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Contributions of extracellular matrix signaling and tissue architecture to nuclear mechanisms and spatial organization of gene expression control

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Abstract

Post-translational modification of histones, ATP-dependent chromatin remodeling, and DNA methylation are interconnected nuclear mechanisms that ultimately lead to the changes in chromatin structure necessary to carry out epigenetic gene expression control. Tissue differentiation is characterized by a specific gene expression profile in association with the acquisition of a defined tissue architecture and function. Elements critical for tissue differentiation, like extracellular stimuli, adhesion and cell shape properties, and transcription factors all contribute to the modulation of gene expression and thus, are likely to impinge on the nuclear mechanisms of epigenetic gene expression control. In this review, we analyze how these elements modify chromatin structure in a hierarchical manner by acting on the nuclear machinery. We discuss how mechanotransduction via the structural continuum of the cell and biochemical signaling to the cell nucleus integrate to provide a comprehensive control of gene expression. The role of nuclear organization in this control is highlighted, with a presentation of differentiation-induced nuclear structure and the concept of nuclear organization as a modulator of the response to incoming signals.

Keywords

chromatin; histone; ATP-dependent chromatin remodeling; cell shape; differentiation; nuclear organization

1. Introduction

The genome has been the focus of an ever increasing number of investigations aimed at understanding how a wide array of differentiated tissues in the body can be spurred from a single genetic identity held within the DNA sequence. A body of literature has demonstrated that differentiation is the result of the selective expression of genes; however, the orchestration of this selective expression remains to be fully understood. In order to begin to unravel the exquisite control of tissue-specific gene expression, it is important to consider the elements of tissue organization that could influence gene transcription. This review focuses on the relationship between tissue organization, as defined by the extracellular matrix, cell shape and internal cellular structure, and the nuclear machinery that directs chromatin remodeling necessary for tissue-specific gene expression.

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1.1. The composite epigenetic machinery within the cell nucleus

Epigenetic control of gene expression plays a central role in determining tissue specificity. It is the result of dynamic changes in chromatin structure that are led by at least three mechanisms, encompassing posttranslational alterations of histones, displacement of nucleosomes along the DNA, and methylation of CpG islands in the promoter and regulatory regions of genes. These mechanisms depend on enzymes and motor proteins organized into multiprotein complexes broadly referred to as chromatin remodeling complexes (CRCs). The composition of these complexes determines ultimately whether a gene is expressed or silenced.

Post-translational modifications occurring at the aminoterminal tails of nucleosomal histones include acetylation/deacetylation, phosphorylation, methylation, ubiquitylation, sumoylation, ADP-ribosylation, deimination, and proline isomerisation [1]. Among these modifications, acetylation and methylation of histones are critical for transcriptional regulation by controlling chromatin accessibility. Acetylation of histone H4 in the promoters of genes is linked to mRNA transcription [2], whereas methylation of histones can be found in active genes as well as heterochromatin depending on the histone type and lysine position within the histone [1,3]. For instance methylation of histone 3 on lysine 27 or Lysine 9, is usually correlated with transcription repression [3].

ATP-dependent CRCs are of five different kinds depending on their ATPase and act by altering the presence of nucleosomes on the DNA [4]. These complexes belong to SWI/SNF, ISWI, CHD, INO80, and SWR1 families. SWI/SNF complexes have been primarily associated with transcriptional regulation, by making DNA accessible to either activators or repressors of transcription. ISWI complexes can act both in transcription activation and repression by moving nucleosomes. CHD complexes participate in different activities linked to transcription [5]. INO80 complexes are involved in transcription activation and DNA repair, and SWR1 complexes are involved in the blockage of heterochromatin spreading.

DNA methylation on CpG regions is carried out by DNA methyltransferases. DNA methylation mechanisms in higher eukaryotes include de novo methylation observed during development and carcinogenesis and maintenance of the methylation status during DNA replication [6]. CpG methylation is the basis for the binding of MBD family of proteins that interact with other proteins or complexes involved in the control of chromatin compaction [7]. The degree of methylation of a gene promoter has been associated with its expression level; the more methylation spreads, the least the gene is expressed. But, not all the genes in the genome are regulated by DNA methylation. Interestingly, certain members of the MBD family of proteins show more selectivity for DNA sequences than others, suggesting there might exist some degree of specificity in DNA methylation-based gene expression control.

Although the genome is maintained within the confines of the nucleus shell, it is far from being secluded. Shuttling between nucleus and cytoplasm permits a constant exchange of information and materials necessary to control gene expression [8,9]. Moreover, a continuous link between cell adhesion complexes responsible for the cell's interaction with extracellular components, the cytoskeleton, and the nuclear structure has been progressively unraveled leading to today's picture of the structural continuum of the cell or cell matrix (Figure 1). The effect of the extranuclear environment on gene expression control is a critical factor in tissue-specific differentiation and, as we will discuss later in this review, part of the effect is mediated by the structural continuum.

1.2. The characteristics of tissue organization involved in gene expression control

Tissue differentiation *in vivo* can be defined as the acquisition of structural and functional characteristics of a particular tissue. Such differentiation is not solely accompanied with a

specific gene expression profile; it is also linked to the acquisition of a particular internal organization and shape of the cells within that tissue, which can be referred to as tissue architecture.

