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Review

Nuclear Structure-Gene Expression Interrelationships: Implications for Aberrant Gene Expression in Cancer[1]

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Abstract

There is long-standing recognition that transformed and tumor cells exhibit striking alterations in nuclear morphology as well as in the representation and intranuclear distribution of nucleic acids and regulatory factors. Parameters of nuclear structure support cell growth and phenotypic properties of cells by facilitating the organization of genes, replication and transcription sites, chromatin remodeling complexes, transcripts, and regulatory factors in structurally and functionally definable subnuclear domains within the three-dimensional context of nuclear architecture. The emerging evidence for functional interrelationships of nuclear structure and gene expression is consistent with linkage of tumor-related modifications in nuclear organization to compromised gene regulation during the onset and progression of cancer.

Introduction

The rules that govern nuclear architecture remain to be established. However, there is long-standing recognition that transformed and tumor cells exhibit striking alterations in nuclear morphology as well as in the representation and intranuclear distribution of nucleic acids and regulatory factors. The emerging evidence for functional interrelationships of nuclear structure and gene expression is consistent with linkage of tumor-related modifications in nuclear organization to compromised gene regulation during the onset and progression of cancer.

The contributions by multiple levels of nuclear organization to control of gene expression will be evaluated. We will focus on the conceptual and experimental basis for the hypothesis that parameters of nuclear structure support cell growth and phenotypic properties of normal and tumor cells by facilitating the organization of genes, chromatin remodeling complexes, transcripts, and regulatory factors within the three-dimensional context of nuclear architecture. We will address perturbations in mechanisms that direct regulatory factors to subnuclear sites that may contribute to aberrations in control of transcription and posttranscriptional processing of gene transcripts.

Components of Nuclear Organization Contributing to Control of Gene Expression

As the complexities of transcriptional control become increasingly evident, there is growing awareness that the fidelity of gene regulation necessitates coordination of transcription factor metabolism and the spatial organization of genes and regulatory factors. There is compelling evidence that multiple components of nuclear architecture contribute to the activation and suppression of genes. Mechanisms that are operative *in vivo* include transcription factor synthesis, nuclear import and retention, posttranslational modifications of factors, and the direction of factors to subnuclear sites that support gene expression. Factor turnover is subject to a series of regulatory steps. Plasticity is essential to accommodate the stringent requirements for gene expression in a biologically responsive manner. Remodeling of chromatin and nucleosome organization to accommodate protein-DNA and protein-protein interactions at promoter elements is key to physiological control of transcription. The reconfiguration of gene promoters and assembly of specialized subnuclear domains reflect the orchestration of both regulated and regulatory mechanisms.

From a biological perspective, each biochemical parameter of factor metabolism and activity requires control, and components of nuclear organization are linked to structure-function interrelationships that mediate the transcription and processing of gene transcripts. However, rather than representing regulatory obstacles, the complexities of nuclear biochemistry and morphology provide the required specificity for physiological responsiveness to a broad spectrum of signaling pathways to modulate transcription under diverse circumstances. It is therefore understandable why modifications in nuclear architecture and nuclear structure-function interrelationships accompany and appear to be causally related to compromised gene expression and DNA replication under pathological conditions.

Sequence Organization. Appreciation is accruing for the high density of information in both regulatory and mRNA coding sequences of cell growth and phenotypic genes. The modular organizations of promoter elements provide blueprints for responsiveness to a broad spectrum of regulatory cues that support competency for transient developmental and homeostatic control as well as sustained commitments to tissue-specific gene expression. Overlapping recognition elements expand the options for responsiveness to signaling cascades that mediate mutually exclusive protein-DNA and protein-protein interactions. Splice variants for gene transcripts further enhance the specificity of gene expression. However, the linear order of genes and flanking regulatory elements is necessary but insufficient to support expression in a biological context. There is a requirement to integrate the regulatory information at independent promoter elements and selectively utilize subsets of promoter-regulatory information to control the extent to which genes are activated and/or suppressed.

