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Review

Mechanotransduction and epigenetic control in autoimmune diseases

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ABSTRACT

Differentiation of epithelial cells is required to define tissue architecture and appropriate function of these cells is associated with a specific pattern of gene expression. DNA methylation, post-translational modification of histones and chromatin remodeling are nuclear mechanisms implicated in epigenetic control of gene expression. All factors relevant to tissue differentiation, including cell adhesion and shape, extracellular stimuli and transcriptional control, modulate gene expression and, thus, some of them are likely to impact on nuclear mechanisms of epigenetic control. The epithelial cells of salivary glands from Sjögren's syndrome patients display alterations in cell adhesion and shape. In this review, we summarize how these alterations are thought to lead to chromatin remodeling and, in doing so, bring about changes in transcriptional patterns. Additionally, we discuss how mechanotransduction in cells with impaired structural organization is implicated in modifying gene expression in these patients.

Contents

1. Introduction

Maintenance of and alterations in cellular function are linked to the existence of biochemical signaling pathways that convert extracellular cues into a cellular response. While our general understanding of these processes has increased enormously in the last 20–30 years, mechanisms

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of mechanotransduction remain poorly understood. Experimental evidence indicates that a physical continuum exists within cells, which directly connects the extracellular matrix (ECM) to the nucleus, whereby adhesion receptors (integrins) in the plasma membrane in conjunction with the cytoskeleton are thought to constitute this structure [1]. Cell shape is essential to maintain this continuum. Furthermore, changes in cell behavior depend on mechanical signals received by the cell from the environment [1]. Variations in both gene expression and cell shape are relevant in this context. For instance, changes in responses can be expected if a given cell type adheres to different substrates or may depend on whether these cells are cultured in standard two-dimensional (2D) or three-dimensional (3D) gel-ECM based systems [2]. Such altered gene expression cannot be explained simply as the consequence of independent responses in the cytoplasm, organelles or the nucleus. Rather, the responses must be viewed as the result of an operationally integrated system, within a common cellular environment. In this context, the pioneering work of Bissell et al. [3] has provided insights to differences between normal and pathological cell behavior in 3D cultures. In contrast to 2D cultures, such 3D cultures recapitulate more closely the situation of a cell *in vivo*.

The nature and characteristics of this physical continuum between subcellular compartments and ECM, as well as the transduction of mechanical signals have been extensively studied by Ingber et al. [4]. These authors proposed a tensional integrity model for cell architecture, which they coined "tensegrity". This model considers that structural stability is achieved by the integration of balanced continuous tension and components of discontinuous compression. The tensegrity concept is inspired by the view portrayed in Fuller's geodesic dome, where mechanical stress is uniformly distributed all over the dome surface by means of triangular elements known as struts. In the cellular context, this model proposes that the whole cell is a pre-stressed tensegrity structure. Tensional forces are transduced by cytoskeletal microfilaments, as well as intermediate filaments, and these forces are balanced by interconnected structural elements that resist compression, most notably, internal microtubule struts and ECM adhesions [4].

ECM adhesions, such as hemidesmosomes (HD) are involved in tensional integrity of epithelial cell architecture and generate a structural continuum from ECM to the nucleus [1]. In the plasma membrane, α6β4-integrin connects monomeric and polymeric ECM proteins with cytoplasmatic proteins, including plectin, BP180, BP230 and cytokeratin intermediate filaments, as well as nuclear envelope proteins of the nesprin family [1]. Focal adhesions can also participate in mechanotransduction mediated by additional integrin dimers, which interact with actin microfilaments, and via nesprin, bind nuclear envelope proteins (Fig. 1) [1]. Changes in cell shape, integrity or the position of adhesive elements and cell motility, among other factors, are able to generate forces of tension and compression that propagate to the nucleus, where they induce chromatin remodeling, resulting in activation or repression of gene expression [5].

Epithelial cells from salivary glands of Sjögren's syndrome (SS) patients display alterations in various components of this structural ECM–nucleus continuum [6–11]. In this review, we will focus on the adhesion complex termed HD, since it plays an essential role in ECM interactions with subcellular components, including the nucleus. The final consequence of this connection is the modulation of epigenetic control of gene expression.

