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The Sick Adipocyte Theory: The Forces of Clustering at Glance

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1. Introduction

The concept and repercussions of Obesity have evolved alongside Humankind. First seen as an advantageous trait in the beginning of time, it´s now a double edged sword definition that shows how slowly genometabolic traits are acquired and how quickly can environmental factors turn it around. Being obese is not only a matter of Body Mass Index (BMI) and adiposity, its influence stretches out to include type 2 Diabetes Mellitus (T2DM), Psychological disorders like depression, anxiety disorders, and other eating disorders, Osteoarticular problems, Metabolic Syndrome, Cardiovascular Diseases (CVD) like hypertension, stroke, and myocardial infarction, Neurological disorders, Cancer, and even Immunity-related issues, such as low grade inflammation (Must, 1999; Oster, 2000; Thompson, 2001; Marchesini, 2003; Adami, 2003; Niskanen, 2004; Panagiotakos, 2005).

Obesity has been rising slowly yet steadily ever since the Industrial revolution and its pace has increased since the dawn of the 20th Century. Even though nutritional disorders have plagued Man, it was common to see that undernutrition and malnourishment were the higher numbers around the globe. Yet, the tables were turned when Gardner & Halweil published in 2000 that the number of excess-weight patients surpassed the number of the underweight population, welcoming Humanity to the supersized phase of the *land of milk and honey* (O´Dea, 1992). In 2006, the World Health Organization reported that by 2005 1.6 billion above 15 years of age would be overweight and at least 400 million would be obese, while it is predicted to reach 2.3 billion of overweight and over 700 million of obese adults by the year 2015 (World Health Organization [WHO], 2006). The figures published by Kelly et al, 2008 darken the scope, predicting that by 2030 1.12 billion individuals will be obese and 2.16 million will be overweight.

There are many factors that have influenced the increasing prevalence of obesity worldwide, and have influenced the scientific community to coin the term *obesogenic* environment (Egger & Swinbum, 1997) as the external factors that act as "second hit" triggers in the

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multifactorial theory of obesity (see Figure 1). Many factors have been nominated and proven key to the etiology of obesity, such as dietary energy intake, physical activity, intrauterine environment (fetal programming), and other comorbidities like alcohol intake, physical disabilities, endocrine disorders, drug treatments, among others (Pi-Sunyer, 2002; Caballero, 2007). Physical activity has become fundamental in the intervention strategies for primary (Pate et al., 1995) and secondary prevention (Thompson, 2003) in obese patients, since it has been portrayed as a major independent risk factor for coronary artery disease (Fletcher et al., 1992). It can be defined as any voluntary skeletal muscle movement that consumes energy, usually measured by at least 30 minutes of physical activity that consumes at least 4 METs (*i.e.* brisk walk) (Dunn et al., 1998). On the contrary, physical *in*activity (sedentarism) is the lack of these ~ 30 minutes of energy consumption a day (Dunn et al., 1998), resulting in positive energy balance.

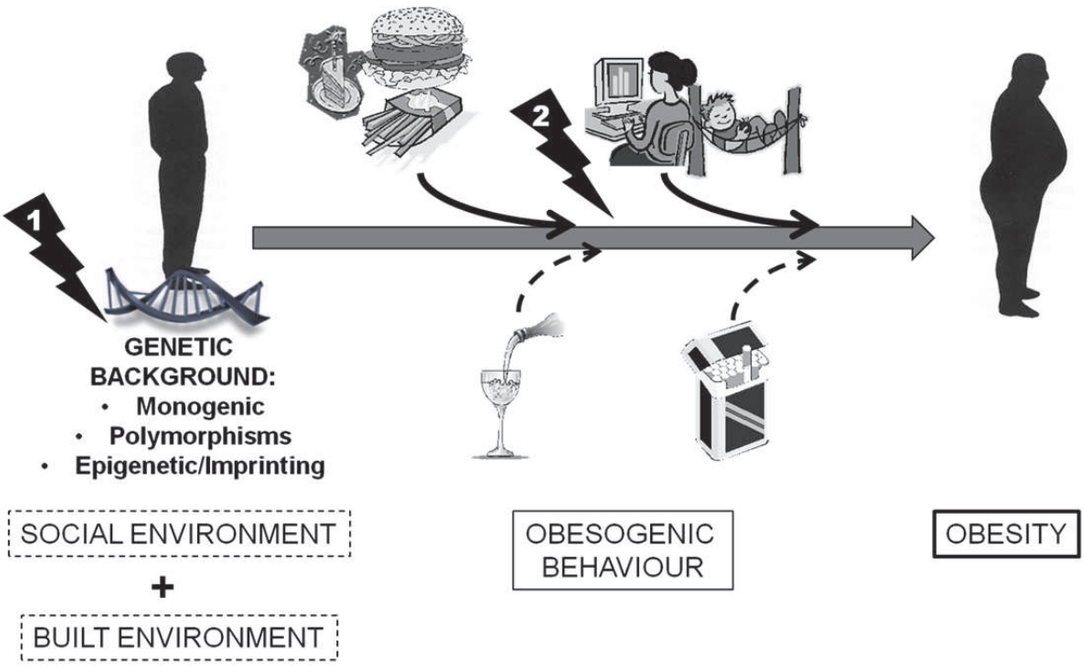

Fig. 1. The Two Hit proposal of obesity. A subject who is genetically-prone to obesity – either due to a monogenic syndrome, associated polymorphisms or imprinting (as seen *in utero*) have the first hit intrinsically. If he is subject to an obesogenic environment and subsequently develops an obesogenic behaviour (second hit), the end result will be progressive weight gain till obesity values are achieved. The obesogenic factors include high fat/carbohydrate diet, low physical activity, alcohol and smoking habits.

One of the interesting aspects about the term "physical activity" is that it´s used as an interchangeable term between "cardiorespiratory fitness", but they aren´t defined equally nor do they have the same impact on the patients. Physical activity relates to energy expenditure while cardiorespiratory fitness relates to oxygen supplition by the heart. However, both terms can relate to the same definition but they don´t explain the same aspects. In a meta-analysis by Williams, 2001 concludes that these terms should be treated as different and independent risk factors, findings that are similar to those reported by Hein et

al., 1992 concerning 4,999 men who were followed for 17 years in the Copenhagen Male Study, using physical fitness and leisure time physical activity as risk factors for ischemic heart disease (IHD). This team reported that being very fit offers no protection to IHD when sedentary, and being unfit and sedentary offers higher risk for this disease. Other studies have examined the relationship between fitness and sedentarism [Fletcher et al., 1996; Rosengren et al., 1997; Pollock et al., 2000; Blair et al., 2001) demonstrating without a doubt that sedentarism has been underestimated for a long time (Saltin, 1992).