Chromatin Organization. Chromatin structure and nucleosome organization provide architectural linkages between gene organization and components of transcriptional control. During the past two decades, biochemical and structural analyses have defined the dimensions and conformational properties of the nucleosome, the primary unit of chromatin structure. Each nucleosome consists of approximately 200 bp of DNA wrapped in two turns around an octameric protein core containing two copies each of histones H2A, H2B, H3, and H4. A fifth histone, the linker histone H1, binds to the nucleosome and promotes the organization of nucleosomes into a higher-order structure, the 30-nm fiber. Nucleosomal organization reduces dis-

tances between promoter elements, thereby supporting interactions between the modular components of transcriptional control. Higher-order chromatin structure further reduces nucleotide distances between regulatory sequences. Folding of nucleosome arrays into solenoid-type structures provides a potential for interactions that support synergism between promoter elements and responsiveness to multiple physiological regulatory signals.

It has been well established that the presence of nucleosomes generally blocks the accessibility of transcription factors to their cognate binding sequences (1). Extensive analyses of chromatin structure have indicated that the most active genes exhibit increased nuclease hypersensitivity at promoter and enhancer elements. These domains generally reflect alterations in the classical nucleosomal organization and the binding of specific nuclear factors. Thus, DNase I digestion has been widely used to probe structures *in vivo* and *in vitro* based on the premise that chromatin accessibility to DNase I reflects chromatin access to regulatory molecules in the nucleus.

Changes in chromatin organization have been documented under many biological conditions in which modifications in gene expression are necessary for the execution of physiological control. Developmental and steroid hormone-related changes in the chromatin organization of the globin and ovalbumin genes served as the initial examples of chromatin remodeling linked to gene expression (2–4). Although these studies predated the identification and characterization of promoter elements and cognate-regulatory factors, they provided the foundation for examining the control of nucleosome placement as a component of transcriptional control.

Transient changes in chromatin structure of a human cell cycle-regulated histone H4 gene illustrate remodeling of chromatin organization to support competency for gene expression during cell cycle progression at the G_1-S-phase transition (5, 6). By combining DNase I digestion of isolated nuclei, indirect end labeling, and genomic sequencing, it was found that two regions in the proximal promoter of this gene exhibit cell cycle-dependent changes in chromatin structure. These regions contain key elements for both basal transcription and cell cycle regulation (7, 8).

Alterations in the chromatin organization of the bone tissue-specific and steroid hormone-responsive osteocalcin gene promoter during osteoblast differentiation provide a paradigm for remodeling chromatin structure and nucleosome organization that is linked to long-term commitment to phenotype-specific gene expression (9, 10). Transcription of the osteocalcin gene in late-stage, postproliferative osteoblasts (11, 12) is controlled by a modularly organized promoter with proximal basal regulatory sequences and distal hormone-responsive enhancer elements (13–22). Modifications in chromatin structure and nucleosome organization at these two promoter regulatory domains parallel competency for transcription and the extent to which the osteocalcin gene is transcribed in response to physiological mediators of basal expression and steroid hormones. This remodeling of chromatin provides a basis for the involvement of nuclear architecture in growth factor- and steroid hormone-mediated control of osteocalcin gene expression during osteoblast differentiation. Basal expression and enhancement of osteocalcin gene transcription are accompanied by two changes in the structural properties of chromatin. DNase I hypersensitivity of sequences flanking the basal, tissue-specific element and the vitamin D enhancer domain are observed (9, 23, 24). Together with changes in nucleosome placement (23), a basis for accessibility of transactivation factors to basal and steroid hormone-dependent regulatory sequences can be explained. In early-stage proliferating osteoblasts, when the osteocalcin gene is repressed, nucleosomes are placed in the proximal basal domain and in the vitamin D-responsive enhancer promoter sequences. Nuclease-hypersensitive sites are not present in the vicinity of these regulatory elements. In

contrast, when osteocalcin gene expression is transcribed postproliferatively and vitamin D-mediated enhancement of transcription occurs, the proximal basal and upstream steroid hormone-responsive enhancer sequences become nucleosome free, and these regulatory domains are flanked by DNase I-hypersensitive sites.

Among the studies that have established a role for nucleosomes regulating steroid hormone transcriptional activation, Archer *et al.* (25) have shown that in cell lines stably transfected with the MMTV[3] constructs, positioned nucleosomes found at the long terminal repeat sequence prevent binding factors such as NF-1 to its cognate site. After ligand activation, glucocorticoid receptor can bind to a site located proximal to the NF-1 binding sequence. A hormone-dependent DNase I-hypersensitive site is generated that renders the NF-1 element available for occupancy and competent for interactions with components of the transcriptional initiation complex (26).

