Differential Role of AMP-Activated Protein Kinase in Brown and White Adipose Tissue Components and its Consequences in Metabolic Diseases

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Abstract

The liver kinase B1 / adenosine monophosphate-activated protein kinase / tuberous sclerosis complex/ mammalian target of rapamycin complex 1 (LKB1/AMPK/TSC/mTORC1) cassette constitutes a canonical signaling pathway that integrates the metabolic and nutrient status of the cell for regulation of cell growth and survival and would thus be expected to be of critical importance in adipose tissue, the main organ in the body dealing with energy homeostasis. Indeed, it has now become clear that changes in AMPK activity and to a lesser extent in protein kinase B (Akt/PKB), guide almost every process in this tissue and that modulation of the activity of the nutrient signaling cassette offers a wide range of options to deal with metabolic diseases. In the present study, I review the current body of biomedical literature on AMPK signaling in adipose tissue and show that although the effects involved are highly cell type specific in general, however pharmacological AMPK activation seems the way toward losses in adiposity. It should thus be exceedingly interesting to observe the results of clinical trial in obese subjects treated with AMPK analogues.

Keywords: Adipose tissue; AMPK pathway; mTOR; Insulin pathway

Abbreviations: AD: Adiponectin; AICAR: 5-Aminoimidazole-4-carboxamide-1-β- D-ribofuranoside; AKT/PKB: Protein Kinase B; AMP/ATP ratio: Adenosine monophosphate/Adenosine triphosphate ratio; AMPK: AMP-activated Protein Kinase; ATG13: Autophagy Gene 13; BAT: Brown Adipose Tissue; CaMKK2: Calcium/calmodulin-dependent Protein Kinase Kinase 2; EBP1: ErbB-3 Binding Protein; eLF-4E: Eukaryotic initiation factors-4E; GLUT4: Glucose Transporter Type 4;IR: Insulin Receptor, IRS: Insulin Receptor Substrate; LD: Lipid Droplets; LKB1: Liver Kinase B1; mTORC1: mammalian Target of Rapamycin Complex 1; p38 MAPK: p38 Mitogen-activated Protein Kinase; P70S6K: P70 ribosomal S6 kinase; PDK: Phosphoinositide dependent Kinases; PI3K: Phosphatidylinositol 3 Kinase; RheB: Ras homolog enriched in Brain; SC: Subcutaneous; TSC: Tuberous Sclerosis Complex; T2DM: Type 2 diabetes mellitus; UCP-1: Uncoupling protein 1; ULK1: Unc-51-like kinase 1; Vis: Visceral; WAT: White Adipose Tissue.

Introduction

Maintaining energy homeostasis is one of the fundamental tasks of the body to control the blood glucose level. Normoglycemia is thus achieved as a result of a multitude of tightly regulated and highly tuned mechanisms in which all tissues are involved and only partly understood. Nevertheless, the adipose tissue and in particular adipocytes together with the skeletal muscle and liver seem to be the most important organs for dealing with challenges to keep body energy and energy metabolic system in homeostasis. On the other hand, normoglycemia is regulated through proper energy delivery to the energy demanding tissues or storage in the adipose tissue through the lipoprotein compartment. Although through most of mankind's history, lack of energy has been the main challenge in current societies,

excess intake of calories and especially fats and sugars as well as their main manifestation and hyperglycemia-related diseases has become a serious problem nowadays. The situation is compounded by the increase of sedentary life-styles and the use of high levels of tobacco [1,2]. Currently, 65% of the global population lives in countries where obesity kills more people than malnutrition (WHO - Global strategy on diet, physical activity and health, 2010). Metabolic diseases related to malnutrition including obesity-induced metabolic syndrome, dyslipidemia, fatty liver and type 2 diabetes mellitus (T2DM) represent an ever increasing challenge to health care. A guiding principle of this idea is that many aspects of these diseases can be better understood through insight into the energy metabolism of adipocytes as well as improved knowledge of adipocytes and their production. Furthermore, the lipoprotein compartment is not only a mediator between the adipose compartment and the periphery with respect to the transport of energy-rich hydrophobic molecules, but also is an important transport modality for adipocyte-generated endocrine signals [3].

