Genetic epidemiology on casual theories and pathogenesis of type 2 diabetes mellitus

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Abstract

Diabetes mellitus type 2 (DM2) is a worldwide public health problem. The etiology of the disease is multifactorial and is characterized by great heterogeneity of metabolic disorders. The most common are the insufficient production of insulin, insulin resistance and impaired incretin system. The specialist must understand the multi-causal nature of DM2 in the post-genomic era. This nature is determined by the additive effect of genes and environment, so there is no simple genetic epidemiological model to explain the inheritance pattern. Hence the need to establish the proportion of disease that is determined by genes and the contribution of environmental factors, the combination of which regulates the threshold or tolerance level for diabetes development. Given this complexity in DM2 in this work are discussed the various existing theories of causality of this disease, which will permit us to understand the interaction between the environment and the human genome, and also to know how risk factors or predisposition to this disease influence, laying the grounds that delimit environment interaction with the genome.

KEY WORDS: Environment. Diabetes mellitus type 2. Genome. Pathogenesis. Public health.

Introduction

The incidence and prevalence of type 2 diabetes mellitus (DM2) has been reported in up to 90% of total diabetes cases^{1,2}. The World Health Organization has predicted that by the year 2025 there will be more than 300 million diabetics in the world and, out of them, 40 million will correspond to Latin America and the Caribbean. Half of them will not be diagnosed before chronic complications begin^{3,4}. There are some indigenous populations where the prevalence of DM2 is lower owing to environmental factors such as the diet (endemic/traditional), which acts as a protecting factor⁵, but there is a process of lack of education with regard to urban nutrition, which considerably increases the prevalence in rural indigenous communities⁶.

DM2 is a disease of multifactorial etiology, characterized by great heterogeneity of molecular defects, such as insufficient insulin production by pancreatic β cells, insulin resistance and incretin system defects, which translate into alterations in the metabolism of fats and proteins^{4,7-10}. There can be overlapping with diabetes of the young mature adult, produced by pancreatic β cells genetic defects, or else there can be overlapping endocrinopathies, infections, gestational diabetes mellitus and autoimmune diabetes forms⁸. It is part of the Down, Klinefelter and Turner syndromes, among others, natural evolution^{8,9}.

Epidemiologically, DM2 occurs more commonly in the adult population^{9,11}. However, there are reports showing an early age of onset, between 18 and before 40 years^{12,13}. As a whole, these works provide evidence of variable onset age. Diabetes has been

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proposed to be related to partial deficit of and resistance to insulin, as well as to the response to oral hypoglycemic agents^{9,11}. It is a complex disorder owing to an association with variable degrees of hereditary predisposition and the participation of environmental risk factors, such as stress, overweight, central or abdominal obesity, sedentary lifestyle, hypercaloric diet, saturated fat and simple carbohydrate-rich and fruit and vegetable-poor diet^{3,4,9-10,12-18}.

Type 2 diabetes mellitus causality theories

The analysis about the pathogenesis of DM2 provides an overview of the interaction of the environment with the human genome and risk or predisposing factors, which should be considered by public health experts when designing epidemiological studies^{7,8}. Genetic and molecular heterogeneity of diabetes is a reflection on DM2 multifactorial nature, which directly impacts on the evolution of chronic complications and treatment response. Therefore, there is no simple genetic model that explains familial aggregation. Studies establishing the percentage of disease that is determined by genes and the contribution of environmental factors are required¹⁹. The present work discusses most theories on the origin of diabetes, from environmental studies in the decade of 1960 to the molecular biomedical investigations in 2016.

Thrifty genotype theory

In 1962, J.R. Neel proposed the “thrifty genotype” theory, which explains that DM2 is an evolution process of the genes of metabolism. It claims that there is a thrifty genotype, which in the Paleolithic population (hunter-gatherers) translated into an efficient metabolic system to assimilate nutrients and store them in the form of fat in periods of food abundance, which warranted their survival in periods of famine during the Fourth Glaciation. The population that had such adaptive genotype lived in that primitive society. Current heirs of these population are Latin American post-colonial societies that, owing to the transition into industrialized societies with high intake of energetic foods (abundant intake) suffer a negative selection that enables the appearance of obesity and diabetes. Neel referred that this process occurred in Europe in the 18th century, where only individuals without the thrifty genotype survived²⁰. The thrifty genotype comprises many genes, and it is a line that has to be followed in diabetes epidemiology in Latin America,