Although it has been known for some time that regulatory activity of the vitamin D receptor requires chromatin remodeling to facilitate the accessibility of promoter-regulatory sequences, direct linkage of histone modifications with altered activities of steroid hormone-responsive promoter elements has been elusive. However, recent reports indicate that coactivators and repressors that interact with the vitamin D receptor include HATs and HDs (27). Modifications have been demonstrated in the acetylation of histones in nucleosomes associated with vitamin D receptor promoter sequences (27). These findings provide valuable insight into mechanisms linking changes in the placement and organization of nucleosomes with the control of transcription. Acetylation neutralizes positive charges of lysine residues and disrupts the association of HAT coactivator complexes with promoter-associated steroid hormone receptors. *In vivo* evidence is thereby provided for a key role of histone acetylation in steroid hormone-induced gene activation, and cofactor acetylation is implicated in hormonal signaling (27).

The Nuclear Matrix. As the intricacies of gene organization and regulation are elucidated, the requirement to resolve a fundamental biological paradox becomes increasingly evident. With a limited representation of gene-specific regulatory elements and a low abundance of cognate transcription factors, how can a threshold concentration for sequence-specific interactions be attained to support the initiation of transcription within nuclei of intact cells? Resolution is in part provided by contributions of the nuclear matrix to transcriptional control. It was this paradox, together with ultrastructural, biochemical, and molecular genetic evidence for involvement of nuclear architecture, that prompted the consideration of contributions by the nuclear matrix to control of gene replication and expression (28–31).

The anastomosing network of fibers and filaments that constitutes the nuclear matrix supports the structural properties of the nucleus as a cellular organelle and accommodates modifications in gene expression associated with proliferation and differentiation and changes necessary to sustain phenotypic requirements in specialized cells (30, 32–34). Regulatory functions of the nuclear matrix include but are by no means restricted to DNA replication (28), gene localization (35), imposition of physical constraints on chromatin structure that support the formation of loop domains, concentration and targeting of transcription factors (36–41), RNA processing and export of gene tran-

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[3] The abbreviations used are: MMTV, mouse mammary tumor virus; NF, nuclear factor; HAT, histone acetyltransferase; HD, histone deacetylase; SAGA, Spt-Ada-Gcn5-acetyl transferase; NuRD, nucleosome remodeling HD; CBP, CREB-binding protein; CREB, cAMP-responsive element-binding protein; AML, acute myelogenous leukemia; ALL, acute lymphocytic leukemia; PML, promyelocytic leukemia; MLL, mixed lineage leukemia; ACTR, activator of retinoic acid receptor; TRAM, thyroid receptor activator molecule; SRC, steroid receptor coactivator; RAC, receptor-associated coactivator; P/CAF, p300/CBP-associated factor; SMRT, silencing mediator of retinoic acid and thyroid hormone receptor; CBFα, core binding factor α; PEBPα, polyoma enhancer binding protein α; RUNX, runt-related.

scripts (42–46), posttranslational modifications of chromosomal proteins, and modifications of chromatin structure (47). Additional linkages between nuclear architecture and gene expression have recently been provided by biochemical and *in situ* immunofluorescence evidence showing that components of the RNA transcription complex are nuclear matrix associated and that nuclear matrix-associated sites of replication exhibit modified subnuclear distribution during the cell cycle (48).

Subnuclear Domains. An understanding of interrelationships between nuclear structure and gene expression necessitates knowledge of the composition, organization, and regulation of sites within the nucleus that are dedicated to replication, transcription, and processing of gene transcripts. During the past several years, there have been developments in reagents and instrumentation to enhance the resolution of nucleic acid and protein detection by *in situ* hybridization and immunofluorescence analyses. The combined application of isotopic and nonisotopic methods, together with a new generation of high-resolution techniques for quantitation and three-dimensional reconstruction from digitally captured images, is providing new insights into the intranuclear distribution of genes and regulatory factors (Fig. 1). We are beginning to make the transition from descriptive *in situ* mapping of genes, transcripts, and regulatory factors to visualization of gene expression from the three-dimensional perspective of nuclear architecture. Initially, *in situ* approaches were primarily used for intracellular localization of nucleic acids and proteins that were first shown by biochemical analyses to contribute to the control of gene expression. We are now applying high-resolution *in situ* analyses for the primary characterization of gene-regulatory mechanisms under *in vivo* conditions.