2. Set

A sedentary patient is a real conundrum, and each one is unique especially if overweight/obese. Adiposity varies in degree and distribution, being classified according to anatomical location as subcutaneous and visceral adipocytes, each with a different metabolic profiling.

2.1 Adipocytes

Classically, white adipose tissue – adipocytes are recognized as the lipid-storing professional cells, and we remark professional because other types of cells can accumulate lipids yet it is not their main objective, as can be seen with myocytes, β-cells and neurons. The key feature of the mature adipocyte is that it can store fat without compromising its integrity or anatomy. The ontogeny of the adipocytes is still poorly understood, yet the process is being researched relentlessly (Gregoire et al., 1998; Darlington et al., 1998; Godínez-Gutiérrez et al., 2002)]. Mesenchymal stem cells differentiate into adipoblasts, which subsequently express early transcription markers and enter the preadipocyte I phase; the markers for the preadipocytes are α2Col6, Lipoprotein lipase, IGF-1 and Krox20. Once the cell´s fate has been decided, mitosis and clonal expansion begins entering the pre-adipocyte II phase, characterized by active C/EBPβ/γ, SREBP-1, PPARγ2 and KLF5. Maturity of the cell cannot begin until it leaves the cell cycle and starts differentiation in coordination with upregulation of late markers which induce cell arrest and begin lipid accumulation: C/EBPα, GLUT4, Perilipin, TNF-α, TGF-β, lipogenic and lipolytic enzymes. The mature adipocyte develops when the markers include the expression and adipocyte-related hormones, cytokines and enzymes related lipid storage and release towards blood circulation. Perhaps the most interesting aspect of adipocyte differentiation is how preadipocytes are driven towards adipocyte profile (Fu et al., 2004; Simons et al., 2005; Sethi et al., 2007), which is all a gameplay of members of the Peroxisome-Proliferator-Activated-Receptors and the CCAAT-enhancer-binding protein (C/EBP) families. The first step is the short-term expression of C/EBPβ and C/EBPγ2, followed closely by C/EBPα which activates PPARγ2, responsible for the adipogenesis genetic program. The sterol-response-element-binding-protein-1c (SREBP1c) activates the lipogenic program through PPARγ, finalizing the accomplishment of the differentiated phenotype; see Figure 2.

The mature adipocyte (Gregoire, 2001; Kershaw et al., 2004; Halberg et al., 2008) is a very specialized cell which is the center of energy storage and provision mechanisms, which is under a very tight central and peripheral control. Besides the basic anatomical role, the adipocytes are also endocrine cells which secrete several factors including leptin, adipsin, angiotensinogen, adiponectin, TNF-α, acylation stimulation protein, SPARC (secreted protein acidic and rich in cysteine), and PGAR/FIAF (PPARγ, Angiopoietin related/fasting-

induced adipose tissue). This adipocyte secretome incorporates adipose tissue to immunologic processes with low grade inflammation phenomena and autoimmunity-related diseases, and angiogenesis due to synthesis of angiogenic factors, various effects from macrophagic-related substances, extracellular matrix deposition and metalloproteinase remodeling (Frünbeck et al., 2001; Kershaw, et al., 2004). Given these features is not unusual to find that adipose tissue is part of several axes such as the adipo-insular axis (Kieffer et al., 2000; Vickers et al., 2001) [36-37], the adipocyte-vessels-brain axis (Elmquist et al., 2004; Guzik et al., 2007; Mietus-Snyder et al., 2008), and the adipocyte-myocyte axis (Sell et al., 2006; Taube et al., 2009).

