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COMMENTARY

Organization of nuclear architecture during adipocyte differentiation

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ABSTRACT

Obesity is a serious health problem worldwide since it is a major risk factor for chronic diseases such as type II diabetes. Obesity is the result of hyperplasia (associated with increased adipogenesis) and hypertrophy (associated with decreased adipogenesis) of the adipose tissue. Therefore, understanding the molecular mechanisms underlying the process of adipocyte differentiation is relevant to delineate new therapeutic strategies for treatment of obesity. As in all differentiation processes, temporal patterns of transcription are exquisitely controlled, allowing the acquisition and maintenance of the adipocyte phenotype. The genome is spatially organized; therefore decoding local features of the chromatin language alone does not suffice to understand how cell type-specific gene expression patterns are generated. Elucidating how nuclear architecture is built during the process of adipogenesis is thus an indispensable step to gain insight in how gene expression is regulated to achieve the adipocyte phenotype. Here we will summarize the recent advances in our understanding of the organization of nuclear architecture as progenitor cells differentiate in adipocytes, and the questions that still remained to be answered.

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The pandemic of obesity has led scientists to focus their attention on the study of adipose tissue and the development of fat cells. During the last 2 decades it has been demonstrated that adipocytes release a variety of factors, including cytokines, chemokines, and many other biologically active molecules, generically called adipokines, that have led adipose tissue to be regarded as an active endocrine organ. Adipokines signal to organs of metabolic importance including brain, liver, skeletal muscle, and the immune system.[1,2] In this way, the adipose tissue plays a central role in modulating the homeostasis of lipid and glucose metabolism, blood pressure, and inflammation. In obese individuals, the secretion of adipokines is deregulated[3] and adipose tissue is infiltrated by a higher number of macrophages compared to normal tissue.[4,5] These events lead to a state of chronic inflammation and metabolic syndrome.[6,7] Conversely, lipodystrophy, a disorder characterized by selective total or partial loss of body fat, is also accompanied by metabolic consequences similar to those observed in obesity, including insulin resistance, dyslipidemia, hepatic and myocellular steatosis and increased risk of diabetes and atherosclerosis,[8] reinforcing the notion that adipose tissue plays a key role in the control of the homeostasis of whole-body metabolism.

In mammals, adipocytes have been classified into 2 distinct types: white, and brown adipose cells. White adipocytes express cell type-selective machinery for triglyceride synthesis from lipoprotein-derived fatty acids, as well as for hormone-stimulated glucose uptake and lipolysis. In addition, they produce adipokines such as leptin, resistin, adiponectin, and TNFα that modulate systemic metabolism, a function shared with brown fat cells.[9,10] The development of methods for separating white adipose tissue (WAT) into adipocyte and stromal-vascular fractions (SVF),[11] led to the discovery that SVF is the source of adipocyte precursor cells.[12] However, the characterization of this cell population remained elusive for several decades and much effort has been done to uncover it. Sengenes et al showed by FACS analysis performed on crude SVF cultured under adipogenic conditions, that the progressive accumulation of lipid droplets was associated with a selective enrichment of the CD34+/CD31- cell population.[13] Rodeheffer

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et al. identified a subpopulation of early adipocyte progenitor cells resident in the WAT vascular stroma as Lin^{-}:$CD29^{+}$:$CD34^{+}$: Sca-1^{+}:$CD24^{+}$ that constitutes in total approximately 0.08% of the cells in the SVF.[14] Using genetically tagged mice, Tang et al. demonstrated that most adipocytes derive from a pool of proliferating and renewing adipogenic progenitors that are already committed either prenatally or early in postnatal life.[15] These progenitors reside in the mural cell compartment of the adipose vasculature, but not in the vasculature of other tissues,[15] an observation supported by early studies using electron microscopy.[16,17] The local microenvironment is a crucial determinant of progenitor fate, function, and maintenance.[18] Thus, the adipose vasculature appears to function as a progenitor niche, possibly providing signals for adipocyte development.

In contrast to WAT, the main role of BAT is to metabolize fatty acids to maintain body temperature, by dissipating chemical energy in the form of heat. This function depends on its high mitochondrial content and the ability to uncouple cellular respiration through the action of uncoupling protein-1 (UCP-1).[6,10,19] There is evidence that brown adipocytes originate from a cell lineage distinct from that of white adipose cells.[20-23] Microarray analysis of primary brown adipocytes showed the expression of a myogenic transcriptional signature.[20] Further, myogenic factor 5 (Myf5), previously thought to be expressed only in skeletal muscle precursors, is also expressed in BAT committed precursors.[22] Myf5 positive myoblast-like cells differentiate into brown adipocytes through the action of the transcriptional regulators PRMD16 and C/EBPβ.[21,22,24] BAT was considered insignificant in adult humans; however recent studies have shown that brown adipocytes are dispersed throughout adult adipose tissue.[25-27] The amount of BAT is inversely correlated with body-mass index, especially in older people. BAT depots respond to changes in temperature, but this response is significantly lower in the overweight or obese than in lean subjects suggesting a potential role of BAT in adult human metabolism.[28-30] Mitochondrial function, which is key in non-shivering thermogenesis in brown adipose cells, is also diminished in white adipocytes at the onset of obesity,[31] exemplifying a negative relationship between obesity and mitochondrial biogenesis that potentially contributes to the development of diabetes.[32,33] Therefore, the balance between BAT and WAT affects energy balance, and any factor that may alter the equilibrium between them may possibly facilitate the development of obesity and loss of metabolic homeostasis.

