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Adipogenesis is under surveillance of Hsp90 and the high molecular weight Immunophilin FKBP51

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Abstract

Adipose tissue plays a central role in the control of energy balance as well as in the maintenance of metabolic homeostasis. It was not until recently that the first evidences of the role of heat shock protein (Hsp) 90 and high molecular weight immunophilin FKBP51 have been described in the process of adipocyte differentiation. Recent reports describe their role in the regulation of PPARγ, a key transcription factor in the control of adipogenesis and the maintenance of the adipocyte phenotype. In addition, novel roles have been uncovered for FKBP51 in the organization of the architecture of the nucleus through its participation in the reorganization of the nuclear lamina. Therefore, the aim of this review is to integrate and discuss the recent advances in the field, with special emphasis on the roles of Hsp90 and FKBP51 in the process of adipocyte differentiation.

Introduction

There is no doubt that adipose tissue plays a central role not only in the regulation of energy balance and lipid homeostasis but also in the homeostasis of whole body metabolism through the release of active molecules, generically called adipokines that signal to key organs such as the brain, liver, skeletal muscle, and the immune system.1-3 Therefore, the adipose tissue is not just a mere deposit of lipids but an active endocrine organ. Different aspects of adipose tissue functions appear to be modulated by the location of the adipose depot (visceral vs. subcutaneous vs. bone marrow);4-5 by the size of the average adipocyte in the tissue;6 by cross-talks between adipocytes and other cell types present in this tissue, such as macrophages;7,8 as well as by adipocyte metabolism of glucose9 and corticosteroids.10-12 In obese individuals, the secretion of adipokines is deregulated13 and adipose tissue is generally hypertrophic and infiltrated by a higher number of macrophages compared to normal tissue,7 events that correlate with measures of adiposity and insulin resistance,14-16 and the establishment of a state of chronic inflammation.13 However, a very recent report shows that up to a certain level, proinflammatory signaling is necessary in the adipocyte for the adequate remodeling and expansion of the adipose tissue.17 Conversely, lipodystrophy, a disorder characterized by selective total or partial loss of body fat, is also accompanied by similar metabolic consequences as seen in obesity, including insulin resistance, dyslipidemia, hepatic and myocellular steatosis, and increased risk for diabetes and atherosclerosis,18,19 reinforcing the notion that adipose tissue plays a key role in the control of whole body metabolism homeostasis.

Great effort has been done to uncover the factors that control not only adipogenesis but also those that exert control in the function of the adipose cell itself. It is well established that glucocorticoids and mineralocorticoids are key regulators not only of fat distribution, but also of adipocyte differentiation,20-24 the induction of lipogenic genes and lipolysis in adipocytes25,26 and are potent inhibitors of adipose tissue inflammatory response.27 Corticosteroids exert their action by binding to their receptors, the glucocorticoid- and mineralocorticoid receptor (GR and MR, respectively) that are present in the cytoplasm (Fig. 1C). For proper steroid hormone action, GR and MR need to be part of a heterocomplex with the 90-kDa and 70-kDa heat shock proteins, Hsp90 and Hsp70, respectively, the acidic protein p23, and a protein that belongs to the conserved and large family of a heterocomplex with the 90-kDa and 70-kDa heat shock proteins, Hsp90 and Hsp70, respectively, the acidic protein p23, and a protein that belongs to the conserved and large family of tetratricopeptide repeat motif; WISp, WAF-1/CIP1 stabilizing protein; XAP2/ARA9, hepatitis virus B X-associated protein 2 /AhR-associated protein 9.

Abbreviations: ALDO, aldosterone; Gelda, geldanamycin; CCNB1, cyclin B1; CyP, cyclophosphamide; DEXA, dexamethasone; EPAC, exchange proteins activated by cAMP; FKBP, FK506 binding protein; GR, glucocorticoid receptor; Hsp, heat shock protein; IBMX, 3-isobutyl-1-methylxanthine; IMMs, immunophilins; LMNA, lamin A/C gene; MEF-51 KO, mouse embryonic fibroblasts null for FKBP51; MR, mineralocorticoid receptor; NE, nuclear envelope; NL, nuclear lamina; NRs, nuclear receptors; PP5, protein phosphatase 5; PHLPP, PH domain leucine-rich repeat protein phosphatase; PML, promyelocytic bodies; PPARs, peroxisome proliferator-activated receptors; PPIase, peptidyL-prolylisiomerase; RelA, NF-κB subunit p65; RelB, NF-κB subunit p68; TPR, tetratricopeptide repeat motif; WISp, WAF-1/CIP1 stabilizing protein; XAP2/ARA9, hepatitis virus B X-associated protein 2 /AhR-associated protein 9.