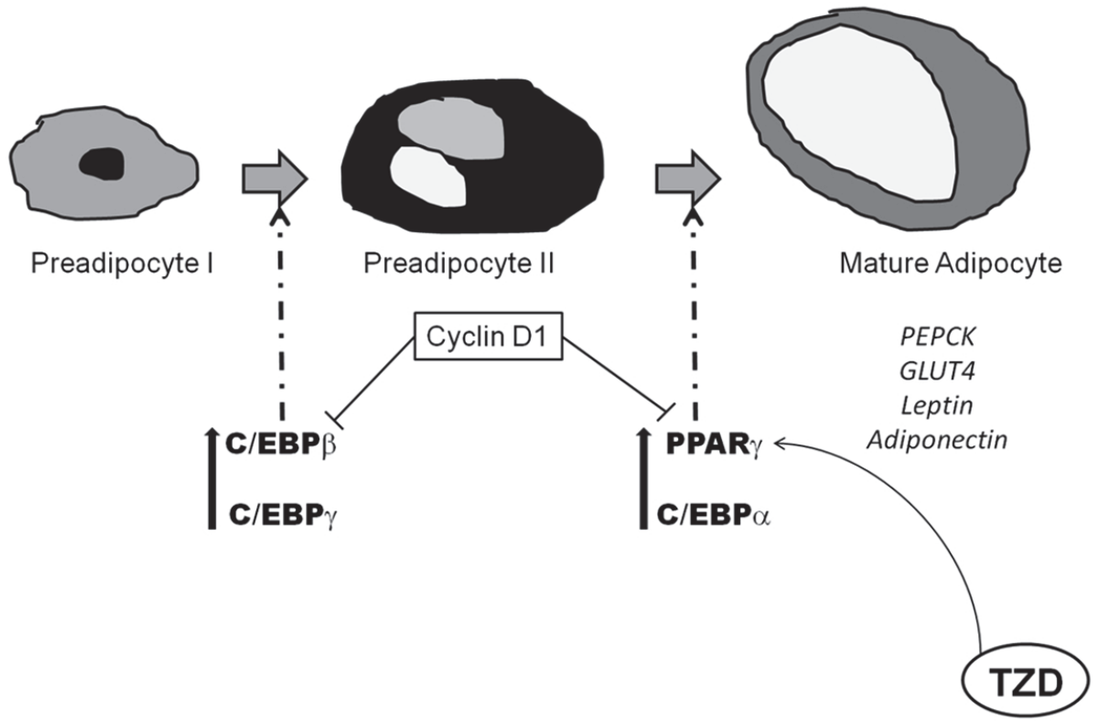

Fig. 2. Adipogenesis. The mature adipocyte goes through several stages of maturation until the professional lipid-storing profile is achieved. The interplay between CCAAT-enhancer binding protein (C/EBP) isoforms with Peroxisome-Proliferator-Activated Receptor-γ (PPARγ) ensures the progression towards final differentiation once the preadipocyte II has left the cell cycle. As long as Cyclin D1 is active, progression to a G_0 phase will be difficult – almost impossible – since this factor inhibits the differentiation transcription factors. Thiazoliniledione (TZD) are known agonists of the PPARγ enhancing the adipogenic program.

2.2 Myocytes

Sarcomeres are the functional elements of muscles cells. The contractile unit is composed of myosin fibers and actin, whose interaction allows the shortening of itself, displaying as a contracted myocyte. There are several classifications for muscle cells (Scott et al., 2001), yet the biochemical differentiation is discussed here. Muscle fibers are classified (Pette & Staron, 1997; Bassel-Budy & Olson, 2006) in Type I, Type IIa, Type IId/x, and Type IIb, having

particular metabolic properties, a) fast-twitch glycolytic fibers (types IIx and IIb), b) fast-twitch oxidative fibers (type IIa), and c) the slow-twitch oxidative fibers (type I). Dynamically, muscle fibers are classified as slow-twitch and fast-twitch motor units, and the fast fibers are subdivided in fast-twitch fatigue-resistant, fast-twitch fatigue-intermediate, and fast-twitch fatigable. Humans have a mixture of these muscle fibers and the number changes as the weight/metabolic profile is modified throughout life. Obese subjects are known to have few type I fibers and more type IIb fibers compared to lean subjects (Hickey et al., 1995). Tanner et al., 2001 reported that obese African-American women had low levels of type I fibers, and lower levels compared to obese Caucasian women, which reflects that fiber content also varies according to ethnicity.

Skeletal muscle is more than just the motor unit which gives us the possibility of movement, it´s also the most important tissue for glucose disposal, making it an essential part in energy metabolism (DeFronzo et al., 1985) and the primary target for insulin-resistance related disturbances (Lillioja et al., 1987). The disposal of glucose into skeletal muscle is fiber-specific, being greater in type I fibers compared with type IIa and IIb (Song et al., 1999) [50]. Type I/slow twitch oxidative myocytes are more efficient in regards of insulin binding, enhanced insulin receptor and post-receptor cascade activities, and higher GLUT4 translocation, compared to Type II/fast-twitch glycolytic myocytes; this suggests that insulin´s actions are more *oxidative than glycolytic*. Type II muscle fibers are insulin resistant (Henriksen et al., 1990; Henriksen & Holloszy, 1991) giving a partial explanation to the insulin resistance observed in obesity, which is also associated with abnormal lipid partitioning and intramuscular lipid accumulation.

2.3 The sick and the dying

In obesity, myocytes are sick while adipocytes die slowly due to asphyxiation. The interaction of both is what makes the adipocyte-myocyte axis so important in obesity and related diseases including Type 2 Diabetes; see Figure 3.

Plasticity – the ability to non-reversibly adapt to external load/pressure – can be seen in adipocytes, expressed as hypertrophy and hyperplasia (Arner et al., 2010). In overfed states, adipose tissue´s capacity to store excessive energy safely reaches its limit, causing a "spill-over" effect all over the body. This nutritional overload mechanism and subsequent damage can be seen in models for catch-up growth (Dulloo et al., 2009; Summematter et al., 2009), where refeeding states are associated with hyperinsulinemia, lipogenesis, plasma membrane switching from polyunsaturated fatty acids to saturated fatty acids, increased triglyceride production, ending in adipocyte hypertrophy and glucose intolerance. How plasticity can be associated to insulin-resistance is a very complex scenario. Genetic background – *thriftiness* – is a strong influential factor (Lindsay et al., 2001; Kadowaki et al., 2003; Prentice et al., 2005). Thrifty related genes and metabolic profiles ensure that all excess energy ingested will be "efficiently" stored, reminiscing those famine/feast days of the hunter-gatherers or the postnatal days of intrauterine-growth-restricted newborns. Thrifty traits have many targets (Prentice et al., 2005), yet 2 are essential: metabolic thrift, which is focused on mitochondrial electronic transport, protein turnover, fuel channeling, and substrate cycling, and adipogenic thrift, which relates to proneness of fat gain.

The physiological adaptation to overnutrition is not without intricacy, since 2 theories have been proposed. The *adipokine dysregulation* conveys the fact that overfed states triggers changes in the quantum and quality of the substances expressed in the adipocyte, for example, adiponectin secretion is lowered in obesity (Arita et al., 1999; Weyer et al., 2001),

while resistin´s is enhanced (Steppan et al., 2002; Vendrell et al., 2004). The second theory is based on *ectopic fat accumulation* of lipids in myocytes, hepatocytes and β-cells, where intramyocellular lipids correlates to insulin resistance (Virkamäki et al., 2001; Moro et al., 2008).

The continued stimulus and lipid accumulation makes the adipocyte (140 – 180 μm in diameter [Brook et al., 1972]) hypertrophy but the size of the cell is limited by the oxygen supply. Hypoxia (Hosogai et al., 2007) and increase synthesis of secretory proteins (Marciniak & Ron, 2006) are the main cause for adipocyte´s endoplasmic reticulum (ER) stress via the unfolded protein response (UPR) pathway. The latter proposal is quite simple to grasp since never-ending signals for secretion goes awry when the unfolded protein in the ER lumen surpasses the folded proteins quota due to a) lack of necessary components for the synthetized molecule, b) frequency of the secretion signal, and 3) shortage of chaperone proteins due to "sequestration" within the abnormal proteins accumulated within the lumen. This traffic alteration has been linked to several diseases including Type 2 diabetes (Scheuner & Kaufman, 2008), Tumor hypoxia and prognosis (Koumenis & Wouters, 2006), Alzheimer´s (Kudo et al., 2006) and Parkinson´s Disease (Ryu et al., 2002).