However, adipose tissue is even more complex than previously thought. It was recently shown that in addition to classical white and brown adipocytes, there is at least a third cell type: beige or brite (brown-in-white) cells.[34-37] They are present in patches dispersed in WAT, and do not derive from the same lineage as the classical brown fat cells. The existence of a progenitor cell that differentiates into beige cells is still controversial. It has been shown that chronic treatment of precursors of WAT with PPARγ ligands leads to the generation of beige cells that express PGC-1α and respond to norepinephrine by increasing UCP-1 gene expression.[35] This effect of PPAR agonists is possibly due to an increase in the half-life of the PRDM16 protein.[38] However, beige adipose cells are devoid of expression of myocyte-associated genes and transcription factors present in classical brown adipocytes.[35] It has also been proposed that browning of WAT upon exposure of mice to cold is a consequence of transdifferentiation of white into beige adipocytes, since neither adipocyte number nor DNA content increases in white fat depots.[36] It was proposed that BAT and inducible beige fat cells participate in non-shivering thermogenesis, an event crucial for mammals as a defense against cold and obesity, under the control of the sympathetic nervous system and β-adrenergic signaling. Interestingly, it has been recently reported that white and beige fat cells have the ability to respond to low temperatures by activating a thermogenic gene program in a cell-autonomous manner.[39] This activation in isolated cells is independent of the cAMP/PKA/CREB pathway downstream of the β-adrenergic receptors.[39] Bone morphogenic proteins (BMPs) regulate both the formation and the thermogenic activity of BAT.[40,41] Disruption of BMPs signaling in BAT causes a severe paucity of BAT and a compensatory sympathetic response in WAT by increasing the number of beige cells.[42] This compensatory mechanism is sufficient to maintain the homeostasis of body temperature and to generate resistance to diet-induced obesity.[42] Importantly, adipose cells with the molecular signature of beige cells are also present in fat depots in humans.[43,44] Thus beige cells may represent a potential target for therapeutic intervention for the treatment of obesity and metabolic syndrome. Unequivocally, adipose tissue is very complex and

heterogeneous; therefore its deregulation can deeply affect whole-body metabolic homeostasis.

Adipose tissue is not static and approximately 10% of our body's fat cells are regenerated each year.[45] In order to support adipose dynamics in the adult, proliferative adipocyte precursor cells must exist and be poised to respond to metabolic demands. During adipogenesis, as in any differentiation process, temporal patterns of transcription are exquisitely controlled upon activation of different signaling pathways that lead to the binding of transcription factors to target genes as well as factors that coordinately modify the chromatin landscape as adipogenesis proceeds, allowing the acquisition and maintenance of the adipocyte phenotype.[10,46,47] All cells of an individual possess the same genomic information; yet we do not know how the precise pattern of gene expression is established and maintained in order to delineate the final phenotype of a cell. During the last decades a great deal of effort has been focused on deciphering the histone code to elucidate how the architecture of nuclear chromatin is organized.[48,49] Covalent histone modifications and their interplay with DNA methylation sites, as well as histone variants and chromatin remodeling events, have emerged as major players, yielding distinct modifications of chromatin which allow or prevent transcription.[48,50] Control of epigenetic signatures is not only involved in a cell differentiation process such as adipogenesis,[51] but also in re- or de-programming during development.[52,53] The *in vitro* reprogramming of somatic cells to pluripotent stem cells (SC) is also accompanied by genome-wide remodeling of chromatin modifications from a somatic to an SC-like state,[54] although the temporal sequence of these changes remains elusive. Nevertheless, understanding transcriptional regulation and decoding the epigenetic code also are not enough to understand how cell type-specific gene expression patterns are generated throughout development or during any process of cell differentiation in an adult organism. In this regard, knowledge of the architecture of nuclear compartments is also critical to understand how gene expression as well as other nuclear functions, such as chromatin replication and DNA repair are regulated.[55]

One of the current pressing questions is how gene expression is integrated into the architectural framework of the cell nucleus, delineating the goal of "epigenomics": the functional integration of epigenetics and nuclear architecture.[55] In the path toward epigenomics, we must become familiar with the complex and dynamic architecture of the nucleus in interphase. The nucleus is highly compartmentalized, but in contrast to compartments in the cytoplasm, nuclear compartments are not limited by membranes. This characteristic favors their highly dynamic assembly-disassembly status, dependent on the cell cycle phase and the transcriptional state of the cell. In the interphase nucleus, the nuclear compartments include the nuclear lamina, the still controversial nucleoskeleton or nuclear matrix, the chromosome territories and nuclear bodies (Fig. 1A). Much effort is being directed toward understanding how gene expression is integrated into the landscape of nuclear architecture. Here we review the first steps taken to dissect the complex organization of the nucleus during the process of adipocyte differentiation.

Nuclear lamina and its importance in the adipocyte

The nuclear lamina (NL) is a filamentous protein mesh-work that lines the nucleoplasmic surface of the nuclear envelope (NE) interacting with inner nuclear membrane proteins and nuclear pores (Fig. 1A),[56,57] reviewed in.[58] The NL consists of a polymeric assembly of nuclear lamins, the A-type (LA and LC) and the B-type lamins (LB1 and LB2), respectively.[59] LA and LC are derived from a single gene (*LMNA*) by alternative splicing and are expressed only in differentiated cells. On the other hand, LB1 and LB2 are encoded by *LMNB1* and *LMNB2*, respectively, and at least one of them is expressed in all cells throughout development.[60] The lamins bind to other NE proteins, including some belonging to the nuclear pore complex (NPC) and the inner nuclear membrane, interactions that are functionally important in regulating the proper assembly of the NE.[61] Although the major fraction of lamins is found in the NL, they are also located throughout the nucleoplasm.[62,63] The NL is thought to provide a structural framework for the NE, contributing to the size, shape and mechanical stability of the nucleus. However, lamins participate not only in the architectural organization of the nucleus, but also in its cellular integrity, possibly through the Linker of Nucleus and Cytoskeleton (LINC) complex.[64] LINC is formed by lamins that interact with the inner nuclear membrane-bound SUN proteins, which in