Tissue differentiation is intimately linked to extracellular matrix (ECM) signaling, ECM-induced changes in cellular morphology, and signaling resulting from soluble molecules. The ECM is composed of a meshwork of fibrillar molecules such as collagens and elastin, and glycoproteins such as fibronectin, laminin and hydrophilic proteoglycans. Cells physically bind to the ECM by making contact with specific ECM molecules via cell membrane receptors. Cell-ECM adhesion elicits intracellular signaling that can be divided into biochemical signal transduction, via phosphorylation cascades and protein translocation to the cell nucleus, and mechanotransduction, via cytoskeleton rearrangement. Mechanotransduction is also activated upon ECM-induced modification of cell shape. Soluble extracellular molecules like growth factors and hormones signal to cells via binding to cell membrane or intracellular receptors. Each of the signaling pathways necessary for tissue differentiation influences gene expression. In order to fully understand how these signaling pathways produce the stable gene expression profile necessary for the maintenance of a differentiated phenotype, it is critical to envision how they integrate within the cell nucleus.

Studies focused on ECM signaling and tissue architecture have helped uncover major mechanisms of tissue specific gene expression control. Firstly, signaling elicited from outside cells reaches the nuclear compartment via soluble and mechanical pathways. Secondly, the organization of the cell nucleus might influence gene expression directly as well as the effects of extranuclear signaling on gene expression. With the intent of presenting the nuclear mechanisms that control differentiation-specific gene expression in a tissue context, we will review the facts that demonstrate the tissue specific nature of gene expression and chromatin organization, and present current knowledge and emerging concepts of gene expression control mediated by the ECM and nuclear structure.

2. Differentiation-dependent gene expression and chromatin organization

Two complementary types of investigations have contributed to the notion that differentiation is accompanied with specific epigenetic modifications responsible for the up-regulation and down-regulation of gene expression. One type of investigations compares different stages of differentiation during development; the other type of investigations encompasses time-course experiments with cellular models of differentiation. Differentiation-specific gene expression has been demonstrated for many tissue types and has been abundantly reported. Here we are focusing on publications that have brought information that challenges old concepts or helps develop new concepts regarding differentiation-dependent gene expression.

2.1. Gene expression profiles associated with the differentiation process

The overriding effect of the expression of a specific set of genes on tissue specific differentiation was nicely demonstrated by forcing differentiation of bone marrow mesenchymal stromal cells into neuron-like cells. Indeed these precursor cells do not normally give rise to neuronal differentiation. The production of neuron-like cells was accompanied with the down-regulation of genes involved in osteogenesis, chondrogenesis, adipogenesis, myogenesis and of genes coding for ECM components, whereas the transcription of genes involved in neurogenesis was increased including that of genes necessary for synaptic transmission and long-term potentiation, neurite outgrowth and genes coding for neuronal receptors [10]. Cells with this neuronal differentiation signature showed functionality via activation of the glutamate receptor channel.

Interestingly, the gene expression profile associated with a particular type of differentiated tissue does not only include genes primarily or solely expressed in that tissue. Studies have demonstrated that among differentiation specific genes are genes responsible for the changes in cellular morphology (e.g., genes coding for adhesion molecules and cytoskeletal proteins) necessary for tissue differentiation. Logically the genes involved in the morphological aspects of differentiation can be expressed in different types of tissues as long as these tissues share a similar morphology. Morphology-dependent expression of a set of genes has been shown upon formation of a multinucleated syncytium by cytotrophoblast cells that mimic parts of human placental development. The 397 genes that were found to be transcriptionally altered upon the 9-day period of analysis fell into six categories, including cell and tissue structural dynamics, cell cycle and apoptosis, intercellular communication, metabolism and regulation of gene expression [11]. In some of these categories, especially the category of cell and tissue structure genes (e.g., integrins, keratins, actin), gene expression changes were correlated to morphological modifications. In another study, comparison of tube formation by trophoblast and endothelial cells revealed that although the end morphological result of differentiation seemed similar (i.e., tube formation), only 73 of the 1628 genes that showed significant expression changes upon microarray analysis in trophoblast cells were common with endothelial cells [12]. Thus, tissue differentiation requires the regulation of genes necessary to achieve a particular the type of morphogenesis as well as the regulation of genes necessary to assure the specific functions of that tissue.

The study of tissue-specific gene expression with samples obtained *in vivo* has permitted the discovery of two important aspects of differentiation-dependent gene expression. Firstly, precursor cells appear to already contain uniquely expressed genes. The analysis of the glial precursor cell population showed 458 genes uniquely expressed compared to other cell populations (e.g., neural stem cells, astrocyte precursors), suggesting that signaling pathways that are important for the differentiation of these particular cells are in place early on [13]. Secondly, although differentiation into a mature cell type is not irreversible, returning to a progenitor state might not be easily accomplishable. Deletion of transcription factor PAX5 necessary for differentiation into mature B lymphocytes in mice led to dedifferentiation into uncommitted progenitors [14]. However, this induction of dedifferentiation was accompanied with the development of aggressive lymphomas. In this study, dedifferentiation from mature cells was not synonymous to return to normalcy.

The examples discussed above suggest that there exists a hierarchy in the differentiation-specific gene expression profile necessary for the acquisition and maintenance of differentiation. Cells could be placed in a predifferentiated stage to facilitate future differentiation and in a postdifferentiated stage to maintain differentiation. How is this hierarchy encoded in the cells? It is possible that the marks of the hierarchical changes are located in the cell nucleus, leading to an organization of the genome that would further determine how cells will react to stimuli. This hypothesis is supported by our observation that the acquisition of apical polarity, a late stage in the *in vitro* differentiation process of breast epithelial cells into glandular structures (acini), leads cells to react differently to the disruption of the chromatin organizer NuMA. Indeed, if the cells are basoapically polarized, altering NuMA and, consequently chromatin organization, induces apoptosis. Whereas, if acinar cells do not have apical polarity, disruption of NuMA using similar techniques triggers cells to enter the cell cycle [15,16].