We are increasing our understanding of the significance of nuclear domains to the control of gene expression. These local nuclear environments generated by the multiple aspects of nuclear structure support developmental expression of cell growth and tissue-specific genes. Initially, control of gene expression and characterization of structural features of the nucleus were conceptionally and experimentally pursued as minimally integrated questions. However, independent pursuit of nuclear structure and function has occurred in parallel with the appreciation that several components of nuclear architecture are associated with parameters of gene expression or control of specific classes of genes. There is long-standing acceptance that the nucleolus is a site of ribosomal gene expression. The nuclear pore is recognized as a site for facilitating the import and retention of gene-regulatory factors as well as the export of transcripts (Ref. 49; reviewed in Ref. 50). SC35 domains have been studied extensively from the standpoints of RNA splicing and the dynamic recruitment of transcript processing factors (44, 51–54). Subnuclear sites where transcription (55) and replication (48) occur have been identified. PML bodies and coiled bodies have been associated with control of gene expression and undergo modifications in structure and potentially function in cancer cells (52, 56). Because these components of nuclear architecture have been defined by *in situ* immunoreactive proteins and/or ultrastructural imaging as well as by biochemical criteria, a viable basis has been established for linkage with gene-regulatory mechanisms.

Mechanisms Mediating Nuclear Structure-Function Interrelationships

The accumulating evidence for association of genes and regulatory proteins with components of nuclear architecture, together with long-standing examples of gene rearrangements and remodeling of chromatin organization, reflects functional interrelationships between nuclear structure and gene expression at multiple levels. Particularly significant from a functional perspective, there are changes in the association and subnuclear distribution of nucleic acids and regulatory factors that parallel and may be causally related to requirements for replication and transcription. However, validating linkages between the architectural organization of regulatory machinery with intranuclear distribution of genes and regulatory factors necessitates an understanding of the mechanisms that control modifications in the representation, conformation, and subnuclear trafficking in relation to biological activities.

Genomic Reconfiguration. The most well-documented and mechanistically understood perturbations in nuclear organization are modifications in genomic organization, gene amplification, and rearrangements of gene loci that are prevalent in cancer. Much remains to be established before the sequence of events that controls gene amplification and recombination is fully defined. However, significant progress has been made in identifying and characterizing the enzymology of replication and recombination (reviewed in Refs. 57 and 58). Components of mechanisms that are involved in cleavage, ligation, and editing are understood for events that are associated with genomic, viral, and other episomal sequences.

Chromatin Remodeling. During the past several years, there have been major advances in the ability to experimentally address the molecular mechanisms that mediate chromatin remodeling (Fig. 1). This is, to a significant extent, attributable to an increased understanding of the enzymatic control of nucleosome structure and organization. ATP-dependent chromatin remodeling enzymes have been identified, and there is increased insight into the activities of the enzymes that covalently modify histone proteins.

A family of SWI/SNF-related proteins and protein complexes has been described in yeast and mammalian cells (1, 59–62) that promotes transcription by altering chromatin structure (61). These ATP-dependent alterations render DNA sequences containing regulatory elements accessible for binding cognate transcription factors and mediate protein-protein interactions that influence the structural and functional properties of chromatin. Although the mechanisms by which these complexes function remain to be formally defined, there is general agreement that the increase in DNA sequence accessibility does not require the removal of histones (63–65). Rather, multiple lines of evidence suggest that remodeling of the nucleosomal structure involves alterations in histone-DNA and/or histone-histone interactions. All chromatin remodeling complexes that have been reported to date include a subunit containing ATPase activity (59, 60, 66–73) and have been shown to be critical for modifying nucleosomal organization. Because these subunits share significant homology, it has been suggested that they belong to a new family of proteins with a function that has been highly conserved throughout evolution (61).