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role of glucocorticoids and mineralocorticoids actions through their binding to GR and MR in adipose tissue biology. However, it was not until recently that studies started to appear demonstrating the role of the chaperones and co-chaperones of the nuclear receptors (NRs) in the process of adipogenesis, and the aim of this review is to discuss these new findings.

**Hsp90 participates in the control of PPARγ**

Hsp90 accounts for 1–2% of the total soluble proteins in resting cells, ~6–7% in cancer cells and up to 10% in stressed cells. There are 2 major cytoplasmic isoforms, Hsp90α (inducible form) and Hsp90β (constitutive form); Hsp90N, which is associated with cellular transformation; and Hsp90 analogs that include Grp94 (94-kDa glucose-regulated protein) in the endoplasmic reticulum and Hsp75/TRAP1 (tumor necrosis factor-associated protein1) in the mitochondrial matrix. Genome analysis revealed that the human Hsp90 family includes 17 genes. In most cells, Hsp90α expression is lower compared to Hsp90β, and its inducible transcription is tightly regulated by the 5′upstream promoter sequences containing several heat shock elements (HSE). The heat shock responsive transcription factor HSF binds to HSE to control Hsp90 expression. In addition, members of the signal transducers and activators of transcription family, STAT1 and STAT3, in complex with HSF1 also participate in the control of the heat shock induction of Hsp90α gene transcription. In regard to adipogenesis, we have recently shown that no change is observed in the protein expression level of Hsp90 during the differentiation of 3T3-L1 preadipocytes. It remains to be explored whether there are differences in the expression of the different Hsp90s during adipogenesis and whether they are deregulated in obesity due to the functional importance of this chaperone in response to cell stress.

Hsp90 is a molecular chaperone that associates with numerous substrate proteins called “clients” in order to modulate their folding and function, among them protein kinases and transcription factors, including GR and MR already mentioned. In this manner, Hsp90 controls metastable proteins that are regulatory hubs in biological networks. Peroxisome proliferator-activated receptors (PPARs) are members of the NR superfamily of ligand-dependent transcription factors. Three subtypes of this receptor have been found, PPARα, -β/δ and -γ, controlling target genes involved in cell growth, differentiation and apoptosis in a variety of cells. Of these NRs, PPARγ has been proven to be a master regulator of adipogenesis, as PPARγ as well as PPARβ/δ interact with Hsp90, albeit to a lesser extent than PPARα. Hsp90 inhibition by geldanamycin leads to the increase of PPARα and -β/δ transcriptional capacity, being proposed that Hsp90 is a repressor of both transcription factors. PPARα•Hsp90 complexes interact with XAP2, and XAP2 appears to function as a repressor based on the observation that expression of XAP2 inhibits PPARα transcriptional capacity in reporter gene assays.

As already mentioned, PPARγ is an Hsp90 client protein. Inhibition of Hsp90 by treatment of 3T3-L1 cells with geldanamycin or its analogs at early time points of the adipogenic process has been shown to prevent the cells from differentiating properly. In fact, disruption of the PPARγ•Hsp90 complex by geldanamycin targets PPARγ to degradation by the proteasome, being thus proposed that the anti-adipogenic effect of geldanamycin may result from the destabilization of PPARγ (Fig. 1D). Since Hsp90 is indispensable for proper GR and MR function, inhibition of Hsp90 also inhibits proper adipogenesis by interfering with GR and MR actions. Hsp90 is essential for a wide spectrum of cellular processes such as protein folding, protein degradation, and signal transduction cascades, having been recently shown that Hsp90 also participates in the maintenance of RNA polymerase II pausing, function required for adequate gene expression when cells have to respond to environmental stimuli. Therefore, the blockade of the adipogenic program upon Hsp90 inhibition could be the resultant of a wider disruption of signaling pathways as well as nuclear events dependent on Hsp90 surveillance that need to be further explored.