2.2. Involvement of the epigenetic machinery in tissue differentiation

The possibility for the cell nucleus to be primed to respond to stimuli necessary for the progression of tissue differentiation is illustrated by the existence of modifications at the level of chromatin during differentiation.

Differentiation has been associated with both global and local rearrangements of chromatin organization. Such rearrangements can be assessed by measuring histone acetylation which is considered a good indicator of transcriptional activity. Although microarray analysis has been the gold standard to identify differentiation specific gene expression clusters, recent studies have revealed the importance of looking also at epigenetic modifications such as acetylation of lysine on histone H3 (H3K9) to measure active transcription more comprehensively [17]. The powerful informative value of these epigenetic changes for gene transcription is thought to be due to the ability of such measurements to inform on the chromatin structure at specific loci.

When comparing differentiated stages and nondifferentiated stages obtained with *in vitro* models of phenotypically normal differentiation, the total amount of acetylated H4 has been found to decrease [18–20]. This global change in histone acetylation seems necessary for differentiation. Indeed, using the model of mammary acini differentiation in three-dimensional (3D) culture, we have shown that induction of histone acetylation upon treatment of mammary acini with histone deacetylase (HDAC) inhibitor trichostatin A (TSA) was sufficient to induce the loss of acinar differentiation, as illustrated by re-entry into the cell cycle and alteration of epithelial polarity [21]. In another study, it was shown that overexpression of histone acetylase (HAT) in murine mammary epithelial cells inhibited the expression of β -casein, a marker of functional differentiation [18]. The global decrease of histone acetylation observed upon phenotypically normal differentiation indicates that chromatin structure adopts a repressive status for gene expression. However, the overall hypoacetylation of histones does not prevent the acetylation of the genes that need to be expressed in order to achieve differentiation. As an example of this, chromatin immunoprecipitation experiments have demonstrated that casein gene expression characteristic of the functional differentiation of mammary epithelial cells was accompanied with acetylation on histones H4 located upstream of the gene promoter [22].

Phenotypically normal differentiation is also accompanied with modifications in the methylation of DNA CpG islands [23]. Notably, the global repressive pattern of chromatin associated with differentiation, already characterized by histone deacetylation, is confirmed by the level of methyl-binding proteins. Upon differentiation of mammary epithelial cells, the level of methyl-binding protein MeCP2 increases [19]. Importantly, induction of DNA hypomethylation with 5-aza-2' deoxycytidine during the formation of mammary acini leads to tissue structures that are only partially differentiated, as shown by the lack of proper distribution of tight junction protein ZO-1, a marker of apical polarity in the breast epithelium [19]. Interestingly, during myogenesis, the increase in MeCP2 level is accompanied with the association of MeCP2 with heterochromatin protein 1 (HP1) in heterochromatin regions, thus reinforcing the importance of producing a repressive chromatin structure during differentiation [24]. Nonetheless, like for histone acetylation, certain methylation-dependent genes that need to be expressed in the differentiated tissue have been found to be specifically hypomethylated, which would favor their expression. Such is the case for the gene coding for the whey acidic protein, a lactation-specific differentiation marker which is hypomethylated in the mammary gland but not in the liver [25], and the cdk inhibitor p57 gene, a marker of myoD-induced myogenic differentiation [26]. Interestingly, the global chromatin modifications indicative of a repressive status for genome expression seem to occur early during the differentiation process. For instance, the differentiation of multipotent germline stem cells into somatic lineage was accompanied early on with hypermethylation of chromosomal centric and pericentric regions [27].

How can we reconcile the selective expression of tissue specific genes and the context of global repression of chromatin, and thus gene silencing, that is associated with phenotypically normal differentiation? The selective expression of genes could be linked to the targeting of ATP-dependent CRCs. SWI/SNF complexes have been associated with muscle, neuron, adipocyte,

and liver differentiation in mammals [28–37]. Notably, Brg1-containing SWI/SNF complexes have been involved in the differentiation of adipose cells and muscle cells [38–41]. Since selective expression of genes is tissue type-dependent, there must be a mechanism by which these widespread CRCs gain some specificity. One possible explanation for tissue specificity of SWI/SNF action is the existence of different components (e.g., BAF60, BAF155, BAF170, BAF250) in the complex depending on the type of tissue or the differentiation status [30,42].

Altogether studies reported in the literature indicate that the organization of chromatin has great predictive value regarding the transcription of specific genes. Moreover, differentiation is accompanied with a global repressive state of chromatin while permitting the expression of specific genes thanks to local chromatin rearrangement. Since a vast majority of the changes in gene expression are acquired upon receiving specific extracellular signals, it is essential to review how extracellular signals affect chromatin structure and the epigenetic machinery.

3. The impact of extracellular matrix signaling on the epigenetic control of gene expression

The discovery of direct contacts between ECM molecules and cell membrane receptors was an important factor in the development of the idea that the ECM is not only a supporting mechanical environment, but also an initiator or modulator of specific signaling pathways inside cells [43,44]. Signaling triggered by nonsoluble components of the ECM that anchor cells to their environment (this is referred to as cell adhesion) encompasses both biochemical pathways and mechanotransduction. The latter mechanism has been progressively identified as a critical component of gene expression control and a strong modulator of the response to biochemical stimuli.