Posttranslational modifications of histones have been implicated in the physiological control of chromatin structure for the past three decades. However, recent findings have functionally linked histone acetylation and phosphorylation with changes in nucleosomal structure that alter accessibility to specific regulatory elements (1). For example, acetylation of the amino-termini of nucleosomal histones has been directly correlated with transcriptional activation. Moreover, it has been observed that core histone hyperacetylation enhances the binding of most transcription factors to nucleosomes (74–76). Nevertheless, there have been reports that chromatin hyperacetylation blocks steroid hormone transcriptional enhancement and steroid-dependent nucleosomal alterations (77–79). Within this context, it was recently shown that hyperacetylation of nuclear proteins alters the chromatin organization of the bone tissue-specific osteocalcin gene promoter in a manner that prevents vitamin D-mediated transcriptional up-regulation. By combining nuclease accessibility, indirect end labeling, and ligation-mediated PCR analysis, it was demon-
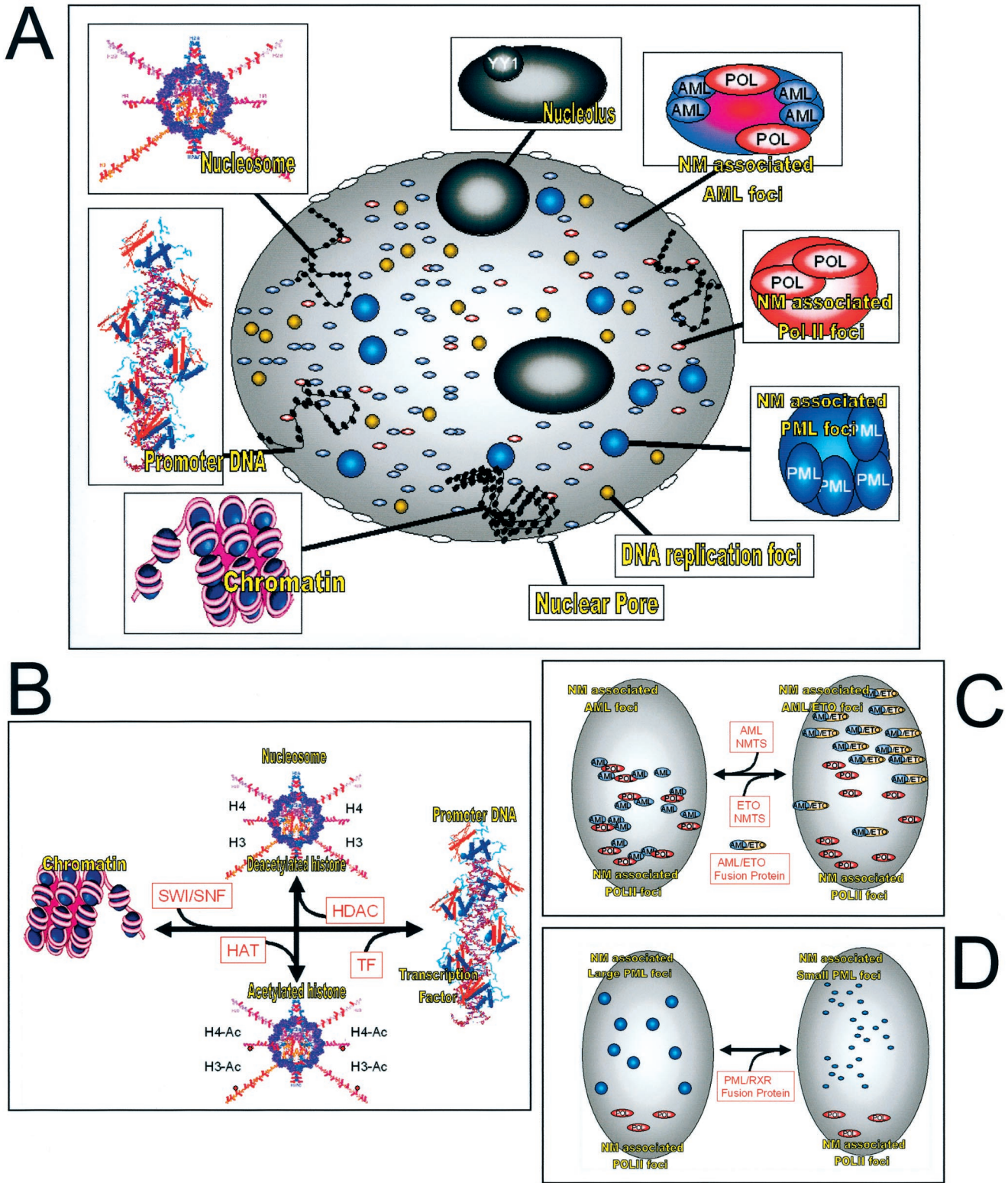
Fig. 1. Modified nuclear structure-function interrelationships in cancer. *A* schematically illustrates the principal components of nuclear architecture that may undergo modifications linked to altered gene expression in transformed and tumor cells. *Insets* on the *left* depict the three principal levels of nuclear organization that support packaging of DNA (gene promoter organization, nucleosomes, and chromatin). *Inset panels* on the *right* illustrate subnuclear foci that support control of gene expression. Each may exhibit pronounced modifications in composition and/or organization in tumor cells that are linked to perturbations in gene expression (nuclear pores, DNA replication foci, PML foci, RNA polymerase II foci, AML foci, the nucleolus, and chromatin remodeling complexes). *B* is a diagram of the enzymatic modifications in chromatin structure that mediate remodeling to accommodate requirements for competency to bind regulatory factors and support transcription. SWI/SNF factors control ATP-dependent nucleosomal reorganization. Chromatin remodeling is facilitated by the dynamic acetylation and deacetylation of H4 and H3 histones that modify histone-DNA and histone-histone interactions. These reversible posttranslational modifications of histones are catalyzed by HDACs and HATs. *C* and *D* are diagrams illustrating modifications in the subnuclear organization of gene-regulatory complexes that result from chromosomal translocations in tumor cells, resulting in alterations in intranuclear trafficking to subnuclear domains. The fidelity of both factor trafficking and gene expression is compromised. *C* shows association of AML factors with transcriptionally active domains. AML/ETO foci are not associated with the transcriptionally active form of RNA polymerase II and are transcriptionally inactive. This nuclear reorganization occurs in AML with the 8;21 chromosomal translocation. *D* shows the reorganization of PML foci that are characteristic of promyelocytic leukemias. There is a dramatic transition from a limited number of large foci in normal hematopoietic cells to an increased number of smaller foci in tumor cells.