**High molecular weight immunophilins in adipocyte differentiation**

IMMs comprise a family of proteins classified by their ability to bind immunosuppressant drugs in which cyclophilins bind cyclosporine A, whereas FKBP51 and FKBP52 do not play a role in immunosuppression, but rather have been related to steroid receptor regulation. The FKBP12-like peptidyl-prolyl isomerase (PPIase) domains 1 and 2 (FK1 and FK2) and a tetratricopeptide repeat motif (TPR). The FK1 domain is required for the binding of the immunosuppressive drug FK506, it confers PPIase activity, and it is also the primary domain required for steroid hormone receptor regulation. The FK2 domain links the FK1 with the TPR domain, lacks detectable PPIase activity and is required in FKBP51 but not in FKBP52 for their interaction with the progesterone receptor heterocomplexes. The TPR domain contains sequences of 34 amino acids repeated in tandem through which FKBP51 interacts with Hsp90. FKBP51 and FKBP52 share 60% identity and 70% similarity; however the former has so far mainly reported to be a negative regulator of steroid hormone receptors while the latter is a positive one. When differentiation of 3T3-L1 preadipocytes is induced, it was reported that FKBP51 has a transient expression at very early time points (day 1 up to day 4 of differentiation) and then its expression decreased to undetectable protein levels. More recent studies demonstrate that FKBP51 and FKBP52 exhibit opposite changes in their level of expression during the process of adipocyte differentiation. FKBP51 expression progressively increases whereas FKBP52 decreases as adipogenesis proceeds. The differences observed between these studies may possibly depend on the development of highly sensitive and specific antibodies now available for the study of these IMMs. Importantly, the changes in level of expression of both IMMs during 3T3-L1 preadipocyte differentiation are in agreement with the high expression of FKBP51 and low levels of FKBP52 in white adipose tissue (J.T. and GGP unpublished results, and). The organization of the Fkbp51 and Fkbp52 genes has been described, showing that hormone regulatory elements lie within intronic sequences distal to the promoter.
Expression of FKBP51 is strongly enhanced by glucocorticoids, progestins, and androgens, while FKBP52 mRNA increases in response to estrogen and heat stress. It remains to be further explored how their expression is modulated in the adipose tissue, and whether they are differentially expressed in pathophysiological conditions like metabolic syndrome or obesity.

FKBP51 shuttles from mitochondria to the nucleus in a PKA-dependent manner at the onset of adipocyte differentiation.

FKBP51 is present in the cytoplasm and mitochondria, and upon oxidative stress the mitochondrial fraction of this IMM rapidly translocates to the nucleus protecting cells from apoptosis. When 3T3-L1 preadipocytes are induced to differentiate, FKBP51 also rapidly and transiently translocates from mitochondria to the nucleus. Adipogenesis is controlled by many signaling pathways that coordinately modulate the sequential activation of transcription factors required for cells to differentiate.

Several reports have shown that the second messenger cAMP is associated with immediate events of adipogenesis by the classic PKA signaling pathway, as well as by the non-classical pathway of the exchange proteins activated by cAMP (EPAC), which function as guanine nucleotide exchange factor for the Ras-like small GTPases Rap1 and Rap2. FKBP51 nuclear translocation depends on PKA but not on EPAC pathway activation, demonstrating a differential role of PKA and EPAC/Rap during adipogenesis.