Energy metabolism and energy metabolic system

Energy metabolism is defined as a finely tuned regulatory system to ensure the balance of the retour of energy in the form of lipids and carbohydrates in the body and is reflected by the level of the glucose in circulation. Circulatory glucose levels depend on four parameters: (i) prandial glucose (food-derived), (ii) the consumption of glucose in the tissues (mainly skeletal muscles and the brain), (iii) the capacity of the body to store excess glucose in the adipose tissue in the form of triglycerides and (iv) the endogenous glucose production through gluconeogenesis in the liver and kidney. The energy metabolic system ensures to regulate the energy metabolism in the body. It is mainly composed of energy transporting and storing molecules (e.g. lipids and glucose), lipid carriers (lipoproteins), the endocrine system (e.g. pancreas, adipose tissue, hypothalamus, growth hormones, thyroid, and adrenal gland hormones), the metabolically active tissues (e.g.

adipose tissue, skeletal muscles, liver, and kidney) and the metabolic pathways (mainly insulin, AMPK and inflammatory pathways). Among the involved systems, adipose tissue and skeletal muscle, as the main energy reservoir and consumer units in the body respectively, play major roles in determination of the quality of the metabolic system function. A disturbance in the function of these two organs can trigger metabolic diseases including metabolic syndrome and incidence of the consequent medical complications including coagulopathy and atherosclerosis. Here, I shall argue that in regulation of energy metabolism, adipose tissue is an underestimated but principal component regulating these processes. broadly similar within eukaryotes. To adjust cell metabolism to the intracellular energy status and extracellular environment, LKB1/ AMPK/TSC/mTORC1 pathway integrates information regarding the intracellular energy, oxygen status, the presence of growth factors and nutrient availability and translates this into the regulation of cell growth (Figure 1) [4,5]. Lower energy status, which is reflected in an increased adenosine monophosphate / adenosine triphosphate (AMP/ ATP) ratio, directly results in higher AMPK activity. Although AMPK can directly influence cellular physiology via the stimulation of glucose import and mitochondrial activity [6], its main action is to influence mTOR activity. AMPK, via TSC, inhibits mTOR, which is known as the central energy sensor of the cell [7]. mTOR activity, via S6 kinase (S6K), provides a protein synthesis-permissive signal, which actively counteracts autophagia [8-10].
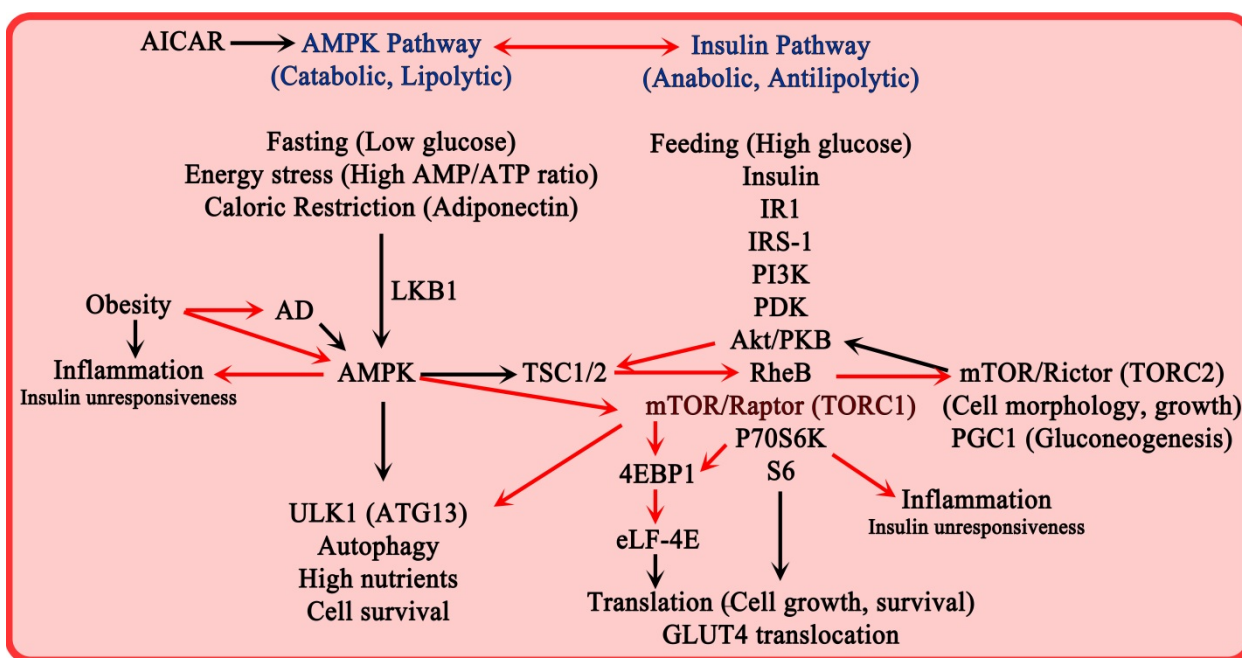

Figure 1: Illustration of the antagonist association between insulin and AMPK pathways: the two main energy metabolic systems of the body. LKB1/AMPK/TSC/mTORC1 pathway is the fundamental nutrient and metabolic status sensing in the body that helps cells to adjust their metabolism to the intracellular energy status and extracellular environment. The anabolic insulin pathway and catabolic AMPK (in the skeletal muscle) pathways have a negative regulatory effect on each other and both determine the level of the energy status of the cell. AMPK pathway is activated following lower energy status, which increases the level of AMP/ATP ratio in the body. Increase of the level of adiponectin following caloric restriction has a stimulatory effect on the stimulation of AMPK. AMPK decreases inflammation by enhancing FAO in cell. It also has a stimulatory effect on autophagy and TSC, which inhibits insulin pathway. RheB in insulin pathway, via positive influence on mTOR/Rictor (TORC1), influences the central energy sensor of the cell. TORC1 inhibits autophagy and stimulates cell growth and survival.