strated that protein-DNA interactions that promote the formation of a distal DNase I-hypersensitive site do not occur under conditions of hyperacetylation (79). Similarly, Bresnick *et al.* (77) have reported that butyrate treatment, which results in chromatin hyperacetylation by inhibiting HD activities, abolished glucocorticoid hormone-dependent formation of the nuclease-hypersensitive site and blocked transcriptional induction of the MMTV long terminal repeat sequence. In contrast, Bartsch *et al.* (80) found that by decreasing the concentrations of HD inhibitors, only moderate acetylation can be obtained. Moderate acetylation leads to enhanced transcription from the MMTV promoter in the absence of hormone and potentiates transactivation by either glucocorticoids or progestins. Because these inducing inhibitor concentrations lead to a type of nucleosomal DNase I hypersensitivity similar to that caused by hormone treatment, it was suggested that moderate acetylation of core histones activated the stably integrated MMTV promoter by mechanisms involving chromatin remodeling similar to that generated by the inducing hormones.

A major breakthrough in experimentally addressing the physiological role of histone acetylation came with the recent purification and subsequent cloning of the catalytic subunits of yeast and mammalian nuclear HATs. Gcn5 encodes a 55-kDa protein in yeast that acetylates both histones H3 and H4 (81). It has been reported that Gcn5 is part of a large (1.8-MDa) protein complex designated SAGA (82), which includes proteins that are also present in complexes involved in transcriptional regulation (1). Recruitment of SAGA by transcriptional activators results in localized acetylation of nucleosomal substrates *in vivo* and *in vitro* (82). Importantly, the transcriptional stimulatory activity of the recruited SAGA complex is dependent on its HAT activity (82).

Other proteins that contain nuclear HAT activity are p300 and its related homologue, CBP (83). These two proteins function as transcriptional adaptors that interact with several transcription factors including cAMP-responsive element-binding protein, jun, Fos, Myb, and Myo D, and with nuclear steroid hormone receptors (84–93). In addition, human TAFII250 and yeast TAFII250 have HAT activity (94). TAFII250 is part of the transcription factor IID complex that recognizes the TATA sequence at the promoter region of most genes and initiates the formation of transcription preinitiation complexes. The presence of HAT activity in this complex suggests that histone acetylation may be a requirement for transcription factor interaction with nucleosomal DNA.

Alterations in mechanisms that mediate the enzymology of histone modifications in cancer cells support involvement in the onset and/or progression of tumorigenesis. Relative examples are accumulating that implicate perturbations in both the acetylation and deacetylation of histones, and the known biochemical targets are increasing. Very importantly, in recent years, a direct correlation between abnormal histone acetylase activity and the potential for cell transformation has been found. Recent studies show the recruitment of CBP by Smad2/3 proteins in the transforming growth factor β signaling pathway (95, 96). There is evidence that mutation of the players in this pathway (*e.g.,* Smad2, Smad4, and p300) leads to the development of cancer (*e.g.,* colorectal carcinomas; Refs. 96 and 97).