FKBP51 interacts with PKA-cα as shown by immunoprecipitation assays, and when PKA signaling is blocked dramatic changes in the electrophoretic pattern of migration of FKBP51 are observed, supporting the notion that FKBP51 is a PKA substrate. By using NetPhosK 1.0, we found that Serine 312 located in the TPR domain of FKBP51, is a candidate PKA phospho-acceptor site. The TPR domain confers to the IMM the ability to bind Hsp90 through the EEVD motif present in the extreme C terminus of the chaperone. FKBP51 localization in mitochondria depends on TPR integrity, since FKBP51 TPR-deficient mutants are constitutively nuclear. Therefore, changes in phosphorylation of Serine 312 present in the TPR domain of FKBP51 may possibly regulate its interaction with Hsp90 and consequently its subcellular localization, possibility that is under investigation.
current investigation. Interestingly, when the interaction of FKBP51 with Hsp90 is disrupted by Hsp90 inhibitors such as radicicol, FKBP51 is no longer in mitochondria and concentrates in the nucleus. As mentioned already, geldanamycin and radicicol inhibit 3T3-L1 preadipocytes differentiation; therefore it is possible that the Hsp90 inhibitors not only affect PPARγ, GR and MR function, but they may also alter the dynamic mitochondrial-nuclear shuttling of FKBP51 at the onset of the differentiation process required for adipogenesis to proceed, resulting in the inhibition of adipogenesis.

During the past few years, several studies revealed a dramatic and dynamic modulation of the chromatin landscape during the first hours of adipocyte differentiation. These changes coincide with cooperative binding of early adipogenic transcription factors, including GR, to enhancers and promoters of many genes. However, genes such as PPARγ are not transcriptionally activated until later in adipogenesis, and it has been proposed that the activation of additional factors and/or signals is required for their later activation. It can be speculated that, in spite of chromatin relaxation and the increased binding of transcription factors at the early stages of adipogenesis, gene expression is kept controlled by factors that restrain the transcriptional capacity of complexes already bound to those sites. When adipogenesis is triggered, FKBP51 translocates to the nucleus and its interaction with GR progressively increases, rendering a GR less transcriptionally active. It is possible that the presence of FKBP51 in the nucleus at the onset of adipogenesis may be critical for the control not only of GR but also for MR. It has recently been shown FKBP51 impairs both the nuclear translocation rate of NF-κB and its transcriptional activity. Interestingly, NF-κB subunits p65 (RelA), p68 (RelB) and 1κB increase their level of expression during the process of adipocyte differentiation. It was reported that endotoxin sensitivity of the classical NF-κB pathway is substantially delayed and attenuated despite increased overall inflammatory response in adipocytes. Thus, we hypothesize that FKBP51, whose level of expression increases as adipogenesis proceeds, may also modulate NF-κB pathway in mature adipocytes. Future studies will demonstrate the existence of other transcription factors that need to be repressed or activated by nuclear FKBP51, at a step of the adipogenic program in which high level of chromatin remodeling takes place and transcription needs to be kept controlled.

Role of FKBP51 in the control of PPARγ

It has been recently demonstrated that FKBP51 interacts with over-expressed PPARγ in COS7 cells, and reporter gene assays shows that FKBP51 is a positive regulator of this NR. PPARγ like other NRs can be regulated by changes in its phosphorylation status. MAPK ERK1/2, and JNK are able to phosphorylate PPARγ at Serine 112 reducing its transcriptional activity. Furthermore, inhibition of p38MAPK increases PPARγ expression and its transcriptional activity. GR is also a substrate of p38MAPK, post-translational modification that increases GR transcriptional capacity. Then, MAPK–dependent phosphorylation of PPARγ and GR has opposite effects on the transcriptional capacities of these NRs: PPARγ transactivation decreases while GR transactivation increases. FKBP51 is a scaffold protein for the interaction between the protein kinase Akt and the PH domain leucine-rich repeat protein phosphatase (PHLPP) that specifically dephosphorylates the hydrophobic motif of Akt (Serine 473 in Akt1), thus inhibiting the kinase activity (Fig. 1A). Stechschulte et al. showed that in mouse embryonic fibroblasts null for FKBP51 (MEF-51KO) elevated Akt activity leads to increased activation of p38MAPK that is able to phosphorylate GR and PPARγ, promoting transcriptional activation of the former and inhibition of the latter. Moreover, they show that knock down of FKBP51 in 3T3-L1 preadipocytes makes cells resistant to differentiation and MEF-51KO have impaired differentiation. The authors proposed a model, in which FKBP51 restrains Akt activation by scaffolding PHLPP, favoring the inactive state of p38MAPK that prevents PPARγ phosphorylation and keeps this NR in a transcriptionally active state to induce the expression of the adipogenic genes. While the role of p38MAPK in adipogenesis is still rather controversial, several lines of evidence demonstrate that Akt is required for proper adipogenesis. Akt is a key component of insulin signaling and is required for PPARγ expression. Over-expression of constitutively active Akt induces spontaneous differentiation of 3T3-L1 preadipocytes, and mice null for Akt1 and Akt2 have impaired adipogenesis. Akt is responsible for phosphorylation and nuclear exclusion of anti-adipogenic factors such as the forkhead proteins FOXO-1 and FOXO-2, and the transcription factor GATA2. Therefore, proper activation of Akt is required for normal adipogenesis and it could be speculated that Akt inhibition by the FKBP51-PHLPP could have a negative effect on this process. In line with this possibility, Tonetto et al. showed that knock down of FKBP51 favors the process of adipogenesis and its overexpression blocks 3T3-L1 preadipocyte differentiation, based on the fact that this IMM also restrains the adipogenic potential of GR, and possibly the pro-adipogenic action of MR. It is possible that the discrepancies between these studies could result, in part, from differences in the protocol of adipogenesis used in each case, as well as differences in the level of expression of FKBP51 (knock out vs. knock down), thus more research work is required to shed light on this conundrum.

