Chapter 3

Epigenetics of Glucose Metabolism and the Basis for T2DM Interventions

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1. Introduction

1.1. Epigenetic regulation

Type 2 Diabetes Mellitus (T2DM) is a disorder caused by genetic interactions between susceptible loci and environmental influences. Simple Mendelian inheritance patterns have failed to describe the genetics of T2DM. In studies looking at single nucleotide polymorphisms, which have been linked to the development of T2DM, no disease-causing mutations have been discovered (Pinney & Simmons, 2009).

Contemporary genome-wide association studies identified at least 17 genetic loci associated with T2DM (Florez, 2008). Epigenetic modification of gene expression is one mechanism by which genetic susceptibility and environmental insults can lead to T2DM (Pinney & Simmons, 2009). Epigenetic changes are defined as mitotically inheritable alterations in gene expression that are not related to changes in DNA sequence (Pinney & Simmons, 2009).

Much of recent progress in understanding epigenetic phenomena is directly attributable to technologies that allow researchers to pinpoint the genomic location of proteins that package and regulate access to DNA. The advent of DNA microarrays and DNA sequencing allows many of these technologies to be applied to the whole genome (Bernardo et al, 2008, Ozanne et al, 2005, Kim et al, 2005).

There are at least two distinct mechanisms through which epigenetic information can be inherited: histone modifications and DNA methylation (Pinney & Simmons, 2009). The amino termini of histones can be modified by acetylation, methylation, sumoylation, phosphoryla-

tion, glycosylation and ADP ribosylation, with acetylation and methylation being the most common modifications. Increased acetylation induces transcription activation whereas transcription repression is usually induced by decreased acetylation. On the other hand methylation of histone is associated with both transcription repression and activation.

The other mechanism of epigenetic regulation is DNA methylation. In which cytosine base is modified, silencing and contributing to X chromosomal inactivation, genomic imprinting, and transcriptional regulation of tissue-specific genes during cellular differentiation. Histone methylation can influence DNA methylation patterns and vice versa (Pinney & Simmons, 2009).

2. T2DM as a thrifty phenotype

Humans represent a thrifty species relative to some other mammals. This indicates that metabolic adaptations had a crucial role in the emergence of present day Homo Sapien lineage, in particular in buffering reproduction from ecological stochasticity (Wells, 2009). In other words, thrifty implies some degree of prosperity deriving from earlier frugality and a careful management of resources. Its use in reference to human metabolism spread after an influential article by James Neel proposed that certain genes relevant to metabolism could have been favored by natural selection in certain environmental conditions (Neel, 1962).

T2DM is considered a thrifty phenotype exceptionally efficient in the intake and utilization of food with basic difference of a quick insulin trigger in response to food-induced hyperglycemia. The survival benefit of this phenotype was to minimize urinary glucose loss when fasting was promptly replaced by feasting, leading to the more efficient utilization of food and tissue-distribution of plasma glucose. A quick insulin trigger that helped primitive man survive famine by storing energy more efficient, now leads eventually to T2DM.

Cahill & Wen (1967) theory postulates that the more insulin resistance an individual, the more efficient will be his ability to decrease proteolysis (and preserve lean body mass) when faced with caloric deprivation. The more efficient one in conserving muscle protein the better changes to withstand prolonged periods of deprivation, to be able to hunt successfully and to escape if preyed upon.

Skeletal muscle takes 80% of insulin-dependent glucose uptake. Hence muscle insulin resistance conserves glucose for utilization by the central nervous system decreasing the amount of muscle protein needed to be converted to glucose (neoglucogenesis).

Summing up the mentioned theories, relative insulin resistance evolved to aid metabolic partitioning between physical activity and other functions during constrained energy supply (Chakravarthy & Booth, 2004) which in turn relate to the selective pressure of a low glycaemic load diet with high meat content (McMichael, 2001) as our gather-hunter ancestors use to eat over ten thousand years ago.

The concept of metabolic programming during early life was prompted nearly 20 years ago in a series of Britain studies by Barker et al, (1989) and Hales et al, (1991) in which the prevalence

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of T2DM was measured in 64 years old men, whose birth weight records were available. It was shown that those with lower birth weight and lower weight at 1 year of age had a higher prevalence of T2DM and glucose intolerance (Hales et al, 1991) than did those with a normal birthweight.