since it explains diabetes in post-colonial societies, which show abundant consumption of highly energetic foods. Many of these genes encode growth factors, hormone receptors, vascular regulators and regulators of the hepatic metabolism of lipids, among others. Formerly, the *APOE* gene had been proposed as part of that genotype⁸. Currently, we have explored the *LRP2*, *HPSE* and *ELMO1* genes in the Mexican population. The proposed genes include *HPSE*, which encodes heparanase, an enzyme that regulates extracellular matrix heparan sulfate metabolism, important in the binding of apolipoprotein E to the vascular endothelium, the alteration of which favors atherogenesis and diabetes-associated vascular dysfunction; *LRP2*, which encodes a lipoprotein receptor, which works through a mechanism of renal endocytosis, since its deregulation drives to dyslipidemia and diabetes; and *ELMO1K*, a cytokinesis regulator in the centrosome, the deregulation of which leads to diabetes. In association studies, these genes have demonstrated their effect on the risk for longstanding diabetes, the clinical phenotype of which is insulin resistance. Interaction of these pleiotropic genes in association studies with their polymorphisms can explain the risk for the development of hypertension, dyslipidemia, fatty liver, overweight and obesity, which are stages previous to DM2²¹⁻²⁴.

Insulin resistance or the not so thrifty gene

Genetic information was slowly shaped, with no big important changes across each one of the evolutionary process stages, from *Ardipithecus ramidus*, of arboreal life, to current *Homo sapiens*, with our nutritional requirements thus being determined. During these evolutionary stages, the “thrifty genotype” emerged, expressed by leptin resistance, as well as the “not so thrifty genotype” characterized by insulin resistance. Muscle insulin resistance was key to survive in periods of famine, which were quite frequent for *Homo ergaster*. Hepatic and renal gluconeogenesis enabled maintaining blood glucose at normal levels during fasting; this adjustment is much more effective if skeletal muscle possesses insulin resistance, since this tissue is forced to use fatty acids originating in adipose tissue reserves, with glucose in turn being reserved for consumption almost exclusively by the brain and red blood cells, since both these tissues are highly dependent on glucose for their metabolic functions²⁰. Muscle insulin resistance, by producing high concentrations of circulating insulin, favors triglyceride

accumulation in the adipose tissue, which favors adipogenesis²⁵. To explain this theory, the *CPN10* gene has been proposed, which encodes calpain 10, a muscle protease; the heterozygous genotype of its polymorphism SNP43 is related to lower mRNA amounts in striated muscle and proteolysis¹⁸.

Insulin resistance was the mechanism that allowed Fourth Glaciation migrants surviving during prolonged fasting periods, preserving muscle mass, which enabled them to successfully hunt at first opportunity or being able to flee from predators. Preserving muscle mass meant increasing glycosuria and decreasing proteolysis. Studies on the *CPN10* gene support this theory, since it encodes a protease of the muscle cytosolic cistern. In the Pima Indians, homozygous carriers of SMP49 polymorphism G allele show lower amounts of mRNA in striated muscle. Variations in this gene have already been associated with DM2 in Mexican populations. We postulate that variants of the *GLUT2* gene (which encodes type 2 glucose transporter and is implicated in renal Fanconi syndrome, a type of hepatorenal glucogenesis with glycosuria, phosphaturia, amino aciduria and mucopolysacchariduria) might support this hypothesis. In an exploratory study in patients with DM2 in a population of southern Mexico, we did not find association of this gene, but it should be further studied, since its product, type 2 glucose transporter, is one of current targets in DM2 treatment, since it is glycosuric².

Thrifty phenotype theory

The thrifty phenotype hypothesis proposes that both intrauterine and childhood undernutrition can program gene expression to the benefit of survival. The brain is protected over other tissues, which leads to a metabolic programming that is conditioned by bioenergetic substrate scarcity^{26,27}. Intrauterine malnutrition, in particular protein deficit, has demonstrated an alteration on the pancreatic function with a decrease in Langerhans cells and a decreased insulin-secreting capability. According to this hypothesis, undernutrition, which is characterized by low birth weight, would elicit an in utero programming that would explain most part of obesity, metabolic syndrome and DM2 in an adult born with low weight for gestational age, and who subsequently is exposed to an environment of alimentary abundance. Moreover, evidence from numerous studies indicates that this programming is not restricted to the first generation^{18,27,28}.