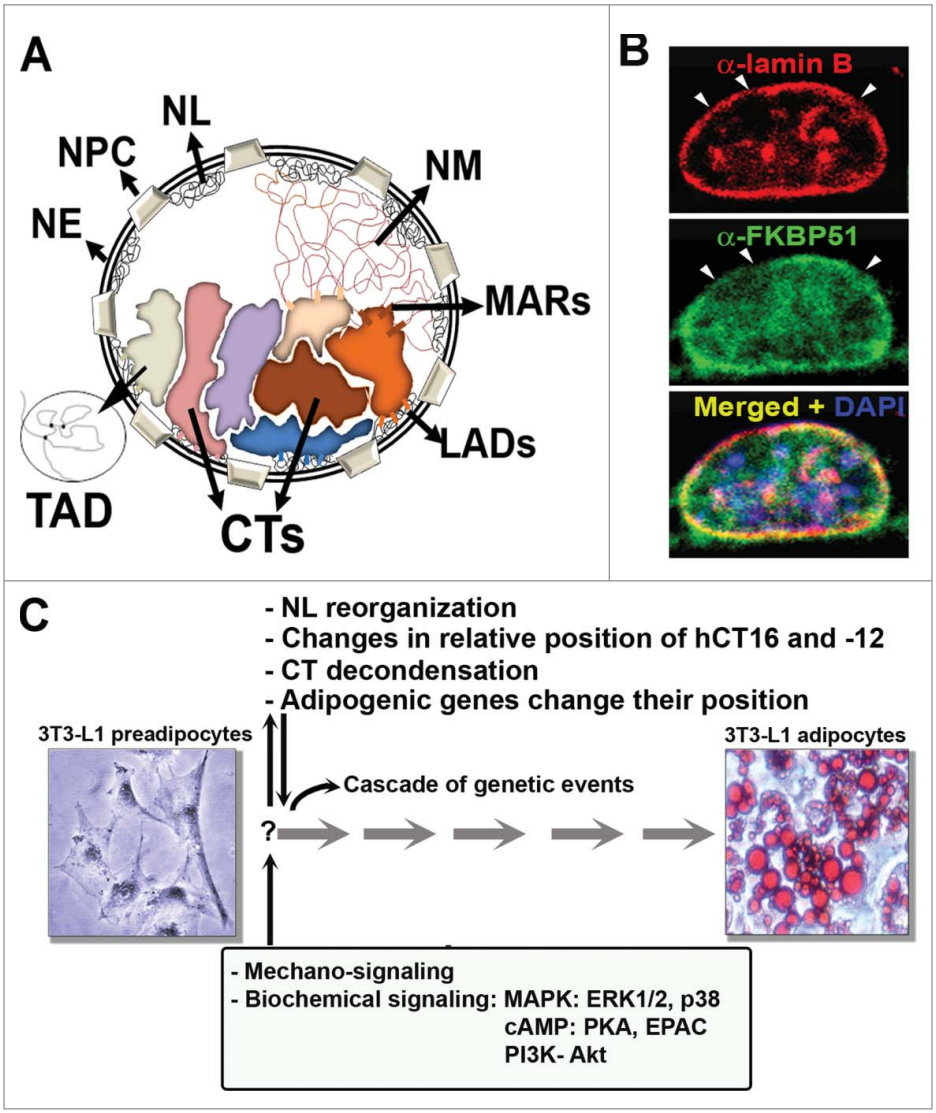

Figure 1. Nuclear architecture during adipogenesis. (A) Schematic representation of the compartments of the nucleus in interphase: NE: nuclear envelope, NPC: nuclear pore complex, NL: nuclear lamina, NM: nuclear matrix, CTs: chromosome territories, LADs: lamin attachment domains, MARs: Matrix attachment regions; TADs: topologically associating domains. (B) Reorganization of the NL during adipocyte differentiation. 3T3L1 preadipocytes grown on coverslips were induced to differentiate for 24h. Indirect immunofluorescence and confocal microscopy imaging shows lamin B (red), FKBP51 (green) and chromatin stained with DAPI (blue), as described.[98] Observe the discontinuous staining of lamin B (arrow heads) due to the reorganization of the NL. (C) Summary of the events of nuclear reorganization that were described during adipogenesis. Images depict 3T3-L1 preadipocytes and adipocytes, the latter with lipid vesicles stained with Oil Red O, as described.[98]

turn associate with the nuclear-cytoskeleton linker proteins in the outer nuclear membrane, i.e. nesprins. Nesprin-1 and −2 contain a binding domain for direct interaction with actin, and nesprin-3 for plectrin, an intermediate filament binding protein. The NL through LINC constitute an interconnected network that is involved in the control of nuclear positioning, mechano-signal transduction, mitosis as well as in the organization of the cytoskeleton.[65] In addition, the NL also participates in DNA replication and repair, RNA polymerase II transcription, and the epigenetic control of chromatin remodeling.[63] The NL provides anchoring sites for interphase chromosomes at the nuclear periphery. In this regard, a high resolution map of the interaction sites of the entire genome with the NL components in human fibroblasts shows that genome-lamina interactions occur through more than 1,300 sharply defined large domains 0.1-10 megabases in size, known as lamin associated domains (LADs).[66] These LADs are characterized by low gene-expression levels, indicating that they represent a repressive chromatin environment.[66] Using 3-dimensional DNA-

immunoFISH, it was demonstrated that repositioning of chromosomal regions to the nuclear lamina is dependent on breakdown and reformation of the NE during mitosis.[67]

The NL was long considered to be a nuclear domain that was not permissive for transcription, since genes positioned at the NL and even tethered to it were silenced.[67,68] However, more recent studies have shown that some transcriptionally active genes are associated with the NL via nucleoporins at the nucleoplasmic face of the NPCs and/or are relocated upon transcriptional activation to nuclear pores.[69-72] H3K27Me3, which marks repressed gene promoters, is enriched at the nuclear periphery in embryonic stem cells (ESC).[73] In contrast, H3K27Me3 was less concentrated at the nuclear periphery of differentiated cells, demonstrating that the nuclear periphery is an epigenetically dynamic compartment that might possess distinct epigenetic marks in pluripotent ESCs compared to differentiated cells.[73] Furthermore, it was recently shown that FKBP52, a component of the Hsp90•Hsp70•p23 heterocomplex bound to steroid receptors,[74] concentrates in a perinuclear structure associated with Hsp90 and p23 in undifferentiated murine neuroblastoma cells (N2a) and embryonic hippocampal neurons.[75] Upon cell differentiation, this structure disassembles and the perinuclear area becomes transcriptionally active.[75] Therefore, in the nuclear periphery different subdomains can be dynamically established with epigenetic marks as well as signaling molecules; some are repressive and enriched in facultative heterochromatin, while others are permissive for transcription to occur when the proper signal is received by the cell.