These findings led to the propositure of the thrifty phenotype hypothesis (Hales & Barker, 2001), which postulates that under conditions of suboptimal in utero nutrition, the fetus must adapt to its environment to ensure survival of the organism, through a "sparing" of vital organs such as the brain at the expense of organs such as pancreas, kidney and skeletal muscle. In addition, it was proposed that metabolic programming occurs to promote nutrient storage to provide a survival advantage in conditions of poor post natal nutrition. However, these adaptations can lead to the post natal development of glucose intolerance, T2DM, CVD and hypertension in conditions of adequate nutrition or overnutrition.

The thrifty phenotype hypothesis is widely used to interpret associations between early nutritional experience and degenerative disease risks (Wells, 2011). Thrifty phenotype represents a short-term adaptive response (preserving vital organs at the expense of less essential traits) to poor energy availability (Wells, 2011).

Many epidemiologic studies in populations worldwide have robustly supported the initial findings that poor fetal growth resulting in low birth weight increases the risk of developing diseases in adulthood, including glucose intolerance, T2DM, CVD and hypertension (Hales & Barker, 2001). The thrifty phenotype hypothesis has served to explain cases such as the high prevalence of T2DM in Pima Indians (Godfrey et al, 2010).

According to the thrifty genes hypothesis (Hales & Baker, 1992) fetal malnutrition as indexed by low-birth weight reduces pancreatic beta cell mass and islet function. These traits then track on into adult life, when they are associated with an increased risk of diabetes, especially if body mass index (BMI) increases (Wells, 2011).

2.1. Alternative hypothesis

T2DM and obesity are not only about energy homeostasis but also about changes in innate immunity, sexual and reproductive function, skin architecture, wound healing and tissue regeneration, memory, cognitive functions, behavior and mechanisms of decision making, social relations and social signaling. Most hypothesis are too glucolipo-centric (e.g. thrifty gene and fetal programming). The only possible exception is the behavioral switch hypothesis by Watve and Yajmik (2007). They argued that insulin resistance is a socioecological adaptation that mediates two phenotypic transitions, reproductive strategy (large number of offspring with little investment in each or smaller number of offspring with more investment in each) and transition from a physically aggressive behavior (soldier) to a socially manipulative one (diplomat). According to this hypothesis, insulin resistance changes the differential budget allocation to tissues, dependent on insulin for nutrient uptake such as skeletal muscle (soldier) to insulin independent tissues such as brain (diplomat). From this hypothesis insulin resistance is likely to have evolved as a switch in reproductive and sustenance strategies rather than an adaptation to feast and famine.

Moalem et al, (2005) hypothesis argued that high plasma glucose lowers the freezing point of blood which prevents formation of ice crystals in cell through super cooling and this has been suggested as an adaptation to the ice age. If high blood glucose is adaptive in cold environment, then ethnic groups who evolved in cold climates should undergo directional selection leading to fixation (Baig et al, 2011).

3. Environment pressures to T2DM

Environmental contributions to the development of T2DM potentially include exposures such as a suboptimal in utero environment, low birth weight, obesity, inactivity and advancing age (Jin & Patti, 2009).

3.1. Suboptimal in utero exposures

Human exposure to an abnormal intrauterine milieu leads to abnormalities in glucose homeostasis and ultimately T2DM (Pinney & Simmons, 2009). Hence pregnant women exposed to the Dutch Hunger Winter, the period in late World War II during which daily caloric intake was limited to 400-800 kcal delivered infants with lower birth weight. By age 50, these offsprings had impaired glucose tolerance compared to offspring who were in utero either the year before or after the famine (Ravelli et al, 1999). Other interactive effects of birth weight and current weight for insulin resistance (Newsome et al, 2003; Fagerberg et al, 2004) and glucose intolerance/diabetes (Forsen et al, 2000; Bhargava et al, 2004) has been demonstrated also.

The epidemiological studies from Hertfordshire (UK) found that men who were the smallest at birth (< 2.5kg) were seven times more likely to have glucose intolerance or T2DM than those who were heaviest at birth (Hales, 1991).

Epigenetic modifications affecting glucose regulation and insulin secretion have been described in the intrauterine growth retardation (IUGR) liver, pancreatic β-cells, and muscle. Studies have demonstrated that genes essential to pancreatic development are susceptible to epigenetic modifications that could ultimately affect gene expression (Pinney & Simmons, 2009).