In 2004, Trayhurn & Woods suggested for the first time that it was hypoxia the culprit for low-chronic inflammation of obesity, conveying that as the adipose tissue advances and the outer sectors become hypoxic, inflammatory cytokines and acute phase proteins are locally secreted to enhance angiogenesis and stop the vicious cycle. Hypoxia in adipose tissue is due to hypoperfusion, especially after the 100 μm diameter phase of the hypertrophic adipocyte, suggesting that achieving 180 μm is a hypoxic state (Ye et al., 2007). In adipose tissue, low oxygen levels can alter gene expression, being related to decreased adiponectin mRNA, which is controlled by C/EBP and is inhibited by UPR-induced CHOP (C/EBP homologous protein) (Hosogai et al., 2007). It also can modify adipocyte secretome (Wang et al., 2007), resulting in enhanced expression of Hypoxia Induced Factor-1α (inducing GLUT1 mRNA), IL-6, leptin, Plasminogen activator inhibitor 1 (PAI-1), and Vascular Endothelial growth factor (VEGF), while haptoglobin and adiponectin are markedly decreased. Taking this one step further, hypoxia inhibit insulin post-receptor cascade though HIF-1α and HIF-2, which is thought to be crucial for the insulin resistance state observed in obese patients (Regazzetti et al., 2009); this is mediated by lowered autophosphorylation of the insulin receptor by means yet to be understood, but apparently it involves the mTOR (mammalian target of rapamycin) (Dann et al., 2007), S6K pathway (Um et al., 2006) and subsequent activation of NF-κB (Michiels et al., 2002). Almost 6 years later, hypoxia is now known to be a glucose metabolism modulator, which at first can induce glucose uptake – via GLUT1 synthesis and export – but can later decreased due to IRS-1 and insulin receptor phosphorylation, while at the same time, it can induce free fatty acid (FFA) release, leading to adipocyte dysfunction and worsening of peripheral insulin resistance (Yin et al., 2009; Copps et al., 2009).

To finally dissect adipocyte´s cyanotic life, macrophages enter the picture. Adipose tissue is not a homogenous organ, in fact is very heterogeneous and is populated with adipocytes, fibroblasts, vascular endothelia and immunologic cells. One of these, are the macrophages, who contribute significantly to the inflammatory array of signals being sent from the adipocyte (Weisberg et al., 2003). Insulin resistance depends of the abdominal adipose tissue distribution and plasticity, rather than pre-adipocyte and small adipose cells (Hauner, 2010). Adipose tissue macrophages are responsible perpetuating pre-adipocyte state and

differentiation signal (Lacasa et al., 2007), by secreting TNF-α and IL-1, known suppressors of the adipogenic program via NF-κB which quashes PPARγ dependent genes. Macrophage´s secretome include VEGF, TNF-a, IL-1b, IL-6, reactive oxygen species (ROS), and prostaglandins. Monocyte recruitment towards the adipose tissue is regulated by many molecules, but C-C motif chemokine ligand 2 (CCL2) and its receptor (CCR2) are perhaps the most important ones (Bruun et al., 2005), so importantly that blocking macrophage infiltration surrounding dead/dying adipocytes is a proper therapeutic goal (Bruun et al., 2005).

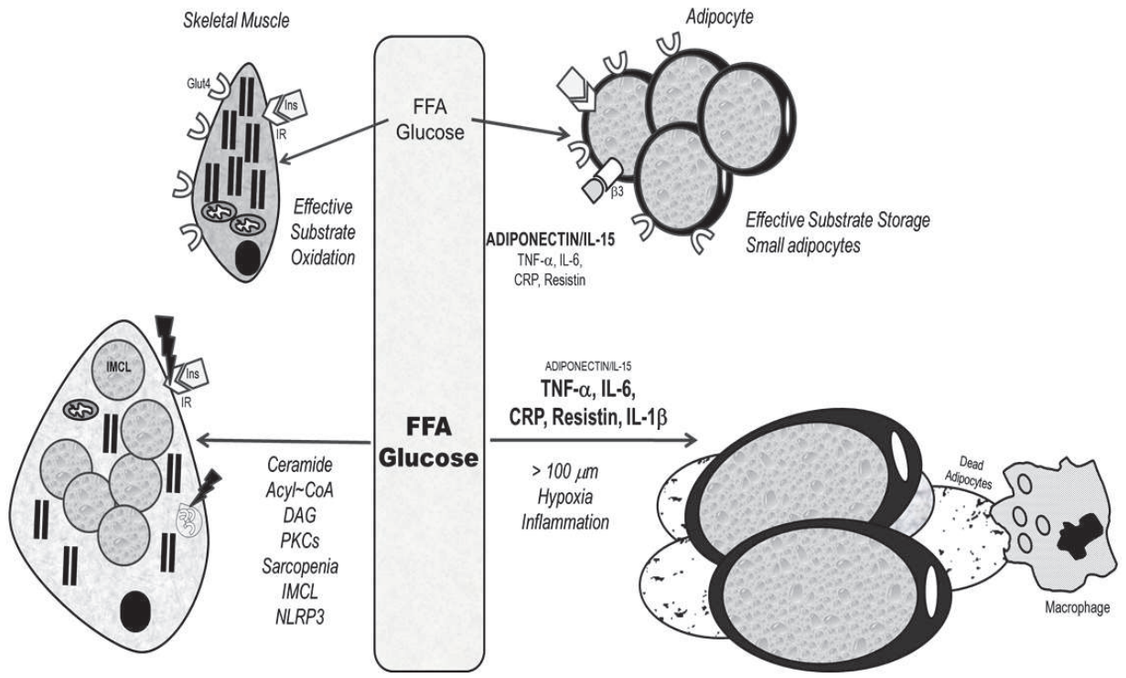

Fig. 3. The Sick and the Dying. This diagram depicts the effects of elevated free fatty acids (FFA) and hyperglycemia on adipocytes and myocytes, as it is observed in obese patients. Once the injury is fixed and has reach a point of no return, both cells begin plasticity to cope with the hostile environment. The sick myocyte loses sarcomeres at the expense of intramyocellular lipid droplets, which are source of acyl~CoAs, diacylglycerol (DAG) and ceramides, who in turn focus on serine/threonine phosphorylation of Insulin receptor and IRS-1, blunting the insulin pathways – becoming insulin resistant- Meanwhile, the growing adipocyte becomes hypoxic, releasing several cytokines who in turn affect myocyte´s already weaken metabolism, perpetuating the metabolic disturbance. As the adipocytes die in the sidelines of the adipose tissue, macrophages are recruited, worsening the inflammatory microenvironment.