Human diseases such as Peutz-Jeghers syndrome (PJS) and TSC knockout animal models and in vitro experiments indicate that both the LKB1 kinase and the TSC1:TSC2 complex are essential proteins in regulating cell growth under conditions of metabolic stress [11]. In addition, the system is under control of the PKB/Akt pathway.

Anabolic stimuli, like insulin, employ this pathway to increase mTOR activity. The effect of nutrient signaling in adipose tissue is highly cell type-dependent and thus modulation of this pathway may hold great clinical promise through this system. type-dependent and thus modulation of this pathway may hold great clinical promise through this system.

The link between obesity and metabolic disorders

The development of humanity has undoubtedly included many episodes of extreme starvation and as a result we are highly capable of storing excess energy in the form of lipids in the body for usage at a later time. The subcutaneous fat layers are the physiological place for this storage and could also protect us against cold. During the activity, the stored energy is released allowing better survival. However, calorie restriction is not much of an issue anymore throughout the word, therefore obesity is depressingly common. Obesity is the new major risk worldwide. An overload of energy in the form of triglycerides within lipid droplets (LDs) of adipocytes (Figure 2) is the main cause of obesity [12]. Numerous epidemiological studies implicate that hypertrophy of adipocyte compartment is linked to energy metabolic

disorders such as insulin unresponsiveness and type 2 diabetes mellitus and their afflictions including coagulopathy, atherosclerosis and cardiovascular diseases. The notion that the adipocyte compartment is an important component of the normal and aberrant energy balance and its associated disorders comes from the association that has been made between obesity and metabolic disorders. The nature of the problem is further compounded by the observation that both obesity and its associated disorders seem to display even greater prevalence over the world. The factors driving the obesity epidemic are mainly both the changes in diet with a greater dependency on sugars and fats with a concomitant decrease in fibre in combination with a reduced physical activity. Also, failure to develop a good therapy in dealing with metabolic disorders remains to be an issue here. Efficient breakdown of fat may be further compounded by differences between individuals with respect to threshold levels of lipid storage and release as well as differences in gut flora components. In turn, obesity provokes systemic chronic inflammation, which is directly related to metabolic disorders, cardiovascular disease [13] and malignancy [14]. Hence, I would highlight the role of obesity in initiation of inflammation [12,15] and energy metabolic system disturbances including metabolic syndrome and atherosclerosis.
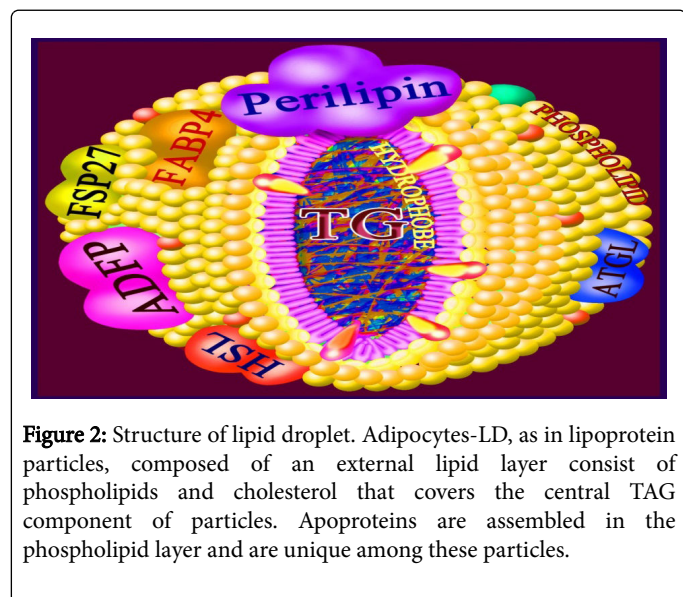

Figure 2: Structure of lipid droplet. Adipocytes-LD, as in lipoprotein particles, composed of an external lipid layer consist of phospholipids and cholesterol that covers the central TAG component of particles. Apoproteins are assembled in the phospholipid layer and are unique among these particles.