Pdx-1 is a homeodomain-containing transcription factor that plays a critical role in the early development of both the endocrine and exocrine pancreas and in later differentiation and function of the β-cell. The Pdx-1 is one of 15 genes (of 1749 examined) with cytosines within the promoter that were methylation susceptible (Pinney & Simmons, 2009).

A change in histone acetylation is the first epigenetic modification found in β-cell of IUGR animals. Islets isolated from IUGR fetuses show a significant decrease in histones (H3 and H4) acetylation at the proximal promoter of Pdx-1 leading to a loss of binding of critical activator (USF-1) to the proximal promoter of Pdx-1. This decreased binding markedly decreases Pdx-1 transcription (Park et al, 2008; Qian et al, 1999; Sharma et al, 1996). After birth, histone deacetylation progress is followed by a marked decrease in H3K4 trimethylation and a significant increase in dimethylation of H3K9 in IUGR islets. H3K4 trimethylation is usually

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associated with active gene transcription, whereas H3K9 dimethylation is usually a repressive chromatin mark. Progressive of these histone modifications parallels the progressive decrease in Pdx-1 expression that manifest as defective glucose homeostasis and increased oxidative stress in aging IUGR (Park et al, 2008).

Oxidative stress plays a significant role in β-cell deterioration (Simmons et al, 2005) that is particularly relevant to T2DM. IUGR induces mitochondrial dysfunction in the β-cell leading to increased production of ROS and oxidative stress (Simmons et al, 2005).

Reduced glucose transport in muscle is a trademark of insulin resistance in IUGR offspring (Thamotharan et al, 2005; Ozanne et al, 2005). Under normal physiological circumstances, glucose transport occurs by facilitated diffusion, a rate-limiting step in glucose utilization (Fueger et al, 2005). This process of glucose transport is mediated by a family of structurally related membrane-spanning glycoproteins, termed facilitative glucose transporters (GLUTs; Slc2 family of transport proteins). Of the isoform cloned GLUT 4 is the major insulin-responsive isoform expressed in insulin-sensitive tissues such as skeletal muscle, adipose tissue and cardiac muscle (Karnieli et al, 2008).

The promoter region of GLUT is the myocyte enhancer factor 2 (MEF2) whereas MyoD is responsible for GLUT 4 expression during myoblast to myocyte differentiation. These two proteins synergistically enhance skeletal muscle GLUT4 transcriptions and gene expression (Moreno et al, 2003).

IUGR is associated with an increase in MEF2D (form that acts as an inhibitor) and a decrease in both MEF2A (that acts as an activator) and MyoD (a coactivator) binding to the GLUT 4 promoter in skeletal muscle. No differential methylation of these three CpG clusters in the GLUT4 promoter was observed but it was found that DNA methyl transferases bindings to the GLUT4 gene were increased and this fact was associated with exposure to increase methyl CpG binding protein 2. Covalent modifications consisted of histone 2 lysine I4 (H3KI4) deacetylation triggering methylase-mediated dimethylation of H3K9 leading to partial inactivation of GLUT4 transcription in post natal and adult IUGR.

Thus, perinatal nutrient restriction resulting in IUGR leads to silencing histone modifications in skeletal muscle which in turn directly decrease GLUT4 gene expression, effectively creating a metabolic knockdown of this important regulator of peripheral glucose transport and insulin resistance and contributing to the adult T2DM phenotype (Raychaudhuri et al, 2008). Studies show that histone modifications can be stably inherited in a caloric-restricted model of IUGR, mimicking the Dutch famine experience (Pinney & Simmons, 2009).

3.2. Low birth weight

Although insulin resistance is considered a hallmark of the thrifty phenotype in later life (Hales & Barker, 1992) studies of small-for-gestational age infants show that the primary initial metabolic adaptations to IUGR comprises greater insulin secretion (Wells, 2011, Mericq et al, 2005, Soto et al, 2003) which seems to promote length gain during the first months of post natal life.