The progressive growth and demise of adipocytes have collateral damage – a very sick insulin resistant skeletal myocyte. The sick myocyte not only has impaired insulin signaling, but also decreased expression of myogenin (muscle-specific transcription factor involved in myogenesis), IL-6, IL-8 and MCP-1 (monocyte chemotactic protein), with higher ceramides levels and lower mitochondrial capacity (Sell et al., 2008). How the muscle becomes insulin resistant is (still) a matter of debate, even though several mechanisms have been proposed.

Sir Phillip Randle (1963) was the first one to formulate a theory trying to explain how fuel substrates changed in muscle and how this would explain skeletal muscle insulin resistance (Randle et al., 1963). The Randle´s Hypothesis (glucose-fatty acid cycle) proposes that FFA compete with glucose as fuel substrate for mitochondrial oxidation, increasing β-oxidation within the myocyte. The consumption of FFA would in turn inhibit pyruvate dehydrogenase and phosphofructokinase, acting as barriers in the glycolytic pathway and reduced glucose uptake and oxidation. Over 30 years later, Shulman, 2000 singlehandedly dethroned Randle´s hypothesis, by stating that low FFA intramyocellular metabolism or enhanced lipid uptake leads to cytosolic accumulation of metabolites such as diacylglycerol, ceramides and acyl~CoA, which in turn activate serine/threonine kinase (PKC) cascade that end with the phosphorylation and inhibition of Insulin Receptor and IRS-1, blunting insulin post-receptor pathways, decreasing PI3-k activation and glucose uptake via GLUT4.

Beyond the glucose utilization bluntering, others morphological changes occur within the sick myocyte. Skeletal muscle also shows plasticity traits, anatomical and functional. It can use glucose or lipids for fuel production; however, in obesity lipid oxidation is decreased due to diminished enzyme capacity and reduced carnitine-palmitoyl transferase 1 (CPT1) activity (Kelley et al., 1999). Triglyceride (TAG) accretion in muscle can be attributed to 2 causes: reduced fatty acid oxidation (Kim et al., 2000) or enhance TAG synthesis (Hulver et al., 2003). Intramyocellular lipids (IMCL) are a far better predictor of muscular insulin resistance than BMI or waist-hip ratio (Pan et al., 1997), and it inversely correlates to visceral visfatin levels (Varma et al., 2007). IMCL turnover determines the amount of accumulation inside the myocyte, which modulates the level of lipid metabolites that can alter the PI3K pathways, via activation of PKC isotypes. Breakdown of the IMCL results in acyl~CoAs which can be readily oxidized in mitochondria (Guo, 2007), but it has been reported that obese mitochondria are slow oxidizers (mitochondrial dysfunction [Rabøl et al., 2010; Pagel-Langenickel et al., 2010]) and are positioned in different parts of the cytosol, slowing oxidation and increasing the cytosolic lipid droplet, making this lipid handling alteration a metabolic risk for insulin resistance (Koonen et al., 2010). There is a paradox in this whole IMCL issue: highly trained athletes use IMCL as a source for energy during exercise (Klein et al., 1994), so it makes for quite a riddle. Since from a sports point of view IMCL is advantageous, then the harm is not whether the IMCL are formed or not, it´s the availability of toxic lipid intermediates.

Now, how does a dying adipocyte, full of TAG and choking on ER stress, can make the susceptible myocyte sick? Since adipose tissue is considered an endocrine organ, then cross-talks with other organs is plausible. The first evidence of this dialogue was published by Dietze et al., 2002 using skeletal myocytes cultured in the same medium as adipocytes. They reported a profound disturbance in insulin signaling, characterized by nulled insulin-stimulated phosphorylation of IRS-1, reduced Akt activation, inducing an insulin resistant state. Several of the adipokines have been implicated in the process, including TNF-α (Hotamisligil, 1999), resistin (de Luis et al., 2009), IL-6 (Rotter et al., 2003), leptin (Shimomura et al., 1999), adiponectin (Yamauchi et al., 2001), MCP-1 (Sartipy et al., 2003) and RBP-4 (Graham et al., 2006), among others. One important feature between adipose-induced muscle insulin resistance is the role of the macrophages, which are slowly becoming pivotal for (adipose) and skeletal muscle insulin resistance. Macrophages cultured with palmitate serum medium secrete major proinflammatory cytokines that lower insulin action (Samokhvalov et al., 2009) via JNK mediated decreased phosphorylated Akt (Varma et al., 2009). SIRT1, a member of the Sirtuin family of NAD-dependent deacetylases, is able

to blunt macrophages capacity for inducing insulin resistance in Zucker fatty rats, shedding light to the complex axis (Yoshizaki et al., 2010). All in all, adipokine mediators are able to induce reversible (regeneration of myotubes and IL-6 secretion) and irreversible (IL-8 and MCP-1 secretion and myogenin expression) changes in the muscle proteome promoting insulin resistance in the myocyte (Sell et al., 2008; Kewalrami et al., 2010).