The importance of NL is highlighted by the existence of a group of pathologies known as laminopathies that affect specific tissues and are caused either by mutations in the lamin A/C (*LMNA*) gene or by mutations in the *FACE-1 g*ene affecting the correct post-translational processing of prelamin A (reviewed in[76]). 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[65]). 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 Dunningan-type familial partial lipodystrophy (DFPLD), partial lipodystrophy with mandibuloacral dysplasia (MAD), both associated with mutations in *LMNA* gene; Berardinelli-Seip congenital generalized lipodystrophy (CGL); and some cases with Barraquer-Simons acquired partial lipodystrophy (APL) associated with mutations in lamin B2.[77] Lipodystrophy can also be acquired, for example, in patients under treatment for human immunodeficiency virus.[78] Most of the DFDLD mutations in *LMNA* are missense within the 3′end of the gene, downstream of the nuclear localization signal, and it has been proposed that these mutations may alter the interactions of lamin A with transcription factors or other DNA binding molecules.[79]

The accumulation of the lamin A precursor has also been described in lipodystrophic cells.[80] The transcription factor sterol regulatory element binding protein 1 (SRBP1) that is present in adipocytes interacts with pre-lamin A in fibroblasts obtained from lipodystrophic patients, as well as in fibroblasts from normal subjects forced to accumulate pre-lamin A by treatment with farnesylation inhibitors.[80] It was proposed that the lack of proper lamina maturation determines the sequestration of SRBP1 at the nuclear rim, thus decreasing the pool of active SRBP1 that normally activates PPARγ, a key regulator of the acquisition and maintenance of the adipose phenotype,[81,82] thus impairing preadipocyte differentiation.[80] It is noteworthy that mutations in *PPARγ* are also responsible for other forms of partial lipodystrophy.[83-85] Retention of SREBP-1 at the NL and reduced PPARγ expression were also observed in 3T3-L1 preadipocytes treated with some of the HIV protease inhibitors (i.e., Indinavir) employed in treatment of viral infection, drugs that have been reported to cause lipodystrophy as a side-effect.[86] Therefore, SREBP-1 retention at the nuclear rim of lipodystrophic cells can be associated with the presence of increased levels of pre-lamin A irrespective of the occurrence of *LMNA* mutations, findings that help to explain the pathophysiology of both inherited and acquired lipodystrophies. Furthermore, overexpression of both wild-type or of mutated lamin A-R482A (present in DFPLD) in 3T3- L1 preadipocytes inhibits lipid accumulation, triglyceride synthesis and expression of adipogenic markers, such as PPARγ2.[87] In contrast, embryonic fibroblasts lacking A-type lamins accumulated more intracellular lipids, exhibited elevated *de novo* triglyceride synthesis, and

increased basal activation of Akt1, a well known mediator of insulin signaling.[87] Therefore, A-type lamins may act as inhibitors of adipocyte differentiation when their expression level is inappropriate, consistent with the proposal that mutations that cause lypodystrophy may reflect a "gain of function" in these proteins, resulting in higher binding affinity to pro-adipogenic transcription factors such as SREBP-1, that are sequestered at the NL and are thus prevented from activating their target gene(s).

Ultrastructural studies suggest the presence of a dispersed lamin network throughout the nucleus.[88,89] The existence of a dispersed, veil-like nucleoplasmic lamin network was also shown using GFP-tagged lamins and bleaching techniques, which showed that a considerable fraction of intranuclear lamins, visible as diffuse nucleoplasmic fluorescence, is stably integrated in the nuclear interior.[62,90] The exact molecular structure of this lamin veil is unknown; it possibly offers the spatial possibility for lamins to interact with chromatin or to bind to nuclear histone proteins as shown *in vitro*.[91,92] Therefore, although the role of this fine lamin network in cellular processes is so far unclear, these findings suggest they provide a scaffold for transcription and DNA replication. Interestingly, cell lines transfected with GFP-lamins with mutations similar to those found in Dunnigan's type lipodystrophy patients showed that these mutated lamins do not incorporate properly into the nucleoplasmic veil,[93] and in this manner possibly contribute to the abnormalities found in this type of lipodystrophy.

The nuclear lamina is reorganized at the onset of adipogenesis

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.[94] Emerin participates in the control of β-catenin[95] whose sustained activation inhibits the process of adipogenesis.[96] Increased expression of emerin controls 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.[94] Interestingly, it was demonstrated that the NL is fragmented at the early stages of adipogenesis[97,98] (Fig. 1B), event that is accompanied by the loss of not only lamin A, but also C, B1, and emerin at the nuclear rim.[97] 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 their low level of protein expression.[97] In contrast, lamin B2 remains at the nuclear rim throughout the process of adipogenesis.[97]