AMPK pathway and its association with insulin pathway

AMPK is a conserved serine / threonine protein kinase, the main sensor of the intracellular energy and one of the main regulators of metabolic pathways [16]. AMPK is activated in situations that the level of the intracellular energy is low, either through low absorption of fuel molecules during fasting or via high consumption of energy during exercise or following the increase of free fatty acids (FFAs) and their esterification. Therefore, its activity is associated with the AMP/ATP ratio and it inhibits all the anabolic pathways such as gluconeogenesis and the synthetic pathways of lipids, glycogens, and proteins and stimulates the catalytic pathways such as fatty acid oxidation (FAO), glucose transport [17], glycolysis and mitochondrial biogenesis to produce energy 6. AMPK through regulation of the FAO and fat mass influences body weight, insulin sensitivity, systemic glucosehomeostasis, lipid and protein metabolism and mitochondrial biogenesis [18]. The FAO function of AMPK in the skeletal muscle, heart and liver is applied through stimulation of malonyl-CoA

decarboxylase (MCD) and inhibition of acetyl-CoA carboxylase-2 (ACC-2) [19]. Both enzymes consequently decrease the level of malonyl-CoA and augment the carnitine palmitoyltransferase I (CPT1) activity. CPT-1 enhances the entrance of FAs to the mitochondria for oxidation. In the skeletal muscle, AMPK pathway enhances glucose transporter type 4 (GLUT4) activation and FAO and via peroxisome proliferator-activated receptor gamma (PPARγ) coactivator 1-alpha (PGC1-α) phosphorylation stimulates mitochondrial biogenesis [20]. In the heart, AMPK pathway stimulates glycolysis and FAO [21] and in the liver, AMPK pathway stimulates FAO and inhibits gluconeogenesis and synthesis of cholesterol, fatty acid and glycogen [22]. In the adipose tissue, AMPK pathway inhibits both the β-adrenergic-induced lipolysis and the adipocyte differentiation markers [23].

AMPK pathway and insulin pathway have a mutual negative regulatory effect on each other 18 and also on the fatty acid metabolism enzymes [24]. Insulin pathway, through inhibition of AMPK pathway, enhances the lipid synthesis [25] while AMPK has a bi-functional effect on the insulin pathway. On one hand, AMPK has an inhibitory effect on the insulin pathway either through inhibition of phosphoinositide 3-kinase (PI3K) class 3 [26], Raptor-mTOR-GBL complex (called mTORC1 or mammalian target of rapamycin complex 1) [27] and P70S6K [18,28] or through enhancement of the insulin pathway inhibitors such as TSC1/2 [7,18] and eukaryotic elongation factor-2 kinase (eEF2K) [28]. Adipose tissue, through adipokines like leptin and adiponectin and their stimulatory effect on the AMPK, inhibits the insulin pathway [19]. On the other hand, AMPK decreases insulin unresponsiveness in skeletal muscle cell either via enhancement of the FAO and augmentation of the FFAs-induced negative influence on the insulin pathway [29] or via its anti-inflammatory effect [30]. In fast-twitching muscles, it also stimulates the hexokinase II gene expression and GLUT4 upregulation and translocation, which leads to glucose uptake as in insulin hormone [6]. Therefore, stimulators of AMPK could be used for the treatment of T2D.

Moreover, AMPK inhibits secretion of insulin by pancreatic beta cells [31] and it stimulates insulin sensitivity in the muscle and liver through enhancing serine phosphorylation of insulin receptor substrate 1 (IRS-1) [32]. Caloric restriction, via increase in the level of adiponectin and AMPK stimulation, inhibits S6K and consequently its inhibitory effect on IRS [33] and insulin pathway. It also via the stimulation of TSC, the inhibitor of the insulin pathway, upregulates IRS and enhances insulin sensitivity [19]. In obese state, due to the low level of adiponectin and the simultaneous leptin unresponsiveness and via AMPK inhibition, S6K activity is increased, which induces insulin unresponsiveness. Therefore, during exercise, AMPK in the skeletal muscles stimulates the recruitment of glucose transporters to the plasma membrane and glucose absorption. This event, which has an additive effect on insulin pathway, happens via a mechanism distinct from the insulin pathway and its subsequent fate is also different from the insulin pathway [19].

Integration between the AMPK and insulin pathways modulates therisk of diabetes in obesity susceptible individuals. AMPK signalling pathway also interacts with and inhibits the inflammatory pathways. Leptin and adiponectin, via influence on AMPK apply their anti-inflammatory effect. In obesity, low levels of adiponectin and leptin unresponsiveness lead to AMPK inhibition and stimulation of chronic inflammation. Its anti-inflammatory effect is mainly mediated via inactivation of Rel or nuclear factor kappa-light-chain-enhancer ofactivated B cells (NFkB) signaling [34]. Excess of intracellular energy

during obesity inhibits the AMPK pathway which leads to stimulation of the inflammatory pathways such as c-Jun N-terminal kinases(JNKs) and tumor necrosis factor- alpha (TNFα).