In the Spanish study the body weight differences between small-for-gestational age and normal birth weight infants were 36% at birth, 7% at 2 years and 3% at 4 years of life; however, at 2 years both groups showed similar lean mass and fat mass, from 2 to 4 years the small birth weight gained less lean mass and more abdominal fat than the normal birth weight as well as becoming insulin resistance (Ibanez et al, 2006). Within this pattern of catch-up growth, the onset of insulin resistance appears dependent on a higher level of weight gain (Torre et al, 2008) and is associated with the emergence of central adiposity (Ibanez et al, 2008).

The low birth weight neonates appear to have a higher central fat distribution; however, it would be more appropriated to regard this as a consequence of their reduced peripheral fat (Wells, 2011). In fact, the older English men study (64 to 72 years old) showed that birth size did not directed induce a more central fat distribution. Rather, the primary effect of low-birth weight is to constrain lean mass, muscle mass and peripheral fat. With the post-natal weight gain the fat deficit reduced but the deficit in lean mass remained larger (Kensara et al, 2005). Thus, even though the central fat and insulin resistance emerge post-infancy, they are related to the magnitude on catch-up growth immediately after birth (Wells, 2011). In the Helsinki cohort study T2DM has been associated with rapid weight gain from 7 years (Baker et al, 2009).

3.3. Increased cell fat

Obesity and abdominal fatness courses with insulin resistance as well as myosteatosis named states of glucotoxicity. Serine phosphorylation of the insulin receptor substrate is a critical mechanism of insulin resistance. This process is stimulated by ceramide and cell free-fatty acid and also by C-Jun N-terminal Kinase (JNK), part of a larger mitogen-activated protein kinase (MAPK) family (Exposito et al, 2002). Genetic and diet-induced obesity were shown to markedly increase in JNK activity in liver, muscle and adipose tissue (Hirosumi et al, 2002). Moreover by hyperglycemia/hyperinsulinemia reduces β-oxidation of free-fatty acids by decreasing CPT1 activity due to the increase of MalCoA.

Obesity has been associated with decreased expression of metabolically active genes (e.g. PPAR-α and medium chain acyl-CoA dehydrogenase) in skeletal muscle (Tateishi et al, 2009). Another class of enzymes involved in epigenetic control of metabolism is nicotinamide adenine dinucleotide (NAD+)-dependent sirtuins which target both histone and non-histone proteins (Schwer & Verdin 2008). The most well characterized member, SIRT1, regulates several metabolic pathways including adipogenesis, mitochondrial biogenensis, glucose utilization, fat oxidation and insulin secretion.

3.4. Insulin resistance as muscle mass protector

Insulin resistance emerges post infancy, when weight gain is disproportionate to length and the balance between adipose tissue and muscle mass in high (Ibanez et al, 2006). Such a late emergence of insulin resistance does not strongly support the notion that it represents a metabolic strategy for protecting insulin-insensitive brain (thrifty phenotype hypothesis), whose fuel demands are relatively greatest in the first weeks of life. It does not either represent anticipatory adaptation to poor energy availability in adult life (predictive adaptive response

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hypothesis). An alternative hypothesis is that insulin resistance in early childhood may supply aid in protecting muscle tissue from high glucose load and corresponding high insulin levels arising from excess weight gain (Lustig 2008), once linear growth is canalized.

Therefore insulin resistance emerges when thrifty growth pattern (low lean mass and reduced metabolic capacity) is subsequently exposure to high metabolic load, and confers protection against it. The lower the skeletal muscle mass the lower tolerance of muscle tissue to a given glucose load (Wells, 2011). Without such metabolic load, growth variability in early life (early growth later disease) appears to have little consequence for metabolic risk (Wells, 2011).

The magnitude of neonate catch-up growth and the muscle mass, fat mass accretion indicates early hormonal adaptations (Martin-Grouet & Ozanne, 2005).

Metabolic capacity comprised by lower pancreatic β-cell mass and the capacity to secret insulin is over passed by the neonate metabolic load of nutrition. Sedentary behavior, which reduces metabolic flexibility, and diet high in refined carbohydrates (Taubes, 2008) challenge the ongoing regulation of blood sugar content and cellular metabolism.

Through many of the components of metabolism considered adaptive for adult life (low metabolic capacity) in the predictive adaptive response hypothesis (insulin resistance and central adiposity) seem to emerge under the "magnifying glass" effect of the modern obesogenic niche (high metabolic load), and may supply represent "protective normalization to preserve homeostasis".