Theory of programming (Barker hypothesis)

This association theory postulates that if there is a stimulus or aggression in utero (intrauterine malnutrition) during a critical period, this produces a temporary or permanent change in the structure and function of the body (fetal programming)^{29,30}. Currently, four birth phenotypes related to diseases at adult age have been identified, out of which two explain alterations related to glycemic control. The first one indicates that slim newborns tend to be insulin resistant when they become adults, and the second short height and high weight infants with lower insulin production, which generates DM2 at adult ages. This gives rise to the hypothesis of fetal origin of disease, which would originate DM2 and chronic conditions owing to fetus adaptation to intrauterine malnutrition^{31,32}.

Genomic imprinting

The human being has a unique epigenetic mark that is partially inherited and partially generated in utero, with changes in adult life^{33,34}. These epigenetic changes are generated by different routes, such as histone and gene methylation, histone acetylation, ubiquitination, sumoylation, phosphorylation, ribosylation, glycosylation and non-coding RNAs. In the conception phase, two moments of switching off and programming of a new gene have been documented to exist: the first moment occurs during gametogenesis and, the second, at pre-implantation, when the genome is demethylated; during these two methylation processes, the epigenetic program becomes vulnerable to alterations generated by the fetal environment, with some theories suggesting that these alterations would generate disorders in adulthood, such as DM2³⁵. However, recent data indicate that during childhood, adolescence and puberty epigenetic alterations that would affect the endocrine system can also occur, since at these stages there is a relative increase in DNS synthesis and cell growth^{36,37}.

Nutrition plays a protective role, but also can trigger these processes. Currently, the decrease in methyl groups' donors (folates, methionine and choline) dietary intake, and the consumption of sulfur-poor diets, have been identified to produce a modification in cysteine formation, thus being associated with a decrease in DNA methylation. However, unlike gene polymorphisms, which are permanent, there environmental

are not; nevertheless, factors such as stress, little exercise, inadequate diet, inflammatory processes, hyperglycemia, obesity and oxidative stress will condition overexpression of some genes. In addition, something important about errors in the DNA methylation process is that they increase as the subject gets older, thus causing an increase in the risk of suffering from DM2^{38,39}.

Environmental factors, such as hyperglycemia, which are generated by foods with high glycemic index, contribute to produce toxic compounds by four fundamental pathways: the polyol pathway, the formation of advanced glycation end-products (AGEs), the protein kinase C activation pathway and the hexosamine pathway; this causes higher production of oxygen reactive species (ROS), nitrogen reactive species and O_2^- increase, thus generating an oxidative stress situation that leads to pathways directed to epigenetic alterations and apoptosis⁴⁰.

Diverse studies explain that hyperglycemia affects the expression of certain genes and chromatin modifications, as it is the case of the association between the chemical changes of histone H3 amino-terminal tails and lysine-specific methyltransferase Set7. This expression helps to improve chromatin accessibility and β -cell genes transcription, which indicates that this is the cause of vascular gene expression in response to previous hyperglycemia episodes⁴⁰. This is supported by findings in an experimental model with sheep that suffered moderate maternal undernutrition, where methylation of gene promoters (POMC) and fetal hypothalamus glucocorticoid receptor were found to be reduced, thus altering energy balance regulation and being associated with DNA methyltransferase lower activity and methylation alteration, as well as with histone acetylation, which generated the hypothesis that hypocaloric or protein-poor diets during pregnancy are implicated in the offspring being programmed towards the development of obesity and DM2⁴¹.

Another study with monozygotic twins of between 53 and 80 years of age, divergent for DM2, identified 789 CpG sites in skeletal muscle and 1458 in the subcutaneous adipose tissue, which were differentially methylated⁴², with some of them being located in genes as important as *PPARGC1A* and *HNF4A*, which could lead to an increase in hepatic glucose production that, in turn, would contribute to increase hyperglycemia risk and, if maintained, to generate insulin resistance and DM2. Volkmar et al.⁴³ described a considerable number of hypermethylated genes in

DM2 patients' islets, which participate in pathways that have been identified to preserve β -cells survival and functioning. It is suggested that these epigenetic mechanisms are implicated in β -cell dysfunction and DM2 genesis.