3. Go

3.1 Glycemic control

Physical activity and diet are the primary tools to intervene and modify lifestyle in the obese patient, yet it's not exclusive, since these strategies can also be applied to type 2 diabetics, hypertensive patients, and other insulin-disturbances related diseases. Physical activity can be defined as any daily activity undertaken for at least 30 minutes a day that ends in caloric consumption, and it´s deficiency is considered an individual risk factor for cardiovascular disease (Carnethon, 2009). It has been proposed the basic etiology of complex diseases is associated with disturbances of oxygen metabolism (Koch & Britton, 2008), making cardiorespiratory fitness a fine predictor for health risk (Lee et al., 2005), metabolic syndrome (LaMonte et al., 2005) and type 2 diabetes (Sawada et al., 2010). Regular exercise improves glycemic control, weight reduction and manages metabolic risks associated with adiposity. The molecular basics for this improvement have been extensively reviewed somewhere else (Hayashi et al., 1997; Hamilton et al.; 2000, Rose et al., 2005) and are shown in Figure 4. The mechanisms that are at play to ensure glucose uptake and consumption seem redundant since it centers on the translocation of GLUT4 towards the membrane, enhanced by AMPK, Ca^{++}/Calmodulin dependent protein kinase , and Nitric Oxide, and act as insulin mediators during and after exercise mediating increases glucose and fatty acid oxidation (Turcotte & Fisher, 2008). The main destination of glucose uptake is to replenish the glycogen stores in the skeletal muscle, and it does not depend on insulin signaling, since there is no increase IRS-1, IRS-2 or PI3K activation.

Focusing on the muscle fibers, constant exercise is known to induce a switch of muscle fibers towards the type I ones. Fiber shifts are thought to be the end result of fast myosin chain induction, with concomitant reduction of slow type I myosine. This muscle functional plasticity can be induced by any type of exercise, endurance, sprint or heavy resistance (Andersen et al., 1994; Fitts, 2003). The basic changes of fibers is characterized by reduction of type IIb percentage with slow increase of type IIa and type I, turning muscle metabolism into an oxidant kind over time, and become resistant to fatigue since the myocyte recovers from "metabolic stunnedness" and efficiently synthetizes ATP during and after exercise. The mechanisms underlying these adaptations are still poorly understood, but it is possible that AMPK and calcineurin activate parallel pathways that control myocyte adaptation (Röckl et al., 2007).

AMP-activated protein kinase (AMPK) is a pivotal regulator of intracellular energy during stressful states like starvation, hypoxia, exercise, among others, and it is central in the hormonal control of metabolic processes that consume or produce ATP (Lim et al., 2010). AMPK is active when AMP/ATP ratio rises, inhibiting ATP consuming pathways and enhancing ATP producing processes like glucose and FFA oxidation. During exercise, AMPK is activated and immediately phosphorylates and inhibits acetyl~CoA carboxylase (ACC), the key enzyme that synthetizes malonyl~CoA – negative allosteric modulator of

CPT1. Once CPT1 is released from control, β-oxidation continues full force (Musi et al., 2001). AMPK also modulates glycogen synthesis by increasing glucose availability inside the cell via phosphorylation and inhibition of Akt-Substrate 160 (AS160), main break for translocation of GLUT4 vesicles, and, regulates IMCL breakdown via phosphorylation of Hormone sensitive lipase (Jørgensen et al., 2006). And on a final note, AMPK can modulate the expression of GLUT4 by regulating GLUT4 enhancer factor (GEF) and myocyte enhancer factor 2 (MEF2) (Holmes et al., 2005) guaranteeing an appropriate glucose-uptake phenotype. Calcineurin – cyclosporine-sensitive, calcium-regulated serine/threonine phosphatase – is an enzyme that controls the signaling pathway for myogenic processes by modulation of the MyoD and MEF2 transcription factors (Chin et al., 1998), considered fundamental for fiber remodeling (Schiaffino et al., 2002; Bassel-Duny et al., 2003) with PPARδ as downstream effector (Wang et al., 2004).

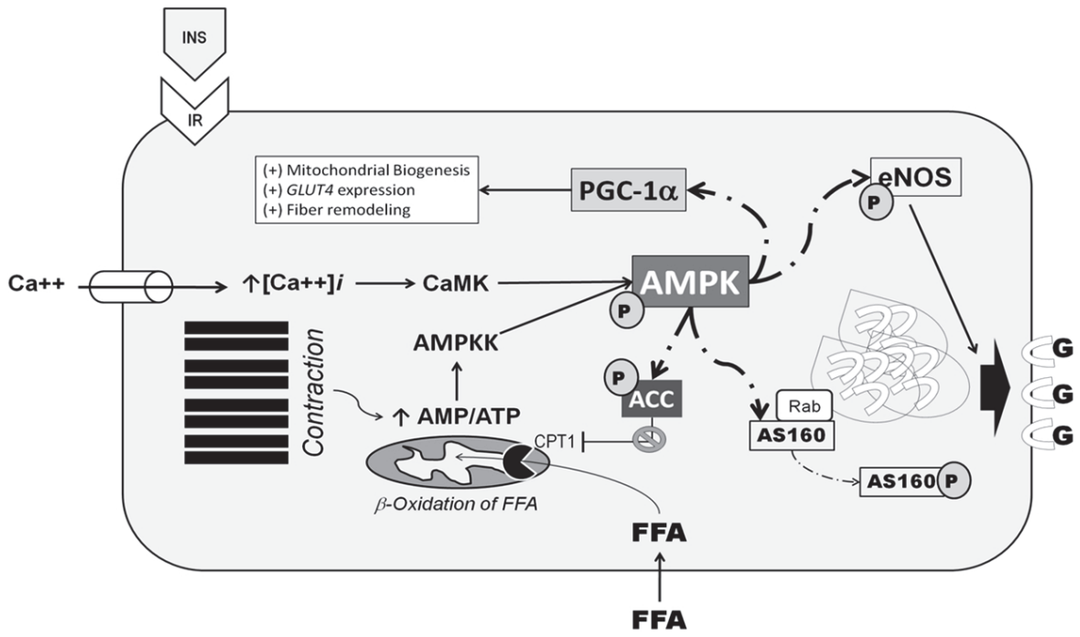

Fig. 4. Molecular basics of exercise. Once the AMP/ATP rises continuously according to muscle workout, AMPK kinase (AMPKK) is activated, alongside Ca++/calmodulin dependent Kinase (CaMK), both known to phosphorylate the a-subunit of AMPK, activating it. AMPK then inhibits by phosphorylation Acetyl~CoA Carboxilase, enzyme known to synthetize malonyl~CoA, main negative modulator of carnitine-palmitoyl transferase 1 (CPT1); blocking malonyl~CoA synthesis, β-oxidation is enhanced, using free fatty acids (FFA) from circulation and from lipid storage inside the myocyte. Secondly, AMPK activates PPARγ coactivator 1α (PGC-1α) which co-induces the PPARγ adipogenic program. Next, AMPK phosphorylates and activates endothelial Nitric Oxide Synthetase, which generates nitric oxide which serves as a vasodilator (increasing and maintaining blood flow) and is also an enhancer of GLUT4 translocation. Finally, AMPK phosphorylates Akt Substrate 160 (AS160), who is blocking Rab-GTPase molecule from initiating the movements of the GLUT4 vesicles towards the membrane. Once AS160 is "neutralized", GLUT4 are exported to the plasma membrane, increasing glucose uptake.