2. Alterations in structural continuum of acini and ducts

The morphology of acinar and ductal cells is the consequence of the architectural organization of acini and ducts. The cell shape depends on the presence of structures that maintain cell polarity once established. In the apical region, tight junction (TJ) protein complexes generate cell polarity by restricting the flow of plasma membrane proteins between membrane regions. Thus, two structurally and functionally distinct membrane domains containing specific components are generated, namely the apical and basolateral cell poles. In the basal region, cell polarity is controlled by adhesion complexes that link the ECM to the actin cytoskeleton (focal adhesions) and intermediate filaments (HD) through integrin-type adhesion receptors [2]. The basal lamina (BL) is a particular ECM component connected directly to the cell via polymeric laminin and type-IV collagen networks, which are additionally cross-linked, predominantly by proteoglycans and nidogens. The pyramidal form of acinar and ductal cells emerges as the result of the interplay between cytoskeletal filament networks attached to cell–cell and cell–ECM adhesions [2].

ECM remodeling is regulated by MMPs and their cognate tissue inhibitors (TIMPs). Acinar and ductal cells of SS-patients show increased MMP3 and MMP9 together with decreased TIMP1 levels, which facilitate degradation of BL components [10]. The α6β4-integrin is redistributed within the basal plasma membrane and is then endocytosed upon loss of the laminin-332 connection, an essential component of HD organization (Table 1) [8,11]. In the apical domain, TJ alterations lead to apical pole disorganization with the concomitant loss of microvilli and an increase in the diameter of the acinar lumen [12]. Expression of ezrin, a microvilli protein, is increased and it relocalizes to the basal region of acini [13]. Nuclei from acinar cells lose their polarity and some acinar cells even lose BL attachment [6,9]. As a consequence, the cells undergo changes in shape. Taken together, these observations suggest, within the context of the tensional integrity model, that salivary epithelial cells of SS-patients are in a state of increased stress. The resulting alterations in the ECM-nuclear continuum trigger changes in gene expression of acinar and ductal cells, which in turn favor further modifications of the functional architecture. Indeed, studies from our group comparing salivary epithelial cells from SS-patients and controls by micro-array analysis detected a total of 528 genes with significant differences in mRNA expression levels [14]. Given that several of these genes are known to contain CpG-rich islands and potential methylation sites (see next section) it would appear reasonable to speculate that at least a fraction of these transcriptional alterations reflect changes in epigenetic regulation.

3. Epigenetic mechanisms

Gene expression depends on specific regulatory DNA elements upstream of the coding sequence, the activation state of different transcription factors and the structural organization of the chromatin. The latter variable is epigenetically controlled by a variety of modifications, including DNA methylation and post-translational histone modifications (acetylation, methylation, sumoylation, phosphorylation and ubiquitination) [15]. Such changes in chromatin structure may either repress or enhance gene transcription. Methylation occurs in a tissue-specific manner across the genome on C5′ of the cytosine ring in motifs known as CpG islands [16]. Methylation within the promoter or intron regions usually suppresses gene expression. Moreover, post-translational histone processing is a mechanism of epigenetic control that modifies the accessibility of transcription factors to gene sequences. Thus, the acetylation of histones H3 and H4, mediated by histone acetyl transferases (HAT), favors activation of transcription. Conversely, the methylation of histone H3 in lysine 9, mediated by methyl transferases, produces suppression of transcription [16]. Another mechanism of epigenetic control involves microRNAs (miRNAs). These are small RNAs of 19–25 nucleotides that reduce gene expression, either by precluding mRNA translation or by enhancing mRNA degradation. This is generally thought to be achieved by binding to the 3′UTR of the respective mRNAs [17].

Many studies have demonstrated that DNA methylation and histone deacetylation can synergistically regulate gene expression by means of mediator proteins like MECP2 (methyl CpG binding protein). The tight cooperation between these two mechanisms is important to maintain nuclear architecture. Therefore, changes in