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.[97] In support of this, we have recently reported that the high molecular weight immunophilin (IMM) FKBP51, a member of the glucocorticoid receptor (GR)•Hsp90•Hsp70•p23 heterocomplex required for proper signaling of steroid nuclear receptors,[74] translocates from mitochondria to the nucleus at the onset of adipogenesis.[98,99] In the nucleus, FKBP51 not only co-localizes with lamin B in the fragmented pattern of the lamina (Fig. 1B), but also interacts with lamin B.[98] The transient relocalization of FKBP51 from mitochondria to the nucleus depends on an increase in intracellular cAMP and PKA activation.[98] Interestingly, PKA-cα also translocates to the nucleus, and concentrates in the NL possibly through its interaction with FKBP51.[98] Several phosphorylation sites, including those for the cyclin B1-(CCNB1)-CDC2 complex, PKC, and PKA are important in nuclear lamina disassembly.[100,101] Therefore, we propose that enrichment of PKA-cα in the NL may facilitate its reorganization through phosphorylation of lamins during the process of adipogenesis. We hypothesize that the accumulation of PKA-cα 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, similar to a mechanism shown for the control of AP-1 transcriptional activity upon the sequestration of c-*fos* in the NL in an ERK1/2 dependent manner.[102] Nuclear dynamics during adipogenesis can be analyzed in 3T3-L1 preadipocytes treated with dexamethasone, isobutyL-methylxantine (IBMX) and insulin to induce the adipogenic program.[103] Notably, co-treatment of the preadipocytes with dexamethasone and IBMX, which increases cAMP levels and activates PKA, also increases the presence of GR in the nuclear periphery, where it exhibits a high level of co-localization with FKBP51. This observation raises the

possibility that, dependent on cAMP-signaling, the nuclear bioavailability of GR may be regulated by FKBP51 which retains GR in the NL at the early stages of adipogenesis; in this manner, the IMM may participate in regulating the expression of GR target genes.[98] When the adipocyte phenotype is achieved, and possibly upon maturation of adipocytes, the fraction of cells expressing lamins A, C and B1 at the nuclear rim increases, though overall lamin A/C protein levels remain low,[97] suggesting a mechanism that concentrates lamins in the nuclear periphery. Uncovering the functional importance of such parallel changes in regulation of nuclear architecture will provide insight into molecular mechanisms that control adipogenesis as well as the pathophysiology of adipose tissue.

The organization and dynamics of the NL is also a field of intensive research in the context of its interconnections with the NE, the cytoskeleton, and mechano-signal transduction. Mechanical stress exerted at the outer cell surface causes changes in nuclear shape, possibly through the LINC complex.[104] In this way, interactions between the plasma membrane and the cytoskeleton may regulate gene expression in response to mechanical stress initiated at the cell surface, with the advantage that mechano-transduction propagation is faster than chemically based diffusion.[105,106] There is evidence that some NE proteins are involved in gene regulation in response to mechanical stress. In this regard, emerin knockout mouse embryonic fibroblasts subjected to mechanical stress are defective in expressing mechano-sensitive genes.[107] However, disruption of the LINC complex does not always deregulate mechano-sensitive genes in response to mechanical stress,[108] raising the possibility that other signaling pathways may act synergistically with mechano-transduction. Tissues can be classified as being soft and stiff based on their capacity for bearing low or high levels of mechanical stress, respectively. Fat tissue, like brain and bone marrow, belongs to the group of soft tissues. In line with this classification, stem cells cultured on matrices of different elasticity have different capacities to differentiate into various cell types, as demonstrated for muscle stem cells.[109] This suggests that differentiation is mechanosensitive. It has been recently shown that matrix stiffness directly influences lamin A protein levels.[110] Bone marrow-derived mesenchymal stem cells (MSCs) have a high lamin A: lamin B ratio that possibly reflects their osteogenic niche origin.[114] When MSC are grown on a soft matrix, the percentage of cells that differentiate in adipose cells is higher than the percentage obtained when MSCs are grown on a stiff matrix (8% versus 1%, respectively).[114] Interestingly, knockdown of lamin A in MSCs greatly favored their differentiation in adipose cells (~20%) on a soft matrix.[110] These observations are in line with the fact that embryonic fibroblasts lacking A-type lamins accumulate more intracellular lipids,[87] and that during the process of 3T3-L1 preadipocyte differentiation there is a decrease in lamin A/C and B1.[97] Overall, tissue stiffness and mechanical stress-dependent changes in lamin A levels, accompanied by differential expression of NE transmembrane proteins,[111] may contribute to the architectural organization of the nucleus that is ultimately required for the control of cell fate choice. As we learn more of the dynamic reorganization of the NL and the cytoskeleton during adipogenesis as a model of cell differentiation, an integrated and better understanding of both the mechano-dependent and -independent mechanisms of control of gene expression will be achieved.

Does the nuclear matrix play a role in adipogenesis?

The nuclear matrix (NM) (Fig. 1A) is defined as the non-chromatin structure of the nucleus and is readily observed in extracted cells under the electron microscope,[112] although its existence is still a topic under discussion. The main feature of this non-chromatin structure is its fibrogranular ribonucleoprotein (RNP) network.[113] NM preparations usually retain approximately 70% of the total nuclear RNA[114] and RNAse treatment destroys this nuclear structure.[89,115,116] The internal nuclear matrix is connected to the lamina and fills the nuclear interior.[117] Chromatin forms loops that were first inferred from measurements of nuclear sedimentation in ethidium bromide[118] and confirmed by their direct microscopic visualization after the stripping of histones.[119] Chromatin loops that range in size from 30 to 110 kb in somatic cells[120,121] and from 20 to 50 kb in sperm,[119,122] are formed by attachments of chromatin to the NM. Chromatin interacts with the NM through DNA sequences called matrix-attachment regions (MARs) or scaffold-attachment regions (SARs) that have 150-200 bp subregions that can become single stranded under torsional stress.[123] Studies performed in *Drosophila* have shown that

MARs are interspersed in the genome at intervals of 26,000-112,000 kb,[124] consistent with the estimated sizes of chromatin loops in flies and mammals.[120,125] MARs bind to specific NM and NL proteins, and one of the best characterized MAR-binding protein is SATB1, which is preferentially expressed in thymocytes.[126] Binding of MARs to the nuclear matrix usually enhances transcription, but it can sometimes repress gene expression.[127] The absence of SATB1 causes the de-repression of at least 2% of all genes, leading to the blockade of normal T cell development.[128] This example of cell-type specificity of chromatin loop architecture in relation to developmentally programmed gene expression demonstrates the importance of nuclear matrix-chromatin interactions in cells. To our knowledge, there is no specific MAR-binding protein described for preadipocytes and adipocytes. The finding of specific MAR-binding protein(s) in adipose precursor cells will be relevant to shed light on the mechanisms that control the repression or activation of genes for precursor cells to acquire the adipocyte phonotype.