P/CAF, another protein that contains HAT activity, is highly homologous to both the yeast Gcn5 and the human homologue hGcn5. P/CAF interacts with p300 and CBP to form functional complexes (98). These findings are consistent with the formation of complexes containing multiple HAT activities that can accommodate requirements for specificity of histone acetylation under different biological conditions.

Nuclear HAT activity appears to be critical during steroid hormone-dependent transcriptional activation. It has been reported that coactivation factors that include ACTR and SRC-1 recruit CBP/p300 and P/CAF to ligand-bound nuclear hormone receptors. SRC-1 and ACTR (and the related molecules RAC3, AIB1, and TRAM-1) have HAT activity. This is an example of multiprotein complexes containing different HAT activities that contribute to modifications of nucleosomal histones that are functionally linked to competency for chromatin remodeling that occurs during ligand-dependent transcriptional regulation (99). Interestingly, AIB1 is expressed at high levels in breast cancer, but not in normal breast tissue. In addition, BRCA1 and BRCA2 are tumor suppressor genes involved in familial breast cancers. Both are thought to have roles in transcription, cell cycle control, and DNA repair. BRCA1 associates with CBP, whereas BRCA2 has HAT activity (100, 101). Thus, HAT activity may play a role in the function of these tumor suppressor proteins.

For histone acetylation to be a physiologically relevant component of transcriptional control, there is a requirement for a cellular mechanism to reverse this posttranslational modification. HDs that enzymatically remove acetate moieties from histone proteins have been studied extensively during the past several years. Multiple forms of this enzyme have been identified and characterized in several organisms (102–106). The mammalian forms designated HDAC1, HDAC2, and HDAC3 were found to be homologous to the yeast form designated Rpd3 (107). HDAC1 and HDAC2, but not HDAC3, are large multiprotein complexes containing corepressor molecules such as mSin3, N-CoR, or SMRT as well as the proteins SAP18, SAP30, RbAp48, and RbAp46 (107). The Sin3A-N-CoR-/SMRT-HDAC1/2 complex and other complexes associated with HD activity can be recruited specifically to gene promoter-regulatory sequences by unliganded nuclear steroid receptors (108, 109). Thus, SAP30, which binds mSin3 and N-Cor, is required for N-CoR/mSin3-mediated repression of hydroxytamoxifen-bound estrogen receptor (110, 111) but not unliganded retinoic acid receptor and thyroid receptor. It has been shown that decreasing the levels of intracellular N-CoR corepressors can lead to tamoxifen resistance in breast cancer (112).

HDAC1 and HDAC2 are also found in another protein complex designated NuRD (113). Thus, human NuRD complexes contain not only ATP-dependent nucleosome disruption activity but also HD activity that is usually associated with transcriptional repression. The deacetylation is stimulated by ATP on nucleosomal templates, suggesting that nucleosome disruption facilitates the access of the deacetylase to its substrates. One subunit of NuRD was identified as MTA1, a metastasis-associated protein with a region similar to N-CoR, indicating that ATP-dependent chromatin remodeling can participate in transcriptional repression by assisting repressors in gaining access to chromatin. It has been determined that the levels of MTA1 mRNA and the corresponding protein correlate with the metastatic potential of several cancer cells (114–116). Although no direct evidence has been reported indicating that higher levels of MTA1 are required for metastasis to occur, HD complexes have been shown to interact with Rb to repress transcription (117–119). The mSin3-associated deacetylases have also been demonstrated to be involved in acute promyelocytic leukemia (120–122). These results led to the speculation that aberrant regulation of NuRD activity may alter the expression of its target genes, leading to metastatic growth potential.

It has been reported recently that HDAC1 and HDAC2 and the histone-binding proteins RbAp46 and RbAp48 form a core complex shared between NuRD and Sin-HD complexes (123). A novel polypeptide highly related to MTA1, MTA2, and the methyl-CpG binding-domain-containing protein MBD3 were found to be subunits of the NuRD complex. MTA2 modulates the enzymatic activity of the HD core complex. MBD3 mediates the association of MTA2 with the core HD complex. MBD3 does not directly bind methylated DNA, but it is closely related to MBD2, a protein that binds to methylated DNA and has been reported to contain demethylase activity. MBD2 inter-

acts with the NuRD complex and directs the complex to methylated DNA. These results indicate that NuRD may silence genes by DNA methylation (123). Interestingly, MBD2 has also been identified as a colon cancer antigen (124), suggesting a potential involvement of NuRD-like complexes in colon cell transformation.