With regard to fat consumption, a pattern has been reported in DM2 pathogenesis that suggests that hyperlipidic and hypercaloric diets generate an increase in the production of short chain fatty acids as long chain fatty acids byproduct, which would lead to changes in DNA methylation that cause promotor hypomethylation and pro-inflammatory cytokines deregulation, generating peripheral insulin resistance³⁸. These results indicate that several epigenetic mechanisms can be implicated in β -cell dysfunction and in diabetes pathogenesis, which opens the door to the study of the role of nutrition, oxidative stress and inflammatory processes.

Four birth phenotypes have been currently identified as being associated with diseases at adult age, out of which two explain alterations associated with glycemic control. The first one indicates that slim newborns tend to be resistant to insulin when they become adults, whereas the second correlates low height and high weight infants with lower insulin production, which generated DM2 at adult ages. This theory, somehow forgotten, is closely related to genomic imprinting. Metabolic programming for adult age takes place at last trimester of pregnancy, and is associated with insulin resistance. One of the genes that might be implicated is the gene that codes for aromatase, *CYP19A1*, since it turns estrogen into androgen in peripheral tissues, such as fatty tissue and muscle, among others. It is associated with a clinical phenotype characterized by virilization, hyperandrogenism, gestational diabetes and insulin resistance, which is a metabolic reprogramming pathophysiogenic mechanism. Some preliminary epidemiological studies, where we have collaborated, in Mexican population with regard to this gene, show their association with DM2 and diabetic retinopathy.

Another line to explore, which requires further study, is the high consumption of saturated fats. Hyperlipidic and hypercaloric diets have been suggested to generate an increase in the production of short chain fatty acids as long chain fatty acids byproducts, which would lead to changes in DNA methylation that cause promoter hypomethylation and pro-inflammatory cytokines deregulation, generating peripheral insulin resistance, which can associate with DM2, with β -cell dysfunction occurring. One of the genes that have been

explored in this sense in the Mexican population is the *TJP1* gene, which encodes type 1 tight junction, which in turn participates in cell-cell contacts and is important in pancreatic morphogenesis during embryogenesis; it also regulates the flow of nutrients, such as glucose and cholesterol, at cell apical and basolateral levels⁴⁴.

Theory of genetically unknown foods

The consumption of foods the human being is not genetically designed for can be a factor leading to the development of DM2. This hypothesis has become fashionable over the past 20 years. Evidence on this subject can be first applied to the consumption of refined sugars in sweeteners (contained in carbonated beverages), which leads to the development of hypertriglyceridemia, a risk factor for the development of DM2. On the other hand. There is a change in the type of consumption of salts contained in food: the human being is metabolically designed for potassium citrate, but many foods currently have high sodium chloride content, a type of salt we have coevolved with, but that can induce nephrosclerosis and favor kidney damage in diabetics, as it has been demonstrated in rodent models. However, potassium citrate is nephroprotector and keeps renal health safe⁸. This is polemic, since humans have coevolved with sodium chloride, but it also explains the high prevalence of systemic arterial hypertension that is closely associated with diabetes, which indicates that there are environmental risk factors, such as a sodium chloride-rich diet, that favor the development of vascular complications in diabetics.

In spite of current controversies around foods manufactured based on genetically modified organisms, which might be regarded as genetically unknown, there are still many open questions about the scope of the concept and its real effects. The horizontal gene transfer mechanisms are not only restricted to microorganisms, but to plants as well, thus being a "natural" transgenesis process. As an example, sweet potato (*Ipomoea batatas* [L.] Lam.) can be cited, a food that has traditionally been consumed for centuries in some countries of the American continent, which has been shown to have a close gene exchange relationship with *Agrobacterium tumefaciens* (bacteria used to generate transgenic vegetables) for thousands of years⁴⁵. Nevertheless, sweet potato is and will be considered harmless by the populations that consume it and by scientific studies that reveal its benefits, as

well as its known risks, for health. In contrast, studies on transgenic foods noxious effect, in particular of transgenic corn, consumed for generations, have not been fruitful or conclusive, since there is no current information in the scientific literature demonstrating their association with the development of DM2. On the contrary, a loss of objectivity, inconsistencies and possible manipulations have been observed associating them with the development of diseases regarded as global health problems⁴⁶. This fact might be related to purely commercial and not scientific conflicts of interests.