The protein composition of the nuclear matrix is complex and analysis by 2D gel electrophoresis revealed 200 major protein spots. A subset of these proteins is cell-type specific, and the expression of some proteins of the NM correlates with malignat transformation.[129,130] Lamins can be detected at sites along nuclear filaments,[89] but they do not seem to form the structural core of the NM. NuMA (nuclear mitotic apparatus protein) is a good example of a NM protein, although its primary function during interphase is not fully defined yet. NuMA shows homology to some structural filament-forming proteins such as cytokeratins, nuclear lamins and myosin heavy chain.[131,132] Overexpression of NuMA lacking the nuclear localization signal results in cytoplasmic aggregates,[133] whereas overexpression of full-length NuMA leads to the formation of a lattice-like structure in the nucleus.[133,134] NuMA can self-assemble into multiarm oligomers *in vitro*.[134] Further, it is resistant to detergent extraction and DNAse treatment, but a fraction of NuMA also interacts with chromatin through its binding to MARs.[135] Such interaction may have an impact in chromatin organization, as shown by changes in chromatin epigenetic markers H4K20Me and acetyl-H4 upon silencing of NuMA.[136] Different nuclear factors have been shown to be associated with the NM, e.g. histone deacetylases, steroid hormone receptors, oncogene proteins like c-myb,[117] proteins of the SWI/SNF complex,[137] and the mitotic scaffold associated protein Sc II.[138] It has been proposed that actively transcribing RNA polymerases are located on the NM near actively transcribed genes, together with bound transcription factors, facilitating their accessibility for binding to the promoter and regulating the expression of their target genes.[139-141]

We showed that a fraction of C/EBPβ, a transcription factor required for proper adipogenesis,[142,143] is associated with the NM.[144] The non-histone nuclear protein Heterochromatin Protein (HP)1α interacts with C/EBPβ, restraining its transcriptional capacity.[144] When we mapped the subnuclear domains where HP1α -C/EBPβ complexes localize, they were distributed mainly in heterochromatic domains, were also found in euchromatin but were completely absent in the NM.[144] Thus, it is likely that the matrix-associated fraction of C/EBPβ that does not interact with HP1α represents the potentially active pool of C/EBPβ that regulates specific genes such as *c/ebpα*, which is activated by C/EBPβ at the onset of adipogenesis.[144] It is of note that active genes can be clustered in specialized nuclear domains termed transcription factories[145-147]; thus the C/EBPβ pool associated with the NM may efficiently regulate clusters of C/EBP target genes. Furthermore, the fraction of C/EBPβ associated with the NM is also sensitive to treatment with the histone deacetylase inhibitor Trichostatin A, suggesting that acetylation of C/EBPβ, and possibly of other nuclear factors, may participate in the regulation of the equilibrium of C/EBPβ bound to chromatin and the nuclear matrix compartments.[144,148]

We also found that the high molecular weight immunophilin FKBP51 interacts with the NM, depending on the presence of ribonucleoproteins and/or RNA.[98] FKBP51 has been shown to be a negative regulator of the transcriptional capacity of the GR as well as the mineralocorticoid receptor (MR).[149,150] Recent studies have revealed a dramatic and dynamic modulation of the chromatin landscape during the first hours of adipocyte differentiation.[151-155] These changes coincide with cooperative binding of early adipogenic transcription factors to transcription factor "hotspots."[154] GR is one of the transcription factors that binds to more than 4,000 sites, and its binding appears to be highly correlated with hypersensitivity to DNase I treatment, suggesting that an open chromatin structure may be required for GR binding,

and/or that GR may be involved in early chromatin remodeling without massive gene transcriptional activation.[153,154] By analogy, one can speculate that in the nuclear matrix compartment FKBP51 may interact with co-repressors, co-activators and/or components of the chromatin remodeling machinery, and in this way exert its control on GR/MR-dependent gene expression.

Does the genome's 3D organization undergo modifications during adipogenesis?

Mammalian cell nuclei with diameters in the range of 10-20 μm contain approximately 2 to 4 m of DNA in G1 and in G2, respectively. DNA is wrapped around histone octamers that constitute the nucleosomes, the first level of chromatin organization.[156] Chromatin threads were named "chromosomes" by W. Waldeyer in 1,888,[157] referring symply to the staining properties of the structures observed. By the end of the 19th and the beginning of the 20th century, Theodor Boveri formulated the hypothesis that each interphase chromosome occupies a distinct portion of the nuclear volume, introducing the term and concept of chromosome territory (CT) (Fig. 1A).[158] Almost a century later, the existence of chromosome territories was demonstrated in pioneering microlaser experiments by Thomas and Christoph Cremer.[162] They used laser-UV-microirradiation to induce local genome damage, followed by pulse-labeling of damaged DNA with ^{3}H-thymidine, and autoradiography to detect ^{3}H-thymidine incorporation in nuclei fixed immediately after the pulse. They thus predicted that inflicting DNA damage within a small volume of the nucleus would yield different results depending on how chromosomes were arranged. If chromosomes occupied distinct territories, localized damage would affect only a small subset of chromosomes, whereas if the chromatin fibers of each chromosome were randomly distributed throughout the nucleus, many of them would be damaged. They showed that only a subset of the chromosomes was damaged, providing the first experimental evidence for the existence of CT.[159] Later, fluorescent *in situ* hybridization (FISH) techniques and the generation of chromosome specific painting probes for a large number of species allowed the direct visualization of individual CTs and their study in the interphase nucleus.[160] The importance of the existence of CTs is reinforced their conservation during evolution over several hundred million years,[161-164] demonstrating that the radial arrangement of chromatin is a fundamental feature of nuclear architecture. The impressive evolutionary conservation argues in favor of an adaptative value, yet the functional implications of non-random radial arrangements are not fully understood.