Taken together, these findings indicate that in general, histone acetylation and deacetylation correlate with activation and suppression of gene expression, confirming that remodeling of chromatin structure and nucleosome organization is obligatory for physiological control of transcription. Alterations in mechanisms that mediate the enzymology of histone modifications can support changes in regulatory events that are involved in the onset and/or progression of tumorigenesis.

Nuclear Matrix-associated Transcriptional Domains. The subnuclear distribution of transcription factors appears to be important for the fidelity of transcriptional control. As mechanisms that mediate the various components of transcription factor trafficking are pursued, additional regulatory parameters of gene expression are being defined. Nuclear import was the first aspect of transcription factor trafficking to be addressed. Consequently, the biochemistry of transcription factor entry to the nucleus is now understood in relation to the structural and functional properties of the nuclear pore within the context of linkages between morphology, biochemistry, and regulatory activities. More recently, attention has turned to nuclear retention and export of regulatory factors from the standpoints of contributions to factor activity as well as the regulated and regulatory aspects of subcellular factor distribution.

The AML transcription factors (also referred to as CBFα, PEBP2α, and RUNX proteins) that support hematopoietic (125–134) and bone tissue-specific (16, 18) gene expression have provided a paradigm for directly examining mechanisms that target regulatory factors to subnuclear sites that support transcription. Functional biochemical and *in situ* immunofluorescence analyses of AML deletion and point mutations have provided an indication of how these transcription factors are directed to nuclear matrix-associated intranuclear domains. It has been shown that: (*a*) sequences required for targeting AML factors to the nuclear matrix reside in a 31-amino acid segment within the COOH terminus that is physically distinct from the nuclear localization signal; (*b*) nuclear matrix association of AML factors is independent of DNA binding activity; (*c*) the principal active and inactive splice variants of the AML transcription factors are differentially localized within the nucleus; and (*d*) the nuclear matrix targeting signal of AML factors functions autonomously. These findings demonstrate that at least two trafficking signals are required for subnuclear targeting of the AML transcription factors; the first supports nuclear import, and the second mediates association with the nuclear matrix. Recent results provide insight into the functional consequences of directing transcripton factors to the nuclear matrix. Invoking the rationale that guilt by association is biologically relevant, it has been shown that 31-amino acid nuclear matrix targeting sequence of the AML transcription factor targets the regulatory protein to a subnuclear domain that supports transcription. Colocalization of AML with transcriptionally active RNA polymerase II has been demonstrated, as have requirements for a functional DNA binding domain and ongoing transcription (135). Functional implications of subnuclear localization of AML transcription factors are more directly provided by studies that establish that targeting to the nuclear matrix-associated sites is obligatory for maximal transactivation activity (35).

From a general biological perspective, there is growing appreciation of sequence requirements for intranuclear targeting of steroid hormone receptors [estrogen receptor (136) and glucocorticoid receptor (137–139)] as well as ubiquitous [YY1 (140)] and selectively utilized [PIT1 (136) and PML (141)] regulatory proteins. Evidence for a nucleolar targeting domain in parathyroid hormone-related protein (142) and YY1 (140) has been reported. Taken together, we are increasing our understanding of mechanisms that mediate the assembly of regulatory components to initiate and sustain transcription within the context of nuclear architecture.

Integration of Regulatory Cues. We are gaining insight into the integration of regulatory signals that control expression by mediating cross-talk between components of signaling pathways that are operative within the three-dimensional context of nuclear architecture. There is growing appreciation that mechanisms modulating chromatin remodeling require the involvement of higher-order nuclear structure (143). The human SWI/SNF and mouse BAF complexes have been shown to be associated with the nuclear matrix (144, 145). Functional implications are provided by the observation that the BAF complex is only associated with the nuclear matrix after mitogenic stimulation of T lymphocytes when genes controlling competency for proliferation and cell cycle progression are activated (145). In resting cells, the BAF complex is primarily present in the soluble nuclear fraction. However, immediately after the induction of proliferation (10 min, 90% of the BAF complex is found tightly associated with the nuclear matrix fraction (145). The specific parameters of chromatin remodeling that are linked to nuclear matrix binding of BAF as well as the cause and/or effect relationships between BAF activity and parameters of nuclear organization will unquestionably be informative.

Further insight into linkages between nuclear architecture, cytoarchitecture