Effect of AMPK signaling on adipose tissue and its components

Survival of a species is dependent on two main processes, which are clearly interrelated: proper maintenance of the level of energy in the body and mounting an immune response to pathogens [35]. Nutrientand pathogen-sensing pathways are both highly conserved pathways, which are interrelated to each other at many points. For instance, the crucial role of mTOR gene in both nutrient pathways as well as immunity is known [36]. mTOR inhibitors are among the most available strong immunomodulators that are often used in transplantation medicine [37]. During obesity, the adipose tissue develops low grade inflammation, which is primed by adipocytes and followed by a concerted reaction of the other constituting cell types of the adipose tissue [35,38]. Adipose tissue is one of the largest tissues in the body and is composed of different cells such as adipocytes, resident macrophages (ATM or adipose tissue macrophages), mesenchymal stem cells (MSCs), preadipocytes, endothelial cells (ECs), and fibroblasts (Figure 3). This diversity of cells in the adipose tissue represents its vast function and importance in different pathways including the metabolic system [39,40] and the immune system 38 and both functionalities are related to the nutrient signaling. In mammals, adipose tissues are categorized into two types of brown adipose tissues (BAT) and white adipose tissues (WAT). Each type is located in either the visceral (Vis) or subcutaneous (SC) part of the body. These two classifications are separate from each other and are important in the evaluation of the metabolic system functionality. In adipose tissue, AMPK via inhibition of both hormone-sensitive lipase (HSL)-induced lipolysis and fatty acid synthase (FAS)-induced fatty acid synthesis has a mutual effect on the lipid pathway [32]. AMPK, via inhibition of HSL, modulates the stimulatory effect of catecholamine-induced cyclic AMP-dependent protein kinase A (cAMP/PKA) pathway on HSL [41]. The negative regulatory effect of insulin and positive effect of TNFα inflammatory cytokine on cAMP and their influence on HSL [42] represent the close and precise network function of vast different regulators such as AMPK, cathecolamins, insulin and inflammatory cytokines in modulation of the lipolitic activity of adipose tissue. AMPK also inhibits the lipolytic pathways via influence on the enzymes such as 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) (in sterol synthesis) [43], glycerol 3-phosphate acyltransferase (GPAT) (in triglyceride synthesis), FAS (in fatty acid synthesis) [32], hepatocyte nuclear factor 4 (HNF4) (in hepatic fatty acid synthesis) [18,44] and sterol regulatory element-binding protein 1 (SREBP-1) [43,45] (in hepatic fatty acid synthesis and very low-density lipoprotein (VLDL) synthesis) [44,46]. The FA oxidation of adipocytes in the adipose tissue is inhibited in order to export the fatty acids to the muscles for oxidation and energy generation [47]. At the level of carbohydrate metabolism, it mediates its negative regulation via influence on glycogen synthase enzyme (for glycogen synthesis) and consequently inhibits glucose storage and so stimulates FAO and triglyceride oxidation [18]. It also inhibits insulin/mTOR/S6K that leads to augmentation of its inhibitory role on IRS and stimulating insulin sensitivity. AMPK inhibit gluconeogenesis by influence on either the PEPCK and G6Pase enzymes or the TORC2 that stimulates the PGC1-α activation [19]. AMPK stimulates glycolysis through PFK2 activation [18].
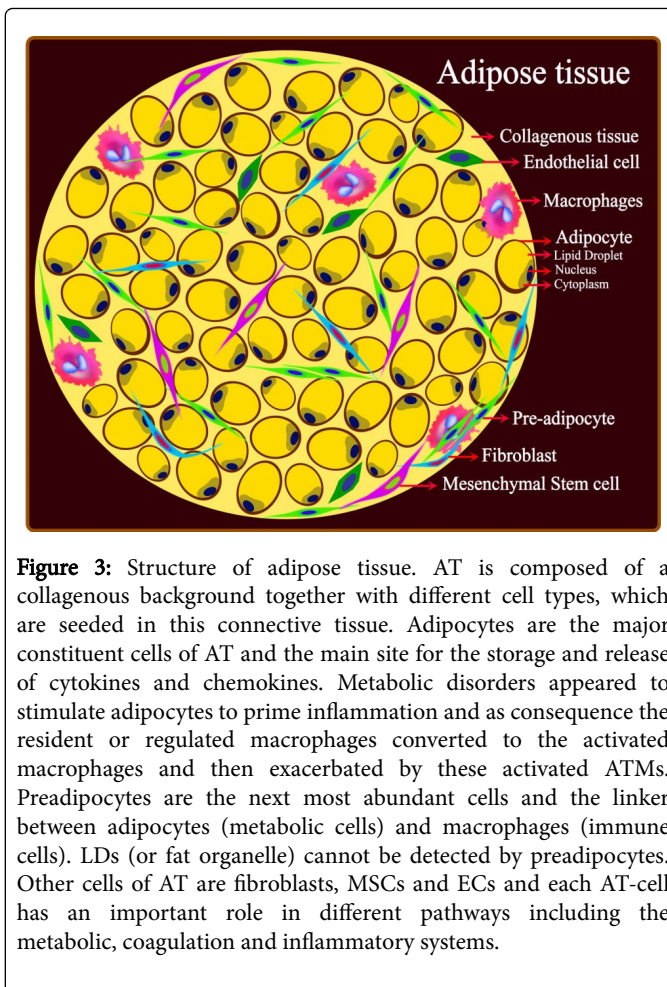