The metabolic costs of body adaptations (e.g. insulin resistance and central adiposity) seem to depend on exposure to an energy-dense diet in childhood, and this is best interpreted as a detrimental effect of the western-industrialized which rather than an adaptive strategy for the long-term future (Wells, 2007).

Moreover while early changes in pancreatic β-cell mass and islet function powerfully determine susceptibility, additional factors such as physical activity, obesity and aging and possibly other process leading to insulin resistance must also play a role in deciding the time of onset and severity of T2DM (Hales & Barker, 1992).

Although obesity, reduced physical activity and aging increase susceptibility to T2DM many people exposed to these risk factors do not develop the disease. Genome-wide association studies have identified a number of genetic variants that explain some of the inter individual variation in diabetes susceptibility (Shahbazian et al, 2007).

In population remaining lean and fit and consuming a traditional diet with low energy density (Prentice & Jobb, 2003), birth weight variability was not associated with adult variability in either the glucose/insulin axis or other risk factors for cardiovascular disease (Moore et al, 2001).

From an evolutionary perspective, those with thrifty or frugal gene who now eat too much and do not get enough exercise are at risk for T2DM.

Ethnic groups, such as the Australian aborigenes, remained hunter gatherers until recently and the recently urbanized individuals of this community developed a high prevalence of diabetes and hypertension (O'Dea 1991).

4. Other exposures

4.1. Oxidative stress

Pancreatic β-cell lost part of their antioxidant defense in association with brain evolution and lost even more in females when placental mammals evolved. Hence pancreatic β-cell and those of females in particular are more susceptible to oxidative damage. Under stress condition the release of stress hormones produces insulin resistance. Reactive oxygen species (ROS) prevent β-cell from secreting insulin at the level required to maintain homeostasis diverts glucose to insulin-independent tissues such as the brain and the fetus (Rashidi et al, 2009).

Excess of deficits in nutrients, hormones or metabolites may trigger changes in DNA or histone gene expression. In addition, changes in small noncoding RNA activity act by modulating gene expression (Godfrey et al, 2010).

Exposure to oxidative stress can directly mediate both DNA methylation and chromatin remodeling in multiple disease models and thus could be a mechanism by which aberrant epigenetic programming leads to T2DM (Yoshida et al, 2006; So et al, 2006; Takahashi et al, 2006; Grady et al, 2008; Feltus et al, 2003; Martin et al, 2008; Cooney et al, 2002; Rauch et al, 2007; Bollati et al, 2009; Franco et al, 2008). Random DNA methylation changes occur during aging in several tissue types and are associated with increased oxidative stress (So et al, 2006; Bollati et al, 2009). Such changes in DNA patterns affect the expression of multiple genes. Replacement of guanine profoundly alters methylation of adjacent cytosines (Franco et al, 2008). Histone sare susceptible to oxidative stress, due to their abundant lysine residues (Ruchko et al, 2009, Tikoo et al, 2008, Drake et al, 2004). It has been discovered that histone demethylases require oxygen as co factor what links epigenetic process to oxygen gradients during development (Hitchler et al, 2007).

Transcriptional PGC 1α coordinates gene expression that stimulates mitochondrial oxidative metabolism in multiple tissues (Puigserver et al, 2003). PGC 1α expression is reduced in diabetic islets and correlates inversely with the degree of DNA methylation (Ling et al, 2008). Importantly, PGC 1α expression correlates positively with glucose-stimulated insulin secretion in human pancreatic islets (Ling et al, 2008).

In β-cells, the insulin gene displays hyperacetylation of H4 and hypermethylation of H3 at lysine 4 typical of active genes.

4.2. Aging

Many of the condition associated with patterns of early growth are traditionally associated with aging. Telomeres are hexameric repeat sequences located at the ends of chromosomes

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and are considered to be robust biomarkers of cellular aging. In the absence of telomerase, telomeres shorten with every cell division. Progressive telomere shortening causes an alteration in telomeric structure and potently induces the cell cycle inhibitor p53. This can lead to the up-regulation of the cell-cycle inhibitors p21 and p16, which leads to cellular senescence. Accelerated telomere shortening is observed in tissues of the short-lived recuperated maternal low-protein offspring, such as pancreatic islets (Tarry-Adkins et al, 2009). This was accompanied by increased pancreatic islet gene expression of p21 and p16 indicative of accelerated cellular aging. Telomeres are known to shorten in the presence of oxidative stress (Von Zglinicki 2002).