On the other hand, it should be considered that the human being is designed for a basal metabolic rate of 4.18 MJ/L (the physiological limit imposed by evolution), and when consuming fat and solid-state sucrose-rich foods in excess (western diet), DM2 genesis is favored owing to an energy balance alteration. Populations that still have the thrifty genotype, such as the Pima Indians, are metabolically incapable to confront these dietary habits, which are diabetogenic for them, while other populations, such as Europeans, have managed to adapt⁴⁷. The Pima Indians, as well as other populations, were metabolically shaped by low fat and energy density nutritional surroundings (thousands of years ago, during the Fourth Glaciation), where diets containing > 10-15% of fat were impossible to obtain⁴⁷. An example is the fact that coronary disease mortality is 16.7-fold higher in the USA than in rural China, where fat intake is lower and cholesterol mean concentration is 3.28 mmol/L (127 mg/dL), in comparison with 5.24 mmol/L (203 mg/dL). European subjects, even in spite their relative adaptation, have been reported to be unable to maintain energy balance (they gain weight) when switching from a low energy density to a high energy density diet⁴⁸. This is not surprising if we consider that, when populations were hunter-gatherers, fat-rich diets were practically inexistent and, therefore, such diets can only be seen in current nutrition.

However, the effect some compounds contained in plants is partially unknown. Currently, in some populations of indigenous origin, such as southern Mexico populations, some vegetable foods, mainly in the form of extracts or infusions, are able to reduce hyperglycemic symptoms and sometimes are even considered as part of diabetes mellitus treatment.

In vitro or in vivo assays with animal models have enabled to identify that the antioxidant and inhibitory activity (phenolic and terpene compounds) of enzymes of the carbohydrate metabolism shown by

these compounds supports their traditional use, or otherwise through the glucose-lowering chemical properties of natural foods⁴⁹, which would imply that the human body has evolved together with the consumption of these foods, mainly in populations that use them as traditional treatments.

Hypothesis of the ischemic origin

On the other hand, a different pathogenesis has been reported, which explains that DM2 primary cause is of ischemic origin due to a transient or permanent blood irrigation on the anterior hypothalamic nuclei, which would elicit descendent parasympathetic pathways and anterior hypothalamus axis hyperexcitation, thus increasing blood glucose and lipid concentrations, as well as adipose tissue accumulation, with the latter being the main implicated in insulin resistance and hyperinsulinemia. Ischemia elicits chronic progressive deficiency in insulin secretion, which favors β -cell necrosis owing to a lack of irrigation. In this sense, islets have been shown to be highly dependent on blood supply, which makes them extremely vulnerable to ischemic changes⁵⁰.

Syndrome of multiple organ resistance and Corkey's model

Both in cardiac and skeletal muscle, the endothelium, hepatocyte, adipocyte and β cell, multiple and simultaneous resistance has been reported to exist at the level of the leptin, adiponectin and insulin receptors, which translate into the coexistence of obesity, hyperphagia and DM2⁵¹. In this sense, Corkey⁵² observed an excessive secretory response of β cells, possibly owing to environmental factors or factor X (fictitious), which leads to hyperinsulinemia and subsequently to insulin resistance. This secretion may also be genetically determined and hence, the factors indirectly modify redox indicators' circulating values, with increased insulin secretion, which is maintained, thus causing hepatic-origin insulin resistance and body mass increase, and subsequently the development of DM2⁵². One of the genes that is worthwhile exploring in the sense of the hypothesis is *ATXN2*, since it has many simultaneous pleiotropic effects on different tissues, and its dysfunction in rodent models produces fatty liver, insulin resistance, obesity and neurological problems. Some polymorphisms are

associated with obesity; in Mexico, we have found association of this gene with variable number of tandem repeats (VNTR) diabetes in patients whose clinical phenotype is insulin resistance and obesity.