Figure 3: Structure of adipose tissue. AT is composed of a collagenous background together with different cell types, which are seeded in this connective tissue. Adipocytes are the major constituent cells of AT and the main site for the storage and release of cytokines and chemokines. Metabolic disorders appeared to stimulate adipocytes to prime inflammation and as consequence the resident or regulated macrophages converted to the activated macrophages and then exacerbated by these activated ATMs. Preadipocytes are the next most abundant cells and the linker between adipocytes (metabolic cells) and macrophages (immune cells). LDs (or fat organelle) cannot be detected by preadipocytes. Other cells of AT are fibroblasts, MSCs and ECs and each AT-cell has an important role in different pathways including the metabolic, coagulation and inflammatory systems.

Brown adipose tissue-adipocytes

BAT and WAT adipocytes have different morphology and opposite functions in mammalian bodies. BAT-adipocytes are characterized by small LDs containing triglycerides, which are accessible for rapid hydrolysis and oxidation of fatty acids, while WAT-adipocytes have one huge LD per adipocyte for energy storage in the form of triacylglycerol [48,49]. Ultrastructurally, brown adipocytes are characterized by a high number of mitochondria packed with cristae and expressing thermogenic genes such as uncoupling protein 1 (UCP-1). UCP plays an important role in energy expenditure and lowering mitochondrial membrane potential and dissipating metabolic energy as heat (thermogenesis).This happens because UCP is used for FAO [50] and it causes proton leakage during proton transport across inner mitochondria membrane (IMM) via uncoupling of oxidative phosphorylation (OXPHOS) from ATP synthesis [51].

In eukaryotic cells, mitochondria are energy suppliers of the cell and within the mitochondria; IMM is the main site of OXPHOS. The nutrients will be oxidized to ensure the release of energy: adenosine triphosphate (ATP). During OXPHOS reaction, the electrons will be delivered from electron donors such as nicotinamide adenine dinucleotide (NADH) to electron acceptors like oxygen, in a reaction called redox to release energy. After oxidation of NADH in mitochondria, the energy will be available for anabolic pathways. By flowing of electrons in the electron transport chain, energy is released

to be used to move protons across IMM. With respect to OXPHOS, two points must be noted: (i) OXPHOS is vital for cells and is used by mitochondria to provide energy to cells and (ii) reactive oxygen spices (ROS) that are considered to be poison for cells are released from the oxidation process in the mitochondria. Even though BAT is the major type of adipose tissue during the development of fetal bodies, during adulthood it is mostly converted to WAT [12]. However, the remaining BAT is functional and active in adults that could be used for combating obesity [52].

Figure 4: AMPK influence on main metabolic tissues. Stimulation of AMPK in the situations that enhance the ratio of AMP/ATP (caloric restriction and exercise) has different effects on body tissues. In the liver, AMPK inhibits the main function of the tissue including lipogenesis and gluconeogenesis. In the skeletal muscles, AMPK via FAO stimulates the insulin sensitivity that leads to attenuation of the inhibitory effects of lipid loads on insulin pathway. AMPK also stimulates GLUT4 gene expression and mithochondrial biogenesis. In the adipose tissues, AMPK has different effects on the brown adipocytes and white adipocytes. AMPK inhibits differentiation of WAT preadipocytes to white adipocytes and facilitates the transition of WAT adipocytes to the BAT adipocytes. This state, stimulates energy dissipation in the body and consequently has the anti-inflammatory and anti-obesity effects. In both the BAT and WAT adipose tissues AMPK counteracts the high-lipid load inflammatory ATMs and decreases the inflammatory effects of ATMs. AMPK also enhances MSC survival via mTOR inhibition. Red arrows and black arrows represent the inhibitory and stimulatory effects of AMPK respectively.