5. Epigenetic of T2DM complications

One major event in the progression of diabetic complications is vascular inflammation with increased expression of inflammatory genes. Enhanced oxidative stress, dyslipidemia and hyperglycemia have also been suggested to influence the development of diabetic complications (Ling & Groop, 2009).

Nuclear factor κB (NFκB) is a transcription factor regulating expression of genes involved in inflammatory diseases, including diabetic complications (Miao et al, 2004).

Poor glycemic control increases NFκB activity through interactions of target genes including the tumoral necrosis factor (TNF) α and cyclooxygenase-2 promoters (Miao et al, 2004). NFκB and interleukin-6 (IL-6) also represent genes with altered histone H3 lysine 9 dimethylation in lymphocytes from patients with diabetes (Miao et al, 2008).

NFκB driven pro inflammatory gene expression seems to play a major role in the pathogenesis of atherosclerosis (Thurberg & Collins et al, 1998, Glass & Witztum et al, 2001). Transient hyperglycemia induces (in vitro) changes in histone methylation at the promoter of NFκB-p65 in vascular epithelial cells, changing NFκB-p65 expression and contributing to vascular complications similar to those seen in T2DM (Brasacchio et al, 2009). Increased NFκB-p65 gene expression was associated with persistently increased H3K4 monomethylation at the NFκB-p65 promoter but not with H3K4 dimethylation or trimethylation. The experiments indicate that increased NFκB-p65 gene expression is associated with persisting epigenetic marks that are maintained when the cell is removed from its hyperglycemic environment, providing evidence that epigenetic modification contribute to altered gene expression and could form the basis for physiologic "hyperglycemic memory".

Interestingly, when genes that reduce mitochondrial superoxide production (e.g. uncoupling protein-1) are over expressed, the changes induced by the transient hyperglycemia are prevented (El-Osta et al, 2008).

An oxidative mechanism seems to mediate the effects of hyperglycemia on inflammatory induction (Exposito et al, 2002). Hyperglycemia-induced oxidative stress occurs along with soluble advanced glycation (AGES) and lipid-peroxidation products which possibly serve as key activation of upstream kinases leading induction of inflammatory gene expression

(Schmidt et al, 1999). Moreover hyperglycemia would induce a higher mitochondrial oxygen reactive species (ROS) production (e.g. muscle cells) that would induce the MAPK with the JNK activation and subsequent transcription of inflammatory mediators (Vallerie et al, 2010).

6. Chromatin remodeling with interventions

6.1. Therapeutic agents

The studies described above clearly showed that environment effects can induce epigenetic alterations. These alterations ultimately affect expression of key genes linked to the development of T2DM including genes critical for pancreatic development and β-cell function, peripheral glucose uptake and insulin resistance. Understanding the role of development of T2DM might unveil a critical window during which epigenetic therapeutic agents could be used as means to prevent the later development of a disease (Pinney & Simmons, 2009).

Experimental treatment of insulinoma cells with incretin hormones such as glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide 1 (GIP) induces β-cell chromatin remodeling which lead to coordinated interactions between specific chromatin-modifying enzymes and transcription factors. The histone modifications (acetylation of lysine and phosphorylation at serine) increase its association with the transcription factor, phosphorylated cAMP-response element-binding protein (phosphor CREB) and with cAMP-response CREB coactivator 2. However it has been noted that changes in histone modifications were not linked to gene expression (Kim et al, 2009).

In addition to incretin hormones, the nuclear receptor proliferator-activated receptor γ (PPARγ) is an important target in diabetes therapy. PPARγ agonist improves glycemic control, increases serum insulin and enhances glucose stimulated insulin release (Finegood et al, 2001; Gerstein et al, 2006; Higa et al, 1999). Whole body glucose homeostasis and insulin secretion improvements were seem in animal with a PPARγ agonist fed either a high fat or normal diet (Evans-Molina et al, 2009).

Cultured islets from animal under oral pioglitazone therapy showed an increase in expression of Ins 1/2 and GLUT2. The specific chromatin remodeling mechanisms described showed increased acetylated H3, increased dimethyl H3K4 association at the proximal promoter of Ins 1/2 and increased mRNA and protein levels (Pinney & Simmons, 2009).