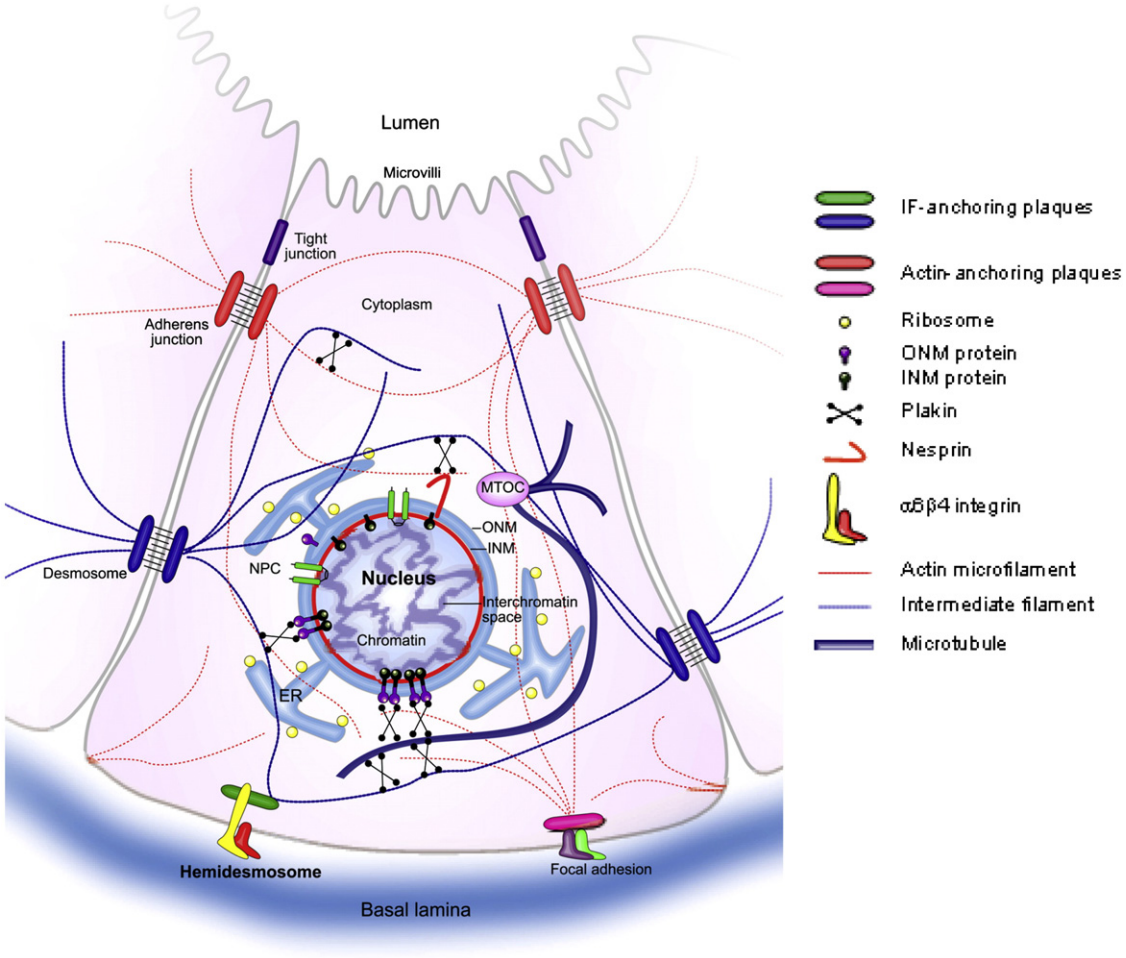

Fig. 1. Continuum structure of a salivary gland acinar cell. The schematic figure shows an epithelial acinar cell with a pyramidal shape and well-defined apico-basolateral polarity. Different components of the cytoskeleton (intermediate filaments, microfilaments and microtubules) are shown to interact with proteins like plakins. The cytoskeleton also connects cell–cell (desmosomes) and cell–ECM (hemidesmosomes and focal adhesion) complexes to the nuclear envelope, where both outer (e.g.: Nesprin) and inner (e.g.: Sun) nuclear membrane proteins are involved. Finally, this continuum is directly linked to chromatin via lamina proteins and hence connects the extracellular environment with the nucleus in a way that can alter gene expression without the need for diffusible intermediates. Alterations in the organization of this continuum are also likely to trigger epigenetic modifications in the genome. In SS-patients, altered cellular mechanotransduction signaling can be caused by changes in: 1. The extracellular environment, examples here being variations in the degree of deformation due to mechanical stress that is experienced by tissues or changes in extracellular matrix (ECM) composition that affect stiffness and biochemical properties; 2. Shape and organization of acinar cells; 3. Elements of the mechanotransduction system itself. INM: inner nuclear membrane, ONM: outer nuclear membrane, ER: endoplasmic reticulum, MTOC: microtubule-organizing complex, NPC: nuclear pore complex.
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epigenetic methylation patterns are likely to have profound effects on cellular function.