3.1 ECM-induced gene expression

The demonstration that ECM molecules control gene expression was mainly provided by plating cells on different ECM substrata and measuring changes in gene expression [45,46]. The existence of ECM responsive elements (ERE) in differentiation genes, that might explain the critical role played by the ECM in gene expression control, was discovered many years ago (e.g., the ERE in the β -casein gene of mammary epithelial cells [47]). Since then, studies have revealed the tremendous complexity of the role of the ECM in the control of differentiation-specific gene expression.

The example of the control of casein expression during mammary epithelial differentiation illustrates well the intricate hierarchy of chromatin changes controlled by the ECM. Laminin is the key ECM signaling molecule in mammary epithelial differentiation. It has been linked to the recruitment of Brg1-containing SWI/SNF complexes and the induction of histone acetylation at the casein gene promoter, hence demonstrating a connection between ECM signaling and the epigenetic machinery [22]. However, casein expression requires a synergistic action between laminin and the hormone prolactin to increase the association of the necessary transcription factors STAT5 and C/EBP β to β - and γ -casein gene promoters. Surprisingly, the increase in histone H4 acetylation at the β -casein gene promoter induced by treatment with TSA was not able to significantly upregulate gene transcription, indicating that acetylation alone is not sufficient to increase β -casein expression. It was further shown that histone acetylation and transcription factor binding acted upstream of Brg1 ATPase activity and that transcription factor binding determined the recruitment of the SWI/SNF complex [22]. Other studies performed with rabbit primary mammary epithelial cells had demonstrated that the ECM signaling mediated by laminin receptor $\alpha 6$ -integrin was influencing H4 acetylation but not transcription factors necessary for casein expression, suggesting that the ECM affects local chromatin structure [48]. The amount and DNA binding activity of transcription factors C/

EBPs and STAT5 necessary for β -casein expression were not influenced by the presence of the type of ECM (basement membrane) normally involved in the differentiation process. Moreover, cells cultured in the absence of ECM showed local histone deacetylation in the 5' upstream region of the α -s1-casein gene. Similar results were obtained upon blocking α 6-integrin binding in cells cultured in the presence of ECM, while the control regions of the α -myosin gene were not affected. Since the regions affected by acetylation of the casein gene are important for STAT5 binding, it was proposed that the ECM maintains chromatin structure in a status that permits the binding of the transcription factors and thus, the recruitment of the transcription machinery.

The findings described above allow us to envision a hierarchy in the response to ECM signaling: the initiation of acetylation of the gene promoters permits the recruitment of transcription factors, which in turn leads to SWI/SNF recruitment and gene expression (Figure 2); however, the mechanism responsible for ECM and prolactin-directed local histone acetylation remains to be unraveled.

As we mentioned earlier, the local hyperacetylation necessary for gene expression in phenotypically normal tissue occurs within an environment that is globally hypoacetylated. To further decipher the mechanisms of gene expression control during tissue differentiation, it is critical to understand how global chromatin repression occurs and the goal accomplished by this global change.

3.2. The role of cell adhesion-induced mechanotransduction in gene expression control

Adhesion to the ECM is intimately associated with modifications in cell morphology. As described previously, the study of differentiation models, including the mammary epithelial differentiation model [18,20,21], has revealed that phenotypically normal differentiation is accompanied with a decreased level of histone acetylation and a global reduction of gene expression. In early experiments, the inhibition of cell rounding using phorbol ester TPA was critical in demonstrating the importance of changes in cell shape for ECM-dependent gene expression. Indeed, without cell rounding there was no synthesis of milk protein β -casein [49]. Moreover, a link between ECM-induced cell morphology and chromatin organization was recently highlighted [20]. Culture of mammary cells on polyHEMA, which rapidly leads to cell rounding without the presence of ECM, was sufficient to induce histones H3 and H4 deacetylation. This effect was not increased by ECM signaling, as adding ECM to preroounded cells did not further decrease histone acetylation. The importance of the cell cytoskeleton in the ECM-induced effect was shown by treatment with cytochalasin D which disrupted actin organization and reproduced cell rounding and histone hypoacetylation. Thus, it appears that the 'tension' level in the cell could control chromatin organization.

The mechanical stress induced by cell adhesion is proposed to convey information within cells by mechanotransduction, through the structural continuum or cell matrix (see Fig. 1) [50]. Mechanotransduction is the central idea behind the concept of tensegrity [51]. This concept has been described by Gien and Hendzel as the stability of structures which is "*based on a synergy between balanced continuous tension and noncontinuous compression components*" [52].

The way by which the ECM could exert its effects on gene expression via mechanotransduction has been abundantly reviewed. Briefly stated, adhesion leads to stress being transferred to a rigid intracellular structure [53,54]. Notably, cell adhesion molecules can transfer external mechanical forces to the cytoskeleton [55,56]. Microtubules can make a cell stiffer upon compression, whereas tensional forces are controlled by the actin skeleton; for instance, actin microfilaments could make the cell stiffer upon stretching [53,54,57]. Adhesion could result in the constant transfer of compressive forces between ECM attachment points and the

microtubules. The presence of connections between the different types of cytoskeleton networks, via plectin notably [58,59], suggests that the balance of forces resulting from this interconnection will be critical for the cell's reaction to mechanical stress [60–62].