Conformational disease and its relationship with aging and oxidative stress

Conformational diseases arise from dysfunctional proteins aggregation in non-native conformations. DM2 can be defined as a conformational disease because one β -cell constituent protein, islet amyloid polypeptide, suffers a change on the tertiary structure, followed by self-association and tissue deposition⁵³. On one hand, DM2 is associated with several metabolic disorders that result in excessive production of ROS and oxidative stress. These ROS set a series of redox reactions in motion, which can result in unstable nitrogen and thiol that contribute to additional redox stress⁵³. The ability of a cell to confront ROS and oxidative stress requires functional chaperons, production of antioxidants, degradation of the protein and a cascade of intracellular events collectively known as unfolded protein response. β cells are known to be particularly susceptible to disturbances in this quality control system, and ROS are known to play an important role in the development or progression of DM2⁵³. Oxidative stress and insulin production contribute to endoplasmic reticulum stress increase, to protein unfolding and to unfolded protein response. Since the cell quality control system is overwhelmed, intermediate islet amyloid polypeptide changes and stable oligomers with β folded sheet antiparallel crossed structure generation are produced, which eventually accumulate as space-occupying lesions within the islets⁵⁴.

In principle, dysfunctions of different organs, such as the pancreas, can be regarded as being the result of a decrease in the number of cells, a fact that Hayflick⁵⁴ documented when observing that human fibroblasts had a limited replication capability in vitro; however, diverse studies refuse that behavior as regards cell aging process cannot be replicated in whole animals (especially in superior vertebrates)⁵⁵.

DM2 has been reported as a conformational disease, associated with the structural transition of physiologic proteins with intermediate stages or of pathologic proteins. It is possible that the relentless nature of progression of this disease can be

understood with regard to the progressive accumulation of aberrant proteins or proteins that are unknown for the body, as it can be appreciated in other conformational diseases such as Alzheimer, those produced by prions or Parkinson, among others. However, when speaking about the relationship of aging with the above-mentioned pathological processes and those related to a decrease in biological processes, such as structural isomer metabolism, it is difficult, in many forms, being able to separate within them the effect adaptability and resistance to stress have, as well as the diminution of the body to be able to maintain biological functions in balance. Several authors propose a number classifications as regards theories about factors that produce aging. In this manuscript, those which might provide an explanation of the genesis regarding the process of insulin pancreatic β -cell production decrease have been addressed. In the Mexican population, specifically in type 2 diabetics with β -cell dysfunction and insulin secretion defect, we analyzed the effect of *TJP1* gene p.A13344 polymorphism, which produces a conformational change type 1 tight junction, which is highly important for pancreatic morphogenesis in the embryonic period and maintains β cells percentage and function in the adult⁵⁶.

Exogenous theories

Among the theories that support a decrease in β cell functioning, there is one about advanced glycation end-products (AGEs). In uncontrolled DM2 there is an increase in the amount of AGEs⁵⁷ (a phenomenon Strehler⁵⁸ referred to as progressive). Owing to AGEs increase, arterial elasticity is modified, with a decrease in collagen solubility and an increase in retinal basement membranes' thickness, with intertwining of polymers such as melanoidins (generated by fructosamine) and protein chains being established⁵⁷.

The oxidative stress theory, where free radicals are protagonists, propose there is β cell progressive destruction secondary to oxidation and metabolism processes generated by anion radicals, hydroxyl radical, superoxide (O_2^-) and hydrogen peroxide (H_2O_2). These are part of the ROS levels, with mitochondrion being sensitive to their accumulation⁵⁹, which is why insulin production will decrease, initially originating an increase in postprandial glucose and elevating the level of AGEs^{60,61}. However, the ROS accumulation theory is currently arguable, since, in *Caenorhabditis elegans*, life expectancy and longevity main

determinant has been shown to be extracellular Cu/ZnS-dependent superoxide dismutase^{62,63}. In this sense, we have proposed the *CSB* gene, which participates in the DNA repair system coupled to transcription. Its dysfunction produces a disease known as Cockayne syndrome (progeria), which includes diabetes mellitus; this can be related with melatonin secondary deficiency due to pineal gland calcification, especially because melatonin is a powerful antioxidant. With no doubt, it is a factor that reduces longevity and increases oxidative stress. We are still exploring it in middle-age and old adult diabetes in Mexico⁶⁴.

In recent studies, hormesis has also been addressed, which refers to biphasic or adaptive effect by means of which low concentrations of certain toxic molecules have positive effects on genes of response to ROS, and high doses are inhibitory, sustaining that certain level of oxidative stress is necessary to prolong life expectancy⁶³.

Genic and mixed theory

This theory proposes that aging is due to factors related with the cell genome; there are more than 100 genes that are closely related to longevity. Aging has been suggested to be produced by alterations in the DNA, or in the transcription to mRNA, or in the translation to proteins, indicating that it is a process programmed in the genome since birth and that is affected by exposure to external agents^{55,65,66}.