3.1. Epigenetics of autoimmune diseases

The participation of epigenetic mechanisms in disease processes was formerly established when DNA methylation was identified as an important factor in tumor biology [18]. Currently, impaired epigenetic control has been linked to the pathogenesis of various autoimmune diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis and SS [19,20]. For T and B-lymphocytes isolated from peripheral blood of SLE and RA patients global and gene-specific hypomethylations are detected [21–23]. Similar observations have been made upon analysis of synoviocytes from RA patients. However, some exceptions have been reported. For instance, the DR3 gene promoter is hypermethylated in these cells. Thus, the methylation status of genes is differentially regulated in a tissue-specific manner and changes can result in the development of a pathological cell phenotype [24]. Recent findings add yet another layer of complexity, since over-expression of miRNAs (miR-574 and MiR-768-2p) was shown to participate in the epigenetic control of gene expression in salivary glands of SS patients [25].

Moreover, environmental factors may modulate DNA methylation inducing changes in chromatin structure and gene expression of T-cells. This mechanism would result in immune system hyperactivity. In this context, demethylating drugs such as 5-azacytidine, procainamide and hydralazine can also induce lupus-like autoimmunity, both *in vitro* and *in vivo* [26–28].

Table 1
mRNA levels, protein levels and localization of type-I HD components in LSG cells from SS-patients in relation to control individuals.

	mRNA levels	Protein levels	Localization
α6 integrin	=	↑	Altered
β4 integrin	=	↓	Altered
BP230	↓	↑	Preserved
BP180	=	↓	Preserved
Laminin332	↑	↑	Altered

=, unchanged; ↑, increases; ↓ decreases. LSG: Labial salivary gland.

3.2. Mechanotransduction and epigenetics

As stated previously, HDs play an important role in shape and cell organization. Changes in architecture and organization of the nucleus are associated with changes in the physical continuum between ECM-cytoskeleton and nucleoskeleton. The cytoskeleton is linked to the nucleoskeleton through a specialized anchorage structure named "linker of nucleoskeleton and cytoskeleton complex" (LINC). Nesprin, sun and lamin protein families are components of LINC [29]. The carboxy-terminal end of the KASH domain of nesprin-3 binds to sun, a nuclear envelope integral membrane protein. Spectrin binds to the amino-end of nesprin-3 and also to cytokeratin intermediate filaments, thereby connecting the nucleus directly with HD [29,30]. Connections within the nucleus are mediated by nuclear lamina (lamins A, B1, B2 and C) and associated proteins like emerin. Lamin proteins are nuclear envelope proteins that may bind directly to chromatin or via intermediate proteins, including emerin, LBR LAP, among others [29] (Fig. 1). These associations modulate changes in chromatin structure. Therefore, the nuclear lamina can be viewed as a transducer of mechanical signals from the cell surface to the nucleus. Mechanical stress produced by cell adhesion to ECM is linked to an increase in H3 and H4 histone acetylation that favors the formation of transcriptionally active chromatin [5,29].

A typical example of mechanotransduction is lactotransferrin production in mammary gland cells. When these cells are grown in the absence of soluble factors, the ECM adopts a round shape and produces lactotransferrin. If culture conditions are changed, cells become flat and lactotransferrin synthesis is suppressed [31]. Integrin redistribution has been proposed to explain these shape changes. In contrast, β-casein production is regulated by both physical and chemical signals [5]. High levels of mRNA for lactotransferrin were detected with DNA microarrays in a cell fraction enriched in labial salivary glands (LSG) epithelial cells from SS-patients [14]. These changes were associated with alterations in the distribution of α6β4 integrin and acinar cell shape. The increase in lactotransferrin gene transcription may reflect activation by novel mechanotransduction signaling pathways. Moreover, in LSG from SS-patients, ECM remodeling may alter the transmission of mechanical forces and thereby generate these new signals.

4. Hemidesmosome organization

The HDs are protein complexes that mediate adhesion of epithelial cells to ECM. The HD core is composed of an α6β4 integrin dimer, which binds to laminin-332 through its extracytoplasmic domain and to plectin via its intracytoplasmic domain [32,33]. This complex is known as type-II HD. Additional binding of BP230 protein (cytoplasm) and BP180 protein (transmembrane) gives rise to type-I HD [34,35]. Both complexes interact with cytokeratin filaments. Altered expression of any of these proteins generates a pathological cell phenotype, as observed in epidermolysis bullosa and bullous pemphigoid. In the second case, the disease state is associated with production of BP230 and BP180 auto-antibodies. For both of the two aforementioned proteins, alterations in expression levels are detected in SS-patients [7]. Full length BP180 protein was decreased without any apparent change in mRNA levels [7] (Table 1). Rather, increased BP180 proteolysis mediated by ADAM17 to generate the LAD-1 fragment was held responsible for these observations.