The effect of mechanical stress on gene expression, including the expression of differentiation-associated genes, was demonstrated in different cell models. Mechanical stiffness similar to that found in natural tissues reproduced with ECM in the laboratory permitted the differentiation of myotubes [63]. Stretching cardiac myocytes activated hypertrophy-associated genes [64]. The link between mechanical forces and chromatin was also demonstrated. In particular, changes in intracellular tension (linked to cytoskeletal organization) were correlated to changes in the levels of histone acetylation [65–67]. It was proposed that the effect on histone acetylation could be due to the sequestration of HDAC to the cytoskeleton and the regulation of HDAC translocation to the cell nucleus observed in certain studies [20]. Thus, the global mechanical effect of the microenvironment on cells could set the general chromatin context.

Interestingly, mechanotransduction appears to influence directly the expression of certain genes, while other genes also need soluble factors or biochemical signaling. For instance, the expression of lactoferrin is controlled by changes in the shape/mechanics of mammary epithelial cells [68], whereas other lactation-related genes like casein also require biochemical signaling for transcription [49]. Differentiation of pluripotent human mesenchymal stem cells into bone or fat cells depends on soluble differentiation factors. However, tissue specific differentiation could only be achieved selectively if the correct adhesion conditions were reproduced (adherent for bone differentiation and non-adherent for fat cell differentiation) [69]. These observations indicate that cell adhesion, and hence mechanotransduction, is necessary to place cells in the proper conditions to receive the biochemical signals that permit the continuation of differentiation specific-gene expression. In order to understand how ECM-mediated mechanotransduction might 'prepare' chromatin, we need to scrutinize the link between the cytoskeleton, the nuclear envelope, and the inner organization of the cell nucleus.

4. Tissue architecture and epigenetic control of gene expression

The study of the inner organization of the cell nucleus is emerging as a critical avenue to further the understanding of gene expression control. In addition to its major subcompartments, the nucleoli, and the higher organization of chromatin into heterochromatin and euchromatin regions, a number of nonchromatin domains have been identified based on their concentration in specific proteins [70]. Some of the organizational features of the cell nucleus are observed in the nuclei of nondifferentiated cells, like the concentration of heterochromatin at the nuclear periphery and the presence of transcription permissive areas around splicing factor speckles. However, a specific organization of the cell nucleus, including chromatin and nonchromatin regions, has been described upon phenotypically normal differentiation. The major characteristics reported so far, regardless of the tissue type, are the concentration of heterochromatin domains around a central nucleolus and at the nuclear periphery [15,16,71–74], DNase sensitive chromatin at the nuclear periphery [15,75,76], and the formation of larger and fewer splicing factor speckles compared to nondifferentiated cells [16,21,77,78] (Figure 3). Understanding the contribution of nuclear organization to differentiation and the factors that influence differentiation-specific nuclear architecture should help further decipher the mechanisms of epigenetic control of gene expression.

4.1. Impact of nuclear organization on differentiation

One way to assess the effect of nuclear organization on differentiation is to directly alter elements that contribute to such organization in differentiated cells. For instance, we have shown the importance of nuclear organization for the maintenance of breast acinar

differentiation by altering directly the organization of the nuclear protein NuMA, using peptides and antibodies targeted against this protein. Altering NuMA organization in breast acinar cells led to the loss of differentiation. Likewise, when NuMA was silenced during the differentiation process, glandular differentiation was not achieved. The action on NuMA was accompanied with drastic changes in chromatin structure, as shown by the redistribution of histone acetylation and histone methylation patterns, prior to phenotypic changes [15,16].

It has been proposed that the specific nuclear organization observed in differentiated cells might be important to lock gene expression in place by maintaining genes in a silent state and enabling the expression of a small number of genes necessary for differentiation [79]. Then logically, differentiation genes should be found in regions permissive for transcription, and the bulk of repressed genes in heterochromatin areas (e.g., the nuclear periphery). A main region for gene transcription is represented by the area directly surrounding splicing factor speckles [80]. Studies performed with models of oligodendrocyte maturation, myogenesis and erythropoiesis have demonstrated that certain genes critical for differentiation are located next to splicing factor speckles in differentiated cells [81–83]. Conversely, a number of genes have been observed in the vicinity of heterochromatin, at the nuclear periphery, when they are silenced [84]. However, it is important to specify that the correlation described above between the status of gene expression and the gene location is not observed for all genes studied so far during differentiation processes [85], which implies that the location-expression relationship theory cannot be generalized.

4.2. Control of nuclear organization by tissue architecture

The ECM and tissue architecture control gene expression, notably during phenotypically normal differentiation. Therefore, it is not surprising to find evidence of their influence also on nuclear organization. Such an influence has been established based on experiments dealing with tissue morphogenesis. For instance breast glandular morphogenesis is associated with a stepwise reorganization of the nuclear compartment with colocalization of certain components (e.g., NuMA and large splicing factor speckles) occurring only at the end of the differentiation process, after cells exit the cell cycle [21]. Acinar morphogenesis was also reported to be associated with relocations of genes within the cell nucleus independently of growth arrest; especially, different locations were measured for several genes when comparing mammary epithelial cells growth-arrested on monolayer culture and cells growth-arrested in 3D culture upon morphogenesis [86]. Further evidence of a link between tissue architecture and nuclear organization was obtained with models of tumor reversion. Reversion of breast tumor cell phenotype was originally used to demonstrate the importance of tissue architecture in directing cell phenotype. Indeed breast cancer cells can be induced to behave phenotypically normally and form acini, although they keep their genetic alterations [87–89]. Using a similar system of phenotypic reversion, we have shown that the formation of acinus-like structures by tumor cells was accompanied with an organization of chromatin and nonchromatin compartments in the cell nucleus that mimicked that observed in non-neoplastic, differentiated breast epithelial cells [16].