FKBP51 and the nuclear lamina reorganization at the onset of adipogenesis

The nucleus is organized in highly dynamic nuclear compartments which correspond to the nuclear lamina that lies below the nuclear envelope, the nuclear matrix or nucleoskeleton, the chromosome territories that comprise the volume of the nucleus in interphase occupied by each chromosome, the interchromatin domain, and nuclear bodies that include the nucleolus, spliceosomes or nuclear speckles, paraspeckles, the Cajal bodies, the promyelocytic (PML) bodies, and transcription factories, among others. A great body of evidence demonstrates that dynamic changes in the nuclear compartments take place during the process of cell differentiation, including adipogenesis. It has been shown that the repositioning of genes from repressive to transcriptionally favorable nuclear compartments and vice versa plays a key role for their proper expression or
nuclear pores (reviewed in). It consists of a polymeric assembly of lamins, members of the type V intermediate filament protein family that correspond to the A-type (LA and LC) and the B-type lamins (LB1 and LB2), respectively. LA and LC are derived from a single gene by alternative splicing and are expressed only in differentiated cells. The NL is thought to provide a structural framework for the NE contributing to the size, shape and mechanical stability of the nucleus. It also provides anchoring site for interphase chromosomes at the nuclear periphery, and plays important roles in DNA replication and repair, RNA polymerase II transcription, and the epigenetic control of chromatin remodeling. The functional importance of the NL is demonstrated by the fact mutations in the lamin A/C (LMNA) gene or in the FACE-1 gene that affects the correct post-translational processing of prelamin A are responsible for a group of genetic diseases known as laminopathies. It has been proposed that mutations that affect lamins might disrupt their binding to yet unidentified tissue-specific partner proteins to generate pathology in a particular tissue (reviewed in ). Laminopathies affecting the adipose tissue are characterized by lipodystrophies with selective and variable loss of adipose tissue, accompanied by metabolic complications including insulin resistance, type 2 diabetes, hypertriglyceridemia, and liver steatosis. These laminopathies include Dunnigan-type familial partial lipodystrophy and partial lipodystrophy with mandibuloacral dysplasia, both associated with mutations in LMNA gene; congenital generalized lipodystrophy, also known as Berardinelli-Seip syndrome; and some cases of Barraquer-Simons syndrome with acquired partial lipodystrophy associated with mutations in lamin B2. Lipodystrophy can also be acquired, as occurs with the lipodystrophy associated with the use of anti-viral drugs in patients infected with human immunodeficiency virus.