Interestingly, it is shown that bone morphogenetic protein-8B (BMP8B) has a stimulatory effect on regulation of the BAT function. Therefore, it has a great influence in thermogenesis and energy balance [53]. The notion of this paper is confirmed in a paper, which presents a close association between bone and adipose tissue under influence of developmental signalling pathways including the Hedgehog signalling pathway [54]. The percentage of BAT in visceral fat is higher than that in the subcutaneous fat tissue [55]. The activation of human BAT represents an opportunity to increase energy expenditure and weight

loss alongside improved lipid and glucose homeostasis. Active BAT is able to uptake large quantities of lipid and glucose from the circulation [56]. Activity of these cells with respect to thermogenesis is largely under the control of innervated-β-adrenergic receptors on brown adipocytes [57]. However, pharmacological approaches to stimulate brown adipocyte activity without central nervous system side effects might hold great promise to combat obesity-related diseases [58] (Figure 4).
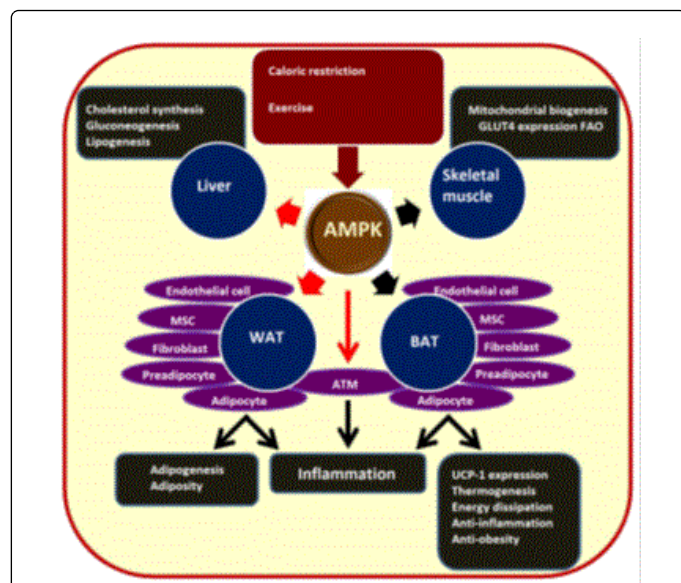
Nutrient signaling plays a pivotal role in brown adipocyte development, quite different from the situation in white adipose tissue adipocytes. Differentiation of brown adipocytes coincides with strong activation of LKB1/AMPK and canonical downregulation of mTORC1, unusually in conjunction with p38 mitogen-activated protein kinase (p38MAPK) activation, which is a kinase normally more associated with pro-inflammatory processes. Stimulation of mTOR prevents brown adipogenesis, whereas forced activation of signaling cassette through 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR)-induced AMPK activation increases UCP-1 expression and induces an accumulation of brown adipocytes in WAT [59]. Thus, in contrast to the classical view in which activation of mTOR promotes acquisition of cellular functionality and in which AMPK activation is associated with energy conservation, during brown adipocyte development AMPK activation is associated with the burning of calorie (storage of excessive energy) in a catabolic process [60,61]. It is hoped that further elucidation of the involved processes could contribute in the fight against metabolic diseases.

White adipose tissue-adipocytes

White adipocytes are the dominant cell type in the adipose tissue. This cell type is characterized by a very long half-life and the ability to store increasing amounts of triglycerides in its LDs in mature adipocytes. However, they concomitantly lose their ability to proliferate [62]. Interestingly, the structure of LDs is comparable with that of plasma lipoproteins, containing a hydrophobic core coated with a hydrophilic monolayer membrane [63-65]; however, there are differences with respect to phospholipids and the type of their protein composition. Many proteins are associated with the LD monolayer membrane [66] (Figure 3). Dysregulation of lipid metabolism in adipocytes as found in obese subjects can, to a large extent, be attributed to the increased size and storage capacity of the LD [12].

Even in lean subjects, LDs may occupy a high percentage of cellular volume of the adipocytes [38]. In contrast to brown adipocyte genesis, the generation of WATadipocytes is negatively regulated by activation of the AMPK pathway. For instance, it has been shown that various natural compounds like methyl cinnamate or mushroom extracts inhibit adipocyte differentiation via activation of the calcium/calmodulin-dependent protein kinase kinase 2 (CaMKK2)-AMPK pathway [67-69] (rather than LKB1, which is the more common activator of AMPK). In rats, chronic stimulation of AMPK is reported to decrease adiposity through inhibition of adipogenesis [70], but whether this is true for human remains unclear as dieting (which activates AMPK in adipocytes) is not reported to reduce the number of adipocytes in the short or medium term [71]. A possible explanation is the differences in leptin effects between humans and rodents. In rats, AMPK stimulation seems to increase leptin effects on adiposity but in humans such effects of leptin are much weaker. Moreover, it is expected that AMPK activation should facilitate triglyceride-loading on plasma lipoproteins in adipocytes and indeed in animals treated

with AMPK inhibitors lower circulating levels of plasma triglycerides have been reported.