Experiments have been developed to understand the contribution of cell shape change to nuclear organization. Notably, it was shown that the alteration of cell shape and adhesion was sufficient to modify nuclear morphology and chromatin structure [90,91]. For instance, maximal cell adherence was accompanied with less accessibility of chromatin to restriction enzyme *AluI*. Interestingly, the actin cytoskeleton seemed to prevent chromatin accessibility, and microtubules or intermediate filaments seemed to favor accessibility, as shown by selective disruption of the different cytoskeleton networks [91]. This finding suggests that the balance of forces achieved in the cytoskeleton is likely to determine the global status of chromatin

organization and that tension forces are particularly important to maintain a closed chromatin conformation.

Further studies are needed to precisely unravel the nature of the relationship between tissue morphology and nuclear structure. We need to know whether cell shape and adhesion affect specific subcompartments in the cell nucleus. We also need to clarify an intriguing phenomenon in gene expression control: treatments that can be used to globally alter chromatin structure (e.g., TSA and 5-aza-2' deoxycytidine) often influence the expression of a relatively small number of genes in any particular cell condition [92–94] (Lelièvre S.A. et al., unpublished data). This observation suggests that the organization of the genome within the cell nucleus could prevent most gene promoters from responding to treatments aimed at changing chromatin organization by directly influencing histone acetylation or DNA methylation. The chromatin remodeling machinery might not reach the gene promoter due to the location of the gene in the nucleus, and/or because of the presence of specific transcription factors that prevent the modifications necessary to alter gene transcription.

5. Cell matrix contribution to gene transcription

Chromatin remodeling is necessary to modify the expression of differentiation-specific genes. Consequently, we can assume that ATP-dependent CRCs have to be targeted to these genes. This hypothesis is supported by reports that link certain families of ATP-dependent CRCs (e.g., SWI/SNF complexes) to the expression of specific sets of genes [95]. Moreover, transcription factors have been shown to determine the binding of ATP-dependent CRCs, thus they could act as determining events in the targeting of these complexes during differentiation. Transcription factor translocation and/or activation are often triggered by signal transduction. Therefore we could envision that signaling controlled by the ECM should lead gene transcription control. However, the availability of DNA sequences to which the transcription factors bind might be determined by the local nuclear environment, hence potentially making nuclear organization the cornerstone of gene expression control. The answer to this power dilemma might be in the cell matrix that provides a way to envision the integrated contribution of the ECM and nuclear organization to gene expression control.

5.1. Connection between the cell matrix and chromatin structure

The story of how mechanical forces might be transmitted to the cell nucleus began to unfold following the discovery of proteins that couple the cytoskeleton and chromatin. Nesprin proteins possess a KASH-domain at their C-terminus that can interact with the SUN-domain of integral nuclear membrane proteins [96,97]. SUN proteins are located on the inner nuclear membrane and interact with giant Nesprins via their carboxy-terminus [98] probably in the perinuclear space. The biggest Nesprins (>1 MDa) located in the outer nuclear membrane are thought to extend up to 500 nm into the cytoplasm and bind to actin microfilaments via their amino-terminus [99]; smaller nesprins can translocate between the outer and inner nuclear membranes via the nucleopores [100]. It was proposed that the link with intermediate filaments and thus, hemidesmosome types of ECM-bound integrins, could be made via nesprin 3. Instead of a calponin homology domain, nesprin 3 contains a binding region for spectrin, a protein known to associate with intermediate filaments [101]. By interacting with different cytoskeleton networks, these nuclear envelope protein complexes could link the ECM, the cytoskeleton and the cell nucleus.

The connection with the inside of the cell nucleus is probably done via the nuclear lamina that associates with the inner nuclear membrane. The lamina is made of intermediate filament proteins, lamins A/C and B. Smaller nesprins located at the inner nuclear membrane can bind to lamin A/C and emerin, an inner nuclear envelope protein, via their spectrin-repeat rich KASH-domain [102]. In addition, SUN proteins can also bind to lamins A/C [103].

The nuclear lamina has been proposed to contribute to chromatin organization, and this region appears to be associated mostly with transcriptional silencing. Indeed, the heterochromatin regions of most chromosomes have been reported to interact with the lamina [104]. Specifically, lamin B receptor binds HP1, an important component of heterochromatin, and histone 3 methylated on lysine 9 [72,105]. Proteins like BAF (barrier to autointegration) that represses gene expression by inhibiting transcription activators [106] and GCL1 (germ cell less-1) that is necessary for chromatin condensation [107] were shown to bind to the lamina-binding protein LEM. Transcription factors MOK2 and Oct-1, known to repress certain genes, were reported to bind and colocalize with lamin A/C and lamin B, respectively [108,109]. The association of these transcription factors with genes within the lamina has been proposed to enable stable silencing. Indeed, the dissociation of these transcription factors from the nuclear periphery correlated with an increased expression of the genes they targeted initially [109, 110].