A relationship has been suggested to exist between cellular aging and mitochondrial genome instability by a mitochondrial-repair decrease effect caused by ROS, which would generate inability to synthesize ATP (and important compound for insulin generation, since it is an energy dependent synthesis), thus resulting in functioning senescence and triggering DM2 in ensuing years⁶⁷. This fact was demonstrated by Fleming et al.⁶⁸ with their intrinsic mitochondrial mutagenesis hypothesis, reporting that mtDNA damage leads to internal membrane inadequate protein synthesis; this is owing to the fact that it lacks histones and appropriate repair mechanisms. However, different authors indicate that mitochondrial repair mechanisms have been identified, including the repair pathway by basement splitting, although recent works have demonstrated that it is not that efficient in mammal mitochondria, and that there are also signs of the presence of more complex repair processes⁶⁸⁻⁷⁰. Therefore,

understanding the mtDNA-repair processes in mammals is a current challenge and is likely to lead to the elucidation of the etiology of common mutations and deletions, which are thought to be the causes of several human disorders, such as DM2 and the aging phenotype.

Theory of waste products accumulation

These are generated in the cellular aging process, and they originate in a rupture of cytoplasmic products that are deleterious for the cell, which causes for cells to be able to avoid their mortality, growing and diluting these waste products. Sheldrake⁷¹ proposed lipofuscin as a deleterious product. One of the compounds that has been the subject of various debates on whether it is cytotoxic for β cells is the amyloid peptide or amylin. It has been profusely debated whether the presence of amyloid substance deposits can be involved in the pathogenesis of DM2, or if it's simply a consequence of the disease. However, the fact that these deposits in patients with DM2 are associated with a reduction in the numbers of β cells suggests that they can constitute an important etiopathogenic factor in the development of insulin insufficient production^{71,72}.

Amyloid peptide circulates in plasma at minimal (picomolar) concentrations, with quantities varying between non-diabetic individuals (from 2 to 13 pmol/L) and individuals with DM2 (5-17 pmol/L) and obesity^{73,74}; however, these increases occur at DM2 initial stages and decrease in parallel with insulin secretion when DM2 is advanced⁷⁵. In the ageing process, amyloid peptide deposits have been found to increase with age and to be related to decreased glucose sensitivity⁷⁶, since the formation of amyloid deposits in vivo is associated with a decrease of 40% to 50% in cell function reduction in DM2⁷⁷. This sensitivity decrease is related to secretion of the peptide, which occurs in parallel to changes in insulin secretion, which indicates that changes in this amylin/insulin molar ratio might be involved in the development of DM2⁷⁶⁻⁷⁸.

Amylin toxicity is produced by β cells apoptotic induction by forming ionic channels, mainly calcium-permeable, which generates an intracellular flow, where the increase in amylin production by exogenous stimulation contributes to apoptosis^{79,80}. Another theory indicates that apoptosis would be generated by an increase in apoptosis-promoting genes *p53* and *p21* expression⁸¹, which is why it is

suggested that treatments with sulfonylureas elevate amylin postprandial concentrations, and that this increase is responsible for generating amyloid fiber deposits and for cell function deterioration⁸², something that doesn't occur with treatments that decrease hepatic glucose production or with insulin or diet^{83,84}.

Considerations for specialist physicians and public health experts

Type 2 diabetes mellitus remains a health problem in the entire world and especially in Mexico. Its nature is complex, given the multiple molecular triggering mechanisms (more than 50 pathways implicated), which is why the health specialist should not only understand the polygenic nature of DM2, but should also explore the multiplicity of environmental risk factors, both with an additive effect that increases the risk or predisposition for diabetes, as well as its chronic complications, in order to be able to establish preventive and predictive measures for this disease in high-risk vulnerable groups.

For this, epidemiological studies are required in order to establish the percentage of disease that is determined by genes and by the environment. The interaction of factors is also complicated, and hence the analysis of all existing theories and hypotheses on DM2 etiology enables a closer approach to the genesis of the disease.

However, the multiplicity of theories cannot be applied to all populations owing to the variance in each ethnic group. Further studies are required in order to estimate how much do they contribute to the risk for development of the disease, with this being the challenge faced by health from the perspective of molecular epidemiology in the postgenomic era.

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