It is not known how the position of the CT is established in the nucleus. Several studies reported a preferential positioning of gene-rich CTs toward the center of the nucleus, and of gene-poor CTs toward the nuclear periphery.[165-169] In nuclei of cultured human fibroblasts, which have a shape resembling a flat cylinder or ellipsoid, a size-dependent distribution of CTs was described.[166,169] CT organization is maintained despite the extraction of more than 90% of the histones and other soluble proteins in DNA-rich nuclear matrix preparations.[170] The NM possibly provides a scaffold or a basic structure to support CTs.[116] It was shown that complete extraction of the internal NM components by RNase treatment followed by 2M NaCl results in disruption of higher order CT architecture, supporting a role of NM in the conformation/maintenance of the CTs architecture.[116] The NM associations suggest that CTs may be constrained with a limited degree of mobility but with enough plasticity to allow motion and possibly dynamic shape changes.[171,172] However, despite disruption of CTs upon removal of the nuclear matrix, the DNA remains predominantly inside the residual nuclear structure, and a small amount of DNA can extend past the nuclear lamina boundary forming a faint DNA halo.[116] These results suggest that the nuclear lamina also plays a role in the anchoring of chromosomal DNA and that specific territorial arrangements require an intact NM.[116] Indeed, in human cells, genome-wide mapping of lamin B1 binding sites has shown that this protein is not evenly bound to all chromosomes, and that the number of lamin B1 interactions per chromosome correlates with their radial positioning.[66] Moreover, modification of the expression of lamins influences the radial positioning of some peripheral CTs.[173] Lamins interact with DNA at MARs and LADs as well as at specific chromatin structures, such as centromeres and telomeres (reviewed in[174]). It has been demonstrated that lamin A/C and the lamin B receptor (LBR), a NE transmembrane protein, not only tethers heterochromatin to the nuclear periphery but also mediates control of gene expression during

cell differentiation.[175] Since lamins are ubiquitously distributed, it has been proposed that cell-type specific combination of NE transmembrane proteins may help to drive the spatial distribution of chromosomes, generating a genome organization distinctive to each cell type (reviewed in[65]). However, it will be necessary to explore whether cell-type specific components of the NM may be partners of NE transmembrane proteins in such a complex and whether it has a central function. In summary, the coordinated action of chromatin interactions with components of the NM, lamins, as well as with tissue specific NE transmembrane proteins could control the precise positioning of chromosomes in the interphase nucleus.

Does the genome's 3D organization undergo modifications during adipogenesis? Kuroda et al examined the relative and radial position of the CTs of human chromosomes 12 and 16 during differentiation of preadipocytes obtained from healthy female donors undergoing cosmetic liposuction procedures.[176] There are 2 key aspects to consider with respect to CT positioning: the absolute radial location within the nucleus and the position of CTs relative to one another. An increased size of CT16, as well as a close association between territories of chromosomes 12 and 16 due to changes in the relative positioning between them were found in differentiated adipocytes, an association not observed in preadipocytes.[176] This change in the relative positioning of CTs 12 and 16 may play a role in the t(12;16)(q13.3;p11.2) translocation present in 95-98% of myxoid and rounded cell liposarcomas. This chromosomal translocation creates a chimeric oncogene comprising part of the *TLS/FUS* gene found at 16p11.2 and part of the *CHOP* gene found at 12q13.3.[177-180] The resultant fusion protein is crucial because it deregulates the expression of the adipocyte differentiation gene *DOL54*.[181] In spite of not knowing the molecular mechanism that leads to specific translocations in tumor cells, close juxtaposition of interphase chromosomes may play an important role, as shown in chronic myeloid and promyelocytic leukemias.[182-185] Although further studies are required to elucidate the mechanism underlying the adipocyte-specific changes in position of chromosomes 12 and 16, this study provided the first evidence of the relative repositioning of CTs during adipogenesis.

A non-random positioning of CTs was also demonstrated during the differentiation of mesenchymal stem cells (MSC) derived from porcine bone marrow, with the most dramatic change in position observed for CT4 moving from the nuclear periphery toward the nuclear interior.[186] In addition, using 3D FISH analysis, it was shown that the architecture of CT changed during the course of MSC adipocyte differentiation. In undifferentiated MSCs, CTs are condensed with gene signals buried inside them. In contrast, in adipose-differentiated MSC, CTs are decondensed, exhibiting approximately twice the size compared to nuclei prior induction of adipogenesis; they also display loops of chromatin emanating from the CT with the gene signal at the end of the loop, oriented toward the nuclear interior.[186] The nuclear positions of genes and the CTs carrying these gene loci have also been examined. The nuclear position of genes involved in adipogenesis is altered: genes that become more internally located in the nucleus are actively transcribed, while genes that move toward the nuclear periphery are down–regulated.[186] More dramatic differences in localization were found for gene loci than for CTs, revealing genes moving from the nuclear periphery to the interior (*PPARG, FABP4, GATA2*), from an intermediate position to the nuclear interior (*SREBF1, CEBPB*) and from a peripheral to an intermediate location (*CREB*).[186] Thus 6 out of 7 genes required for proper differentiation significantly change their nuclear location during adipogenesis. An interesting gene behavior is exhibited by *GATA2*, whose expression is restricted to preadipocytes where it exerts an antiadipogenic effect by the direct suppression of PPARγ.[187] *GATA2* relocates from a peripheral nuclear location to the interior at day 7 post-induction of adipogenesis of MSC, coinciding with its highest level of expression.[186] By day 14, its expression falls and the gene localizes in the nuclear periphery again, consistent with the concept that the nuclear periphery acts as a transcriptional repressive domain. Furthermore, when MSC are differentiated, *PPARG, SREBF1, FABP4* and *GATA2* reside in a different compartment relative to their parent chromosome, showing that genes associated with adipogenesis loop out from their CT during differentiation and suggesting that this event is possibly associated with their increased expression.[186]