The nature of the DNA regions that associate with the lamina has been recently investigated. High resolution mapping of lamin B1-associated domains throughout the human genome revealed that 1,300 large DNA domains could bind the lamina [111]. Most of these domains were gene-poor regions of DNA; notably, 75% of gene deserts (large gene free regions) interacted with lamin B1. The amount of markers of active transcription was very low in promoters of the genes located in the lamin B1-associated domains with a few exceptions. These domains were usually well delineated by the presence of H3K27me3, the insulator protein CTCF, or CpG islands, and were anticipated to represent very specific genomic regions that are isolated from other regions to prevent continuation of heterochromatin formation and silencing. Due to the high concentration of Oct-1 binding motifs in the lamin B1-associated domains, it was proposed that Oct-1 might help target these domains to the nuclear lamina.

It is unlikely that all these DNA domains simultaneously bind to the nuclear lamina. Indeed, the binding of DNA to the lamina appears to be dynamic. For instance development in drosophila is accompanied with the modification of the contact of gene clusters with the nuclear lamina in correlation with their down- or up-regulation [112]. However, the factors that trigger the recruitment of gene regions to the lamina and the reason why some genes might be repressed or sometime expressed when tethered to the lamina [113–115] remain to be understood.

5.2 Mechanotransduction and biochemical signaling to the nuclear machinery

The cell nucleus has been identified as a compartment within which mechanotransduction could occur. One of the key players might be the protein emerin that could bridge the actin cytoskeleton and the nuclear actin polymer [116] via the lamina, thus providing tension forces within the cell nucleus [52]. In addition, there are regions localized throughout the nucleus where chromatin is resistant to DNase action. These regions correspond to anchorage points that occur at matrix-binding regions in the DNA [117]. The existence of such regions suggests that mechanical forces could potentially influence chromatin throughout the cell nucleus. Moreover, interactions between euchromatin and splicing factor speckles could provide additional anchorage points in the cell nucleus which, according to authors, could contribute to changes in chromatin structure via mechanotransduction [118].

Actin is considered to be an essential part of mechanotransduction by promoting the rigid intracellular architecture that participates in the reaction to stress-induced mechanical signals. Actin is involved in the binding of SWI/SNF complexes to nuclear structures [119], hence providing a possible explanation for how mechanotransduction could participate in the control of gene expression. Interestingly, components of ATP-dependent CRCs have been directly linked to mechanotransduction. Expression of Brg1, the ATPase of one of the SWI/SNF complex subfamilies, in SW13 adrenal adenocarcinoma cells deficient in BRG1 and BRM was shown to induce changes in cell morphology and actin-bundles resembling stress fibers

[120]. Knocking down BRG1 expression induced the formation of flat cells and an increase in stress-fiber like structures in a pancreatic tumor cell line [121]. Other subunits (e.g., INI1/SNF5, BAF57) of the SWI/SNF complexes have also been associated with changes in cell morphology and cytoskeletal protein expression and/or arrangement [122].

As expected, transcription factors are necessary, in addition to ATP-dependent CRCs, to regulate the transcription of genes coding for components of the cell matrix. For instance, transcription factor serum response factor (SRF) controls the expression of cytoskeletal genes upon Rho activation and of genes, in general, that are also regulated by SWI/SNF [123]. However, the activation of differentiation specific genes via SRF necessitates tissue specific coregulators (transcription factor MyoD for skeletal muscle differentiation genes, GATA4 for cardiac differentiation genes, myocardin for smooth muscle differentiation genes (reviewed in [123])). Thus, in the cell nucleus, two levels of control are required for tissue specific differentiation: the control of the expression of genes that are related to cell shape and mechanical stress, which might be done by general transcription factors like SRF, and the control of tissue specific genes that require coregulators specific for that tissue.

In view of current knowledge in differentiation-specific gene expression, we could envision that mechanotransduction is primarily linked to shape/adhesion and controls common sets of genes in cells that share similar tissue morphology, while defined transcription factors and coregulators and thus, biochemical signaling networks, permit tissue-specific gene transcription control.

6. Conclusion

In this review, we have emphasized the importance of taking into account the tissue context in order to better understand the nuances and complexity of the epigenetic control of gene expression. Certain authors have proposed that the mechanical environment of a particular tissue defines the cellular response to biochemical signals by influencing gene accessibility [52]. This is a plausible hypothesis that could involve moving chromatin regions to areas, like the splicing factor speckles, that are permissive for gene transcription and other areas, like the nuclear lamina, that are transcriptionally repressive. Indeed chromatin movement has been already documented [124], and it could provide a possible mechanism for gene relocation. Although gene relocation has been observed upon differentiation, it is not systematically happening to all genes that present alterations in their expression [85,86]. If gene movement does not occur, nuclear organization in the vicinity of the gene could also change (e.g., formation of larger and fewer splicing factor speckles; relocation of splicing factor speckles and centromeres as seen during phenotypically normal differentiation).

The factors that trigger nuclear reorganization have yet to be fully identified. Part of the reorganization could be induced by alterations in cell morphology. Furthermore, changes observed toward the end of the differentiation process, when morphogenesis has already occurred, could be due to modifications in cell-ECM interactions. The latter hypothesis is supported by the fact that following cell shape changes, the gene transcription machinery can activate the expression of genes coding for the ECM and/or its receptors and that components of SWI/SNF complexes have been associated with the control of expression of ECM molecules. Thus, the cell nucleus can alter the mechanical environment of the cell. In particular, the expression of SWI/SNF complex component Brg1 has been associated with changes in the transcription of genes that code for cell surface proteins and ECM interacting proteins [125]. These findings illustrate the concept of dynamic reciprocity proposed years ago [126], in which nuclear elements that receive signals from the ECM would, in turn, respond by altering the ECM.