Resident macrophages of ATMs

Obesity leads to metabolic disorders in adipose tissue, which in turn results in an inflammatory environment. Importantly, obesity and its consequent disorders change ATM to activated macrophages in the adipose tissue, which is a hallmark of energy metabolism disorderinduced insulin unresponsiveness [38,72]. The ATMs have attracted substantial attention with respect to metabolic diseases as they have been suggested to be the mediators of the low-grade inflammation present in fat tissues of obese people. Indeed, although conclusive evidence is still lacking and until that time other possibilities have to be kept in mind, these ATMs spatially seem to have a close interaction with adipocytes in the adipose tissue and this interaction is thought to stimulate cells to secrete proinflammatory cytokines [35]. However, Meijer et al. suggested that the primary event in the sequence leading to chronic inflammation in adipose tissue is metabolic disorder in adipocytes, followed by production of immunological mediators by these cells, which is then exacerbated by activated ATMs and finally leads to the recruitment of immune cells [38]. During obesity, the density of macrophages in adipose tissue increases, either due to increased chemokine expression [12] or maybe local proliferation or conversion of MSCs to macrophages [72-75]. Notably, the ATMs in adipose tissue and other tissues containing macrophages also have a role in tissue repair [76,77]. Macrophage infiltration increases fat lipolysis, which leads to an increase of the circulatory FFA levels. FFAs are sedimented in other tissues and consequently induce storage of lipids in metabolically active tissues [12]. AMPK appears to be a key enzyme that counteracts the high-lipid load-induced inflammatory pressure in these macrophages [78]. Animals genetically engineered to be defective in macrophage AMPK activity displayed a highly inflammatory phenotype in their ATMs. Inhibiting FAO (a key effector mechanism of AMPK to improve the cellular energy balance) also was proinflammatory in these cells and conversely pharmacological activation of AMPK counteracted inflammation [79]. If ATMs are indeed of cardinal importance in metabolic diseases, pharmacological targeting of the associated pathways (e.g. using rapamycin which mimics AMPK activation in its inhibitory effect on mTOR) [80] may prove a viable option in dealing with such diseases. Mesenchymal stem cells, fibroblasts and preadipocytes Adipose tissue is a rich source of MSCs, a highly immunomodulatory cell type with the capacity of self-renewal, proliferation, differentiation, plasticity and intimately involved in tissue repair. The concentration of the MSCs in adipose tissue may be hundreds more than bone marrow [81-83] and thus it is reasonable to assume that this cell type can influence the physiology of fat. Although autophagia is in general associated with protection of cells from hypoxic and hyponutrient stress [84], this functionality of the autophagic response may be stronger in the MSC compartment. Indeed, AMPK activation emerged as a major mediator for MSC survival following hypoxia through AMPK-mediated mTOR inhibition dependent autophagic responses [85]. MSCs are able to differentiate into preadipocytes and their precursor fibroblasts [86].

The molecular details to govern the transition of fibroblasts to preadipocytes are slowly emerging and involve regulation through the prolyl isomerase Pin1, possibly through enhancing mTOR signaling by stabilizing its upstream activator PKB/Akt. Preadipocytes have multilocular LDs [49] (in contrast to mature adipocytes which contain one LD) and are thought to be immune active cells through phagocytic and antimicrobial properties [35]. Profiling indicates that molecularly they are closer to macrophages than adipocytes and might be able to differentiate into the former cell type [73]. Remarkably, in obese subjects the capacity of preadipocytes to differentiate adipocytes is impaired [87]. In general, preadipocytes act as a link between the metabolism and innate immunity [73]. It must be noted that autophagy is necessary for adipogenesis and regulation of adipose mass [10,88]. As mentioned earlier, AMPK activation inhibits differentiation of preadipocytes to white adipocytes but facilitates the transition to the brown adipocyte type [23]. In conclusion, AMPK activation has a protective role in these components of fat tissue, whereas mTOR activation increases sensitivity of adipose tissue lipid uptake.

Conclusion

Adipose tissue is one of the main components of the metabolic system. It functions in close association with skeletal muscles and liver for energy homeostasis. It is in two forms of BAT and WAT that are two different forms of this metabolically active tissue and function quite opposite each other in the regulation of energy metabolism of the body, which is represented as normoglycemia in lab results. AMPK activation increases brown adipocytes, thus enhancing energy metabolism while simultaneously promoting lipolysis in white adipocytes and protecting ATMs from inflammatory responses. The combined anti-adiposity profile and anti-inflammatory profile resulting from AMPK stimulation is expected to be highly beneficial when managing metabolic diseases and thus pharmacological therapies of these diseases through manipulation of nutrient signalling pathways appears highly promising.

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