Insight into how chromatin is organized within CTs has been advanced by the development of chromosome conformation capture (3C)[188] and derivative methods (4C, 5C, HI-C and single cell HI-C)[189-193] which allow delineation of the organization of

chromosomes in the 3-dimensional space of the interphase nucleus. With this information, when we zoom into chromosomal structure, we find that chromosomes are comprised of topologically associating domains (TADs) (Fig. 1A) defined as regions of high local contact frequency, separated by boundaries where contacts are relatively infrequent.[194-196] In spite of TADs being too small to be visualized by microscopy-based methods, data obtained by FISH analysis is consistent with data obtained by 3C and related techniques.[194,195,197] Mammalian genomes contain approximately 2000 TADs, and the CCCTC-binding factor and cohesin mediate their establishment and/or maintenance.[194,197-199] Several chromatin associated proteins, transcription factors and cofactors participate in chromatin interactions of TADs that preferentially are intra-chromosomal rather than inter-chromosomal.[192,196,200] Over one million interactions between loci have been detected genome-wide; these contacts make possible the interaction between enhancers and promoters that are kb distances in a linear sense but are in close physical proximity.[201] The 3D organization of enhancers and promoters facilitates the interaction between protein complexes bound at enhancers with those bound at promoters, and can thereby modulate gene transcription in a cell-type specific manner. The same TAD can be found in different cell types or differentiation steps, but may be located in a different nuclear compartment (active *vs*. inactive), as part of a mechanism of control of cell-type or differentiation dependent gene expression. By 3C assay, the *PPARG* promoter is positioned in proximity to the promoters of genes encoding adipokines such as leptin and adiponectin, as well as of genes that encode lipid droplet-associated proteins.[202] This positioning event takes place at early time points post-induction of adipogenesis, when these genes are not actively expressed, but when changes occur in chromatin accessibility and occupancy of the PPARγ promoter by transcription factors responsible for its activation.[151,154,203] *PPARG* is not actively expressed at this early time, possibly because it requires chromatin remodeling events that take place later as differentiation progresses.[153,154,204] The intergenic interactions of the *PPARG* promoter are dependent on C/EBPβ, since knockdown of this transcription factor, required for proper differentiation, abrogates the interactions.[202] Furthermore, pharmacological inhibition of PKA or knockdown of the catalytic subunits of the kinase also prevent the intergenic interactions of the *PPARG* promoter, indicating that genome reorganization, at least for the *PPARG* loci, depends on c-AMP-PKA signaling.[202]

Once the organization of the genome is established in white, brown or beige adipocytes, the chromatin becomes stable, based on the fact that during browning of human white adipose cells by long-term exposure to PPARγ agonists, considerable changes in gene expression are found without major changes in the chromatin landscape.[205] Superenhancers have been defined as clusters of enhancers that constitute regulatory nodes controlling expression of genes defining cell identity.[206] When PPARγ-binding sites located within 12.5 kb from each other were ranked according to the intensity of their Mediator complex subunit 1 signal, over 1100 PPARγ superenhancers were identified in beige adipocytes, and 324 of them were exclusively present in beige adipose cells.[205] These particular PPARγ superenhancers are in the vicinity of beige-selective genes which encode functionally important metabolic regulators involved in fatty acid degradation and β-oxidation. Thus during the reprogramming events of white adipose to beige cells, although no major changes in chromatin take place, the selective activation of PPARγ superenhancers seems to be required.[205] Overall the physical association of coordinately regulated genes facilitates their control, suggesting that active co-regulated genes generate nuclear hot spots for precise and efficient control of transcription.

Future perspectives

When adipogenesis is triggered the architecture of the nucleus of progenitor cells undergoes substantial modifications (Fig. 1C). The NL is reorganized, CTs decondensed and change their relative position, adipogenic genes such as C/EBPβ and PPARγ undergo repositioning, accompanied by dramatic changes in chromatin accessibility, promoters occupancy and superenhancers formation among many other modifications. However, many questions are still waiting for answers, to gain insight not only into adipogenesis, but into cell differentiation processes in general. How are nuclear compartments established to produce a precise pattern of gene expression? Is this a cause or a consequence of the differentiation program? It has been extensively studied all the signaling pathways that control the process of adipogenesis (reviewed in[10,143]), but how do biochemical and mechanical signaling are coordinately transduced in the

organization of nuclear compartments in the adipose or any other cell fate determination? It is known that active genes are preferentially localized in euchromatin, and in many cases even loop out of their CT. In contrast, when genes that normally reside in euchromatin translocate to centromeric heterochromatin or are preferentially positioned at the nuclear periphery during cell differentiation, they are silenced. How are these events regulated? Which signals required for cells to differentiate are transduced by changes of the nuclear architecture? We still know very little about the 3D organization of the genome during adipogenesis, but undoubtedly, future studies will unveil the relationships between the architecture of the genome and the control of gene expression, as part of the mechanism that controls the acquisition of the phenotype of the different types of adipose cells. These studies will depend, in part, on new technologies to prove or disprove the proposed models. After all, Boveri's hypothesis on the existence of CTs waited for almost a century for experimental verification. Studying the dynamics of nuclear architecture during adipogenesis will increase our knowledge of the mechanisms that control cell differentiation, while enhancing our ability to understand adipose metabolism in health and disease.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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