It is difficult to separate mechanical from biochemical signaling to the cell nucleus. A number of molecules that participate in biochemical signaling cascades can be activated upon mechanical stress. For instance, the Rho-GTPases activated by mechanical stress can subsequently alter the actin and intermediate filament cytoskeletal networks [97] via the activation of secondary messengers (e.g., kinases) that could additionally modify a variety of signaling pathways. Moreover, changes in cell adhesion could affect directly the expression of certain genes by triggering transcription factor release or translocation to the cell nucleus.

The nuclear context in which gene expression control occurs does not depend only on incoming mechanical and biochemical signals. Interestingly, DNA sequences contribute to the specificity of transcription, notably in the context of differentiation. The binding-affinity of transcription factors is dependent on both the sequence of DNA response elements and the presence of cofactors. For instance, megakaryocytic acute leukemia (MAL) protein interacts with Brg1 to enable the activation of smooth muscle specific genes by promoting the binding of SRF to low affinity DNA binding sites [127]. Similarly, CRP1 and CRP2 cofactors are associated with SRF-GATA4 induction of smooth muscle specific genes [41].

The importance of DNA sequence in tissue specific gene expression is well illustrated by the example of the control of osteocalcin gene expression. Some DNA sequences favor nucleosome binding, while others prevent nucleosome binding thus, providing easy access for transcription factors (reviewed in [128]). In particular, the presence of nucleosome-positioning and nucleosome-excluding sequences in the promoter region of the osteocalcin gene has been shown to influence SWI/SNF-induced preferential nucleosome positioning [129]. However, the effect of SWI/SNF on nucleosomes also depends upon the binding of transcription factors to target sequences. Indeed, it was proposed that the binding of a transcription activator to its target sequence in the osteocalcin gene triggers the local remodeling by ATP-dependent CRCs necessary for transcription, thus emphasizing the importance of the preparation of the local chromatin environment during osteoblast differentiation [130].

The mechanisms of epigenetic control of gene expression are complex and more investigations are needed in order to bring a comprehensive picture of differentiation-specific gene expression. In addition to the necessary dialogue between the cell nucleus and the cellular environment, the integration of mechanical and biochemical signaling and a specific local and higher order nuclear organization, there are intriguing observations like the colocalization of sets of genes with similar expression levels [131,132] or genes involved in the same differentiation process [133,134] that need to be addressed. In some cases the colocalized genes belong to separate regions of the genome. In those particular cases, a possible explanation for such clustering is the looping of DNA regions [135]. The idea is that bringing genes together in a particular location of the cell nucleus might be determining for the level of expression of these genes. However, the signals responsible for such looping or gene positioning remain to be uncovered.

In summary, the interaction between a gene promoter and factors that control chromatin accessibility cannot be the sole responsible for the specificity of gene expression during tissue differentiation. Likely, one of the keys to the specificity of gene expression control is linked to the higher order nuclear organization established via the modulation of tissue architecture.

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Abbreviations

3D	three-dimensional
CRC	chromatin remodeling complex
ECM	extracellular matrix
ERE	ECM responsive element
HAT	histone acetylase
HDAC	histone deacetylase
HP1	heterochromatin protein 1
SRF	serum response factor
TSA	trichostatin A

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Fig. 1.

The structural continuum of the cell. A wide variety of reports has demonstrated that ECM fibers make contact with cell membrane receptors (black boxes) that are themselves in contact with the intracellular cytoskeleton networks (MF, actin microfilaments; MT, microtubules; IF, intermediate filaments). Some of the cytoskeleton elements make contact with proteins located in the nuclear envelope, which also bind to elements of the nuclear shell (lamina). Finally, the lamina interacts with chromatin via proteins that bind both lamins, the structural components of the lamina, and chromatin-associated proteins. A similar continuum also exists starting from cell-cell contacts (gray boxes).

Fig. 2.

Hierarchy in the process of ECM-induced gene transcription. The example of the casein gene expression associated with mammary epithelial differentiation enables us to build a possible scenario for ECM-directed gene transcription, although some of the detailed mechanisms in the hierarchy of gene transcription remain to be deciphered. One hypothesis could be that firstly, ECM binding to cell surface receptors (R) and possibly prolactin (PRL) signaling lead to the acetylation (Ac) of histones in the promoter region of the gene; secondly, histone hyperacetylation permits the recruitment of transcription factors (STAT5, C/EBPs) upon PRL binding to its receptor; thirdly, the binding of the transcription factors to the regulatory region of the gene triggers the recruitment of SWI/SNF complexes, hence leading to gene transcription (Tr).

Organization of the cell nucleus in a cell lacking functional differentiation

Organization of the cell nucleus in a functionally differentiated cell

Fig. 3.

Patterns of nuclear organization depending on the differentiation stage. A number of reports have shown that upon differentiation into functional tissues (e.g., tissues that have acquired the organization and function typically found in normally developed organs), major characteristics of nuclear organization that can be observed include large splicing factor speckles, the concentration of heterochromatin domains at the periphery of the nucleolus, and the presence of DNase sensitive chromatin at the nuclear periphery (right drawing). Before this differentiation stage or upon loss of this differentiation stage, this typical organization was not observed (left drawing).