Insulin sensitivity restoration is a bit more complicated. Muscle straightening activity has been known to enhance sensitivity among adults, serving as proper program to reduce insulin resistance (Cheng et al., 2007). Glucose uptake and IMCL turnover have been implicated, yet there is paradox lingering around, endurance athletes have higher intramuscular lipids but are highly insulin sensitive (Goodpaster et al., 2001; Meex et al., 2010). Now, this beneficial effect can be obtained whether acutely – daily muscle contraction inducer energy flux – and by chronic modifications – mitochondrial oxidative capacity and induced GLUT4 expression (Thyfault, 2008; Jiang et al., 2010).

3.2 Thriftiness

As we have formerly mentioned, exercise is associated with modification of gene expression, specially affecting genes that control energy deposit and consumption, even in high training statuses. The Thrifty genotype theory published in 1962 (Neel, 1962) proposed that genes that favored energy saving during feast/famine cycles in the Late Paleolithic Era were incorporated into the human genome, because they were advantageous during famine phases. Exercise can modify gene expression according to the type of activity exerted, for example, aerobic exercise (endurance) is not associated with increased phosphorylated $p70^{S6K}$, but high resistance work-out is indeed related (Sherwood et al., 1999). Wendorf & Goldfine, 1991 proposed that during those hunter-gatherers years a selective insulin resistance in muscle had to be imposed, to avoid hypoglycemia during fasting and allow energy storage during feeding, traits that would turn disastrous in a sedentary individual, such as the obese patient. Evidence of this theory can be seen in different racial groups all around the world. The Arizona Pima Indians have the highest prevalence of diabetes in the world with increased sedentarism, compared to the Mexican Pimas (Valencia et al., 1999) and the scenario is similar with the Pacific Islanders in Asia (Zimmet et al., 1990). Needless to say, physical inactivity is then associated with insulin resistance and the genetic implications of exercise and its mediators are an important aspect of the whole concept, and in desperate need of continuous investigation (Abate et al., 2003; Chakravarthy et al., 2004).

3.3 Inflammation

Other metabolic changes are observed during physical training in obese patients, such as anti-inflammatory effects. In previous sections, the low-grade inflammation characteristically seen in obesity was discussed. Pedersen et al., 2007 reported that since the muscle was able to release cytokines under exercise conditions, these signaling molecules should be named *myokines* and the para/endocrine effects should be separated from their usual physiological profile.

Interleukin-6 is perhaps the most important of these myokines, yet the muscle is known to secrete IL-8, IL-15, IL-10 and IL-1ra, and very intense exercise can induce TNF–α secretion (see Table 1) (Petersen et al., 2005; Marini et al., 2010). The IL-6 expression and release patter is astounding, with a 100-fold level in response to exercise. The dilemma lies in this: how does a known insulin resistance-mediating molecule can exert protective effects? The answer lies in the true inflammatory levels and profiles. It has been suggested that IL-6 plays a villain role in the metabolic syndrome, alongside TNF-α. Nevertheless, Kubaszek et al., 2003 reported that the risk genotypes for metabolic disturbances (including obesity and type 2 diabetes) are characterized by increased transcription of TNF-α with decreased expression of IL-6. Now, the reader needs to me reminded that TNF-α triggers the release of

IL-6, not the other way around, so it´s logical to conclude that adipocyte derived TNF-α induces local expression of IL-6 in the adipose tissue (Pedersen et al., 2007), which correlates with the fact that IL-6 is not overtly elevated in diabetic patients and is not highly expressed in lean patients with insulin resistance (Carey et al., 2004). The insulin-sensitizing effects of IL-6 are still controversial, yet it has been reported that the myokine enhances glucose uptake and glycogen synthesis in the myocyte, via activation of AMPK while reducing TNF-α levels (Pedersen et al., 2007).

Myokine	Locus	Effect
IL-6	7p21	Anti-inflammatory when secreted before TNF-α (Carey et al., 2004; Pedersen et al., 2007).
IL-8	4q12-q13	Angiogenesis and neutrophil chemoatraction thru the CXCR2 (Freydelund et al., 2007).
IL-15	4q31	Reduction of body fat, especially visceral body fat (Carbó et al., 2001; Acharyya et al., 2004)
IL-10	1q31-q32	Downregulation of Proinflammatory cytokines and chemokines (de Vries, 1995; Acharyya et al., 2004)
IL-1ra	2q14.2	Restriction and modulation of the inflammatory response during exercise (Ostrowski et al., 1999; Opal et al., 2000; Suzuki et al., 2000)

Table 1. Myokines and their effects concerning Obesity and Metabolic Syndrome.

Parallel to IL-6 effects, IL-15 has progressively risen as a major modulator of fat metabolism and muscle accretion in skeletal muscle over the past 15 years, which have been discussed elsewhere (Carbó et al., 2000; Quinn et al., 2008; Argilés et al., 2009), yet the following aspects need to be discussed. IL-15 is a cytokine which is related to NK cell maturation, which actions are not reserved for the immunology universe. This protein is synthetized also by placenta, muscle and other tissues, supporting the idea of non-immune functions in such organs. Muscle hypertrophy at the expense of myotube accretion by inhibition of protein degradation is observed in animal models (Quinn et al., 2002), and this has been proposed as a therapeutic option for wasting syndromes such as cancer (Carbó et al., 2000) . This effect is probably due to induction of PPAR-δ which mediates protein synthesis in such cells. As for adipose tissue, the cytokine has been related to reduce lipid accumulation in pre-adipocytes enhancing their differentiation, and inducing adiponectin secretion in matured adipocytes (Quinn et al., 2005). These findings were further confirmed, when it was proven that IL-15 effect also reached brown adipose tissue, with an acute induction of thermogenesis via upregulation of Uncoupling Proteins 1 and 3, PPAR-δ and –α and a final association with reduction of white adipose tissue mass (Almendro et al., 2008). The evidence pointed to a more multifaceted muscle-adipose axis with IL-15 as remote modulator (Quinn et al., 2009) when secreted from skeletal muscle, inducing GLUT4, enhancing glucose utilization, reducing adipose deposition and adipocyte size. Further studies have linked polymorphisms of IL-15 and metabolic syndrome propensity, including the following protein SNPs: rs1589241, rs1057972 (Pistilli et al., 2008), with a unique relation to metabolically obese normal weight patients (Di Renzo et al., 2006).