Analysis of the expression level of lamin A and the NE transmembrane protein emerin at the onset of differentiation of 3T3F442A preadipocytes showed that while lamin A expression progressively decreases, emerin expression increases. Emerin participates in the control of β-catenin whose sustained activation inhibits the process of adipogenesis. Increased expression of emerin could control the efficient redistribution of β-catenin from the nucleus to the cytoplasm facilitating its proteasomal degradation and consequently allowing the process of adipocyte differentiation to proceed. Interestingly, it was demonstrated that the NL is fragmented at the early stages of adipogenesis, event that is accompanied by the loss not only of lamin A, but also C, B1, and emerin at the nuclear rim. Later on upon maturation of the adipose cell (day 18 post-induction of adipogenesis) lamins A, C and B1 increase at the nuclear rim independently of the low levels of lamins A/C protein. In contrast, lamin B2 remained constant at the NL throughout the process of adipogenesis. Since the NL participates in the control of many aspects of nuclear events as already described, it was proposed that the decreased presence of most lamin subtypes at the nuclear rim and the fragmentation of the NL results in enhanced plasticity of the nucleus as adipogenesis proceeds. FKB51 translocates from mitochondria to the nucleus at the onset of adipogenesis and, not only co-localizes with lamin B in the fragmented pattern of the lamina, but also interacts with lamin B. Interestingly, PKA-α also translocates to the nucleus, and concentrates in the NL possibly through its interaction with FKB51. Several phosphorylation sites, including those for the cyclin B1-(CCNB1)-CDC2 complex, PKC and PKA are important in nuclear lamina disassembly. Therefore, we propose that enrichment of PKA-α in the NL may facilitate its reorganization by phosphorylation of lamins during the process of adipogenesis. It can be speculated that the accumulation of PKA-α in the NL may be also involved in the control of gene expression at the onset of adipogenesis possibly by regulating the phosphorylation of transcription factors enriched in this nuclear compartment as shown for the control of AP-1 transcriptional activity upon the sequestration of c-fos in the NL in an ERK1/2 dependent manner.

FKB51 and FKB51 knock out animal models

To uncover the functional importance of these IMM, knockout mice were generated. Fkb51-deficient mice were initially observed to display no overt phenotype, but these mice are less vulnerable to the detrimental effects of stress. Interestingly, Fkb51 knockout mice showed reduced body weight compared to wild type littermates; however, upon expose to chronic stress, these animals exhibited a significant increase in body weight, results that suggest that the process of adipogenesis might not be impaired in the absence of FKB51. It has been recently reported by Balsevich et al. a differential spatial pattern of Fkb51 gene induction in different areas of the brain dependent on either diet or stress conditions. In mice exposed to high-fat diet, Fkb51 is induced in the ventromedial hypothalamic nuclei, in accordance with the hypothalamus being involved in the control of energy balance. In contrast, under conditions of chronic stress, the expression of this IMM increases in the hippocampus, area of the brain involved in the response to stress. Inasmuch as environmental stress is another risk factor for the development of obesity, future studies are needed to uncover the role of FKB51 in different areas of the brain, whether this IMM plays a role in the control of appetite and energy balance, and whether FKB51 is implicated in the relationship between control of energy, metabolic homeostasis and stress response. On the other hand, Fkb52-deficient male mice display phenotypes related to partial androgen insensitivity syndrome. Heterozygous Fkb52-deficient mice show increased susceptibility to high-fat diet-induced hyperglycemia and hyperinsulinemia that correlates with reduced insulin clearance, hepatic steatosis and glucocorticoid resistance. Fkb51-Fkb52 double knockout results in embryonic lethality, indicating that these IMMs have some physiological functional redundancies that need to be uncovered by tissue-specific conditional double knockouts.
Final remarks

Undoubtedly during the last decade, great progress has been accomplished in the understanding of the complex biology of the adipose tissue, the pathophysiology of obesity and its role in metabolic syndrome. However, many aspects of the physiology of the adipocyte need to be explored further in depth, including how chaperones, such as Hsp90 and Hsp70, and co-chaperones, such as FKBP51 and FKBP52, may directly or indirectly coordinate the action of signaling pathways and transcription factor complexes function. Their study will not only enrich our basic knowledge but also will possibly be crucial for the design of new therapeutic strategies for the treatment of obesity, lipodystrophies and metabolic problems associated with these pathologies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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