6.2. Physical exercises

Poor physical fitness and a low VO2max predict risk of developing T2DM (Eriksson et al, 1996). Mitochondrial dysfunction, changes in muscle fiber-type composition and insulin resistance are potential mechanisms linking poor physical fitness with an increased risk for disease. All mechanisms of developing insulin resistance can be reversed by physical activity through elevated intracellular PGC-1α (Handschin et al, 2008). Exercise induces the expression of a number of genes that regulate glucose uptake in skeletal muscle, including GLUT isoform 4 (Neufer et al, 1993). GLUT4 expression is further regulated by the transcription factor myocyte

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enhancer factor 2 (MEF2). Some of the biological changes induced by exercise could be due to histone modifications (Ling & Groop, 2009).

At rest, it has been proposed that MEF2 interacts with histone deacetyltransferase 5 (HDAC 5) in the nucleus (McGee & Hargreaves, 2006). Histone tails at the GLUT4 gene are thereby deacetylated by HDAC 5, resulting in a condense chromatin structure and subsequently reduced GLUT4 expression (McGee & Hargreaves, 2006). After exercise, HDAC 5 is phosphorylated by AMP-activated protein kinase (AMPK), dissociated from MEF2 and exported from the nucleus to the cytosol (McGee & Hargreaves, 2006; McGee et al, 2008; McGee & Hargreaves, 2004). MEF2 may then interact with the co activator protein PPARγ co activatior 1α (PGC 1α) and histone acetyltransferases (HATs) in the nucleus resulting in acetylated histones at the GLUT4 gene, enhanced transcriptional activity, and increased GLUT4 expression (McGee & Hargreaves, 2006; McGee et al, 2006; Vissing et al, 2008). Ca++/Calmodulin dependent protein kinase (CaMK) also seems to modulate MEF activity via histone acetylation in response to acute exercise (Smith et al, 2008). Moreover, there is a positive correlation between a gene expression of HAT with the percentage of Type I fibers and VO2max in human skeletal muscle (Parikh et al, 2008).

6.3. Nutrients and food components

Epigenetic modifications can be altered by external or internal environmental factors. These factors have the ability to change gene expression and are now considered an important mechanism in the unknown etiology of many diseases, including T2DM. Nutrients, food components and specific diets can influence epigenetic phenomena, such as DNA methylation and histone modifications (Choi et al, 2010).

Folate has an effect on DNA methylation for carrying a methyl group in its molecule, which is delivered for the synthesis of AdoMet, the unique methyl donor for DNA methylation reactions. Folate is not the sole determinant of DNA methylation as other methyl donor nutrients (methionine, choline, betaine, and vitamin B-12) as well as other environmental factors can also change DNA methylation status (Choi et al, 2010).

Vitamin B-12 is an essential cofactor of methionine synthase in 1-carbon metabolism and affects genomic DNA methylation (Uekawa et al, 2009). Choline is a methyl donor nutrient and maternal choline availability is essential for fetal neurogenesis such as hippocampal development as well as memory function throughout life. Choline deficiency during the embryonic period could change DNA methylation and thereby alter fetal brain development (Niculescu et al, 2006).

Studies with rats have shown that moderate maternal dietary protein restriction alters phenotypes in the offspring resulting in abnormalities such as hypertension, dyslipidemia, and impaired glucose metabolism, which can be reversed by folate supplementation. The altered phenotype induced by a maternal protein restriction diet during pregnancy involves changes in DNA methylation and histone modifications in specific genes, including the glucocorticoid receptor (GR) and PPARα in the liver of juvenile and adult offspring (Lillycrop et al, 2008; Lillycrop et al, 2007).

Histone acetylation is highly associated with inflammation (Villagra et al, 2008). Calorie restriction reduces the expression of inflammatory genes such as NF-kB, AP1, COX-2, and inducible nitric oxide synthase (iNOS). Histone acetylation activates NF-kB (Villagra et al, 2008) and regulates the expression of COX-2 (Coward et al, 2009).

Individual nutrients and bioactive food components or total diet can modify physiologic and pathologic processes through epigenetic mechanisms that are critical for gene expression. Modulation of these processes through diet or specific nutrients may prevent diseases and maintain health (Choi et al, 2010).

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