On a final note, a new twist in the *metainflamamtion phenomena* (Hotamisligil, 2006) observed in obesity has been described. The innate receptors members of the Pattern Recognition

Receptor Family, the NLRPs, are part of an ancestral detection system which recognizes danger associated molecules, resulting in the recruitment of Caspase-1 and the activation of IL-1β and IL-18, known proinflammatory cytokines (Lamkanfi & Dixit, 2009). Receptor NLRP3 has been associated to lipotoxicity sensing by recognizing ceramides production in macrophages and adipocytes, contributing to obesity-related inflammation by synthesis of IL-1β and blunted insulin signaling in liver and adipose tissue (Vandanmagsar et al., 2011). Moreover, IL-1β has been proven to regulate adipogenesis towards a more insulin resistance phenotype (Stienstra et al., 2010), which renders fundamental in a proinflamatory and toxic environment which is seen around the hypoxic and pre-adipocyte rich areas of adipose tissue.

4. Conclusions

Obesity is a multifactorial disease, characterized by adiposity-related consequences and disease, such as type 2 diabetes, cardiovascular disease, obstructive sleeping apnea, osteoarthritis, and cancer. Understanding the molecular dialogue between the 2 principally affected cells – adipocyte and skeletal myocyte – serves as the underlying scientific platform to understand why physical activity is beneficial and mandatory in these patients. The very notion that glucose uptake is enhanced in skeletal muscle during and after exercise provides a great glycemic control strategy, lowering the effects of excessive glucose in circulating plasma, like glycosylated hemoglobin levels (Andrade-Rodríguez et al., 2007; Sigal et al., 2007), increases plasma glutamine and arginine levels for the production of NO and glutathione not only improving vasodilation properties but also increasing antioxidant defenses (Krause & de Bittencourt,, 2008), and myocyte-derived IL-6 enhances glucose induced insulin secretion (Newsholme et al., 2010).

The application of a proper exercise program in obese patients, along with diet and lifestyle modification, ensures that the obese myocyte will get in shape, with a dynamic IMCL turnover, improved glucose and fat oxidation, genetic modulation of fiber remodeling, ending in progressive and sustained metabolic control. The dying myocytes will stop being so stressed with external stimuli and over-availability of substrates, decreasing in size and in oxygen requirements, modulating macrophage recruitment and inflammatory signals derived from them. The application of therapeutic drugs to improve the effects of exercise and act synergistically has been reported.

Thiazolidinediones (TZD) are a group of drugs that activate PPARγ, modulating all the downstream genes regulated by the transcription factor, including acyl~CoA synthetase, phosphoenolpyruvate carboxykinase and lipoprotein lipase, inducing FFA capture and storage in de novo adipocytes, lowering FFA levels in plasma at the cost of fast redistribution ("Lipid-steal" phenomenon) (Bermúdez et al., 2010). In insulin resistant models, TZD correct impaired myocyte insulin action (Zierath et al., 1998), normalize muscular insulin sensitivity and GLUT4 synthesis in conjunction with exercise (Hayener et al., 2000), lower waist-hip ratio due to a selective increase in lower body fat (Shadid et al., 2003), improve exercise capacity in type 2 diabetic patients (Regensteiner et al., 2005), and increase adiponectin levels (Yang et al., 2002) just as exercise does (Kriketos et al., 2004; Højbjerre et al., 2007); which is why the combination of a TZD and exercise are self-complementary in the treatment of insulin resistance (Lessard et al., 2007). The world-famous biguanide, Metformin, is the other pharmacological candidate to enhance exercise effects on the insulin resistance milieu. Exercise has been known to improve metformin

effects (Tang et al., 2001), acting as co-adjuvants in the reduction of the incident of diabetes (Doggrell, 2002), increasing vascular function and lowering Ischemia Coronary Artery Disease patients (Jadhay et al., 2006), and finally, both can reduce the expression of the fat transporter FAT/CD36, blunting the progression of ceramides-mediated insulin resistance in myocyte (Smith et al., 2007). The insulin sensitizing effect of metformin are carried out via activation of AMPK (Hawley et al., 2002), simulating the very first effects on physical activity in skeletal muscle. Finally, Exercise is an ideal lifestyle intervention suitable and rightful to all obese patients, due to its counteracting measures against the molecular derangements observed in obesity, modulating local and systemic metabolic disturbances.

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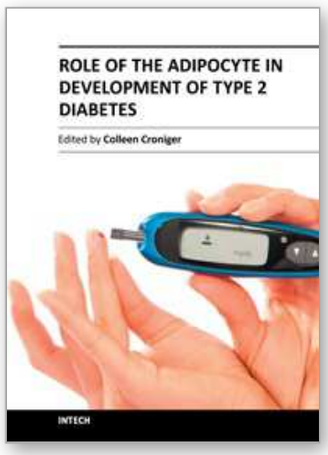

Role of the Adipocyte in Development of Type 2 Diabetes

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Adipocytes are important in the body for maintaining proper energy balance by storing excess energy as triglycerides. However, efforts of the last decade have identified several molecules that are secreted from adipocytes, such as leptin, which are involved in signaling between tissues and organs. These adipokines are important in overall regulation of energy metabolism and can regulate body composition as well as glucose homeostasis. Excess lipid storage in tissues other than adipose can result in development of diabetes and nonalcoholic fatty liver disease (NAFLD). In this book we review the role of adipocytes in development of insulin resistance, type 2 diabetes and NAFLD. Because type 2 diabetes has been suggested to be a disease of inflammation we included several chapters on the mechanism of inflammation modulating organ injury. Finally, we conclude with a review on exercise and nutrient regulation for the treatment of type 2 diabetes and its co-morbidities.

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