immune response. In the elderly the immune response is blunted as a result of the decline in several components of the immune system (immune senescence) and a shifting to a chronic pro-inflammatory status

(the so-called 'inflamm-aging' effect) [94]. Aging is accompanied by a greater increase in sympathetic traffic in women than in men, and inflammation (measured via CRP) seems to be more strongly related to the MS in women than in men [95].

Sympathetic nerve fibers innervate white adipose tissue and stimulate lipolysis, leading to the release of glycerol and free fatty acids. There is also a functional parasympathetic innervation and a distinct somatotropy within the parasympathetic nuclei: separate sets of autonomic neurons in the brain stem innervate either the visceral or the subcutaneous fat deposit. Parasympathectomy induces insulin resistance associated with glucose and fatty acid uptake in the fat depot and has selective effects on local hormone synthesis [96,97].

The autonomic nervous system modulates glucose and fat metabolism through both direct neural effects and hormonal effects. Locally released norepinephrine from sympathetic nerves is likely to increase glucose uptake in skeletal muscle and adipose tissues, independent of insulin, but norepinephrine does not contribute as much as epinephrine to hepatic glucose production. Alterations of central neurotransmission and environmental factors can change the relative contribution of sympathetic outflow to the pancreas, liver, adrenal medulla and adipose tissues, leading to the modulation of glucose and fat metabolism. Recent studies have proposed that leptin, an adipocyte hormone, induces the central nervous system to increase sympathetic outflow independently of feeding [82].

One of the genes involved in aging is mTOR. Its inhibition increases resistance to environmental stress, consistent with a physiological shift towards tissue maintenance and an increase in lifespan [69]. The decreased stress response during aging might be caused by mTOR's diminished expression.

Mammals have developed an endogenous circadian clock located in the suprachiasmatic nuclei of the anterior hypothalamus that responds to the environmental light-dark cycle. The circadian clock influences nearly all aspects of physiology and behavior, including sleep-wake cycles, cardiovascular activity, endocrine system, body temperature, renal activity, physiology of the gastrointestinal tract, and hepatic metabolism. Moreover, disruption of circadian rhythms leads to metabolic disorders like manifestations of the MS [98]. Circadian rhythms are altered during aging [99].

The clock machinery comprises complex transcriptional-translational feedback loops that, through the action of specific transcription factors, modulate the expression of as many as 10% of cellular transcripts. This marked change in gene expression necessarily implicates a global regulation of chromatin remodeling. Indeed, various descriptive studies have indicated that histone modifications (like acetylation) occur at promoters of clock-controlled genes (CCGs) in a circadian manner. Moreover SIRT1 is a central physiological and molecular link that connects chromatin remodeling to circadian and metabolic processes. SIRT1 appears to modulate circadian gene expression by repressing transcription through its HDAC activity in a time dependent manner, presumably by enhancing localized chromatin condensation [100].

Aging and hypertension

Diminished insulin sensitivity is a characteristic feature of various pathological conditions such as the MS, type-2 diabetes and hypertension [101]. There are twice as many hypertensive patients among diabetics than there are among non-diabetics [102].

Patients with essential hypertension are more prone than normotensive subjects to develop diabetes, and this propensity may reflect decreased ability of insulin to promote relaxation and glucose transport in vascular and skeletal muscle tissue [101,103]. Although the etiology of skeletal muscle insulin resistance is multifactorial, there is accumulating evidence that one contributor is overactivity of the RAS [101,103].

Numerous studies focus on comparing the differences in development and aging patterns between hypertensive and normal rats. The contractile responses of vascular smooth muscle to norepinephrine, KCl, 5-hydroxytryptamine, electro-stimulation and calcium-free physiological solution are increased during development and maturity in normal rats. Endothelium-dependent relaxation mediated by acetylcholine as well as isoproterenol, which is mediated by the β -receptor, falls during rat maturation [104].

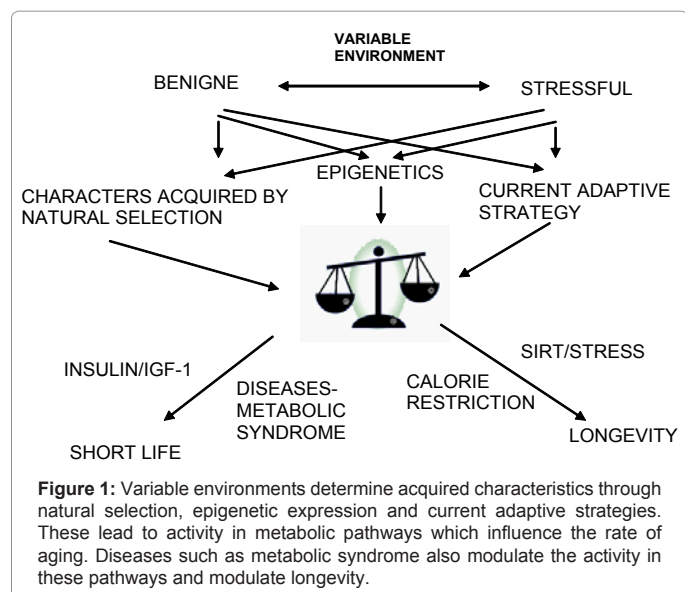
In an experimental hypertension model in rats, based on a fructose-rich diet, endothelin expression is increased in blood vessels, while nitric oxide levels are not modified [105]. In another rat model of hypertension obtained by administering 30% sucrose in the drinking water for 20 weeks, an increased insulin-dependent endothelin response of the vessels has been found [57]. The sucrose-fed rat becomes hypertensive, hypertriglyceridemic, hyperinsulinemic and also has insulin resistance; it develops MS [61]. Some characteristics of the aging process in this model have been reported. Sucrose-fed animals showed increased central adiposity, insulin was increased at 6 months in MS rats and this increase accompanied the maximal blood pressure and contractility. Values for all of these variables decrease after this age. Triglycerides were increased at all ages in the experimental group. Glucose was increased in both MS and control rats at 18 months and is therefore a consequence of the aging process [106]. In control rats, systolic blood pressure did not change at the ages studied. As expected, blood pressure in MS rats was higher than in control animals, showing a maximum value at 6 months of age; this value then diminished considerably and in very old rats (18 months), it was even lower than in control rats of the same age. Therefore rats clearly showed premature aging due to the MS [106].

Future Perspectives and Conclusion

The variability of the environment determines acquired characteristics through natural selection, epigenetic expression and current adaptive strategies. These lead to activity in metabolic pathways which influence the rate of aging. Diseases such as metabolic syndrome also modulate the activity in these pathways and therefore modulate longevity (Figure 1).

The finding of epigenetic factors involved in MS pathogenesis has favored the development of new therapeutic measures. AMPK has been a target for treatment of type-2 diabetes and MS using drugs that stimulate its activity such as metformin or thiazolidinediones. AMPK regulates transport and oxidation of fatty acids, mitochondrial biogenesis in skeletal muscle and insulin synthesis and secretion by phosphorylating transcription factors or transcriptional co-regulators such as FOXO, HNF-4 α and PGC-1 α that are also a target of SIRT1. Additionally, exercise and CR also positively regulate AMPK activity. All these measures decrease morbidity and mortality of SM.

It is important to study the life history of an individual to better understand pathologies since many adult metabolic and heart diseases, such as obesity, MS, type-2 diabetes, hypertension and arterial coronary diseases can be traced to early intrauterine development



and childhood. The study of the diseases in aging individuals is also important since aging not only modifies their characteristics but it may accelerate the aging process. The aging process may also predispose to appearance of diseases. The aging of the world's population contributes to the growing prevalence of the MS.

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