4.1. Control of BP230 expression

BP230 is a cytosolic protein that belongs to the plakin family and binds intermediate filaments. BP230 is a splice variant of the dystonin gene that is located in chromosome 6. Its promoter region contains response elements for TGF-β and IFN-γ [36]. Analysis using bioinformatics in our laboratory identified two CpG islands in the promoter region, which may be subject to methylation and account for down-regulation of gene expression. Levels of BP230 mRNA in epithelial cells of SS-patients are significantly decreased compared to controls. Paradoxically, elevated BP230 protein levels are detected and the protein accumulates predominantly on the basal surface of acini [7]. Taken together, these observations suggest the existence of a complex regulatory network involving changes in gene expression, protein synthesis and degradation [7]. Increased presence of the BP230 protein and particularly increased presence in the basolateral membrane are likely to enhance interactions with elements of the structural continuum, between ECM and the nucleus, and thereby bring about further changes.

4.1.1. Epigenetic control

In SS-patients, the methylation index of CpG islands in the BP230 gene promoter of LSG is increased and may account for the observed reduction in BP230 mRNA [7]. For synoviocites obtained from damaged joints of RA patients, a decrease in global DNA methylation is detected [37,38], while for specific genes like DR3, an inducer of apoptosis, increased promoter methylation was reported and linked to an enhanced survival [24]. Global DNA methylation of LSG from SS-patients may be decreased as in RA and SLE, but specific genes appear to be hypermethylated, as is the case for BP230. Differential changes in promotor methylation may partly explain gene up- and down-regulation detected with DNA microarrays in epithelial enriched LSG samples from SS-patients. One of the top-ranked over-expressed genes in this study was MMP9 [14]. In lymphoma, MMP9 expression is up-regulated by promoter hypomethylation, while in U3A cells stimulated with IFN-γ, MMP9 expression is down-regulated due to sequestration of the histone acetyltransferase CBP/p300 by STAT-1α [39]. Both in normal and SLE T-cells, histone acetyltransferase CBP/p300 is sequestered by CREMα thus decreasing transcription of the IL2 mRNA [40–42]. Interestingly, infiltrating T-cells in salivary glands from SS-patients showed increased IL-2 levels [43] suggesting that different mechanisms modulating IL2 expression may operate in this disease.

As described for MMP9, CUL3 is similarly up-regulated in SS-patients, but by an alternative mechanism. In renal and prostate cancer, CUL3 expression is modulated by several miRNAs. Indeed, down-regulation of miRNAs MIR22, MIR23A, MIR181A and MIR181C induces CUL3 up-regulation [44]. Conversely, MIR23A is highly expressed in parotid exosomes from SS-patients [45].

4.1.2. Gene expression controlled by IFN-γ

BP230 expression can also be regulated by biochemical signals including IFN-γ. Among other cytokines, acinar and ductal cells, as well as inflammatory infiltrating cells from SS-patients produce IFN-γ. Evidence supporting the notion that IFN-γ regulates BP230 expression has been obtained in keratinocytes [46,47]. The IFN-γ signaling pathway induces activation of transcription factors IRF1 and IRF2, which recognize the response elements IRF and IGIE, both located in the BP230 gene promoter region. Upon binding of these factors, transcription of BP230 mRNA is suppressed [36,47].

5. Concluding remarks

An integrated view of biochemical and physical signals is needed for a better understanding of cellular mechanisms leading to epigenetic control of gene expression in autoimmune diseases. Physiological and patho-physiological processes should be addressed by studying the expression of key genes within the context of defined cell architecture. Many factors are involved in the genesis of autoimmune diseases and, thus, the approaches outlined are likely to be helpful in shedding light on these complex issues. Clearly, further work is needed to elucidate how the structural continuum between ECM and the nucleus is involved in autoimmune diseases.

Take-home messages

- Cell shape is important for gene expression.
- Mechanotransduction involves a complex network of protein–protein interactions that activates epigenetic mechanisms.
- The effect of the extranuclear environment on control of gene expression is critical for tissue-specific differentiation and, part of this effect is mediated by a structural continuum that connects the extracellular matrix with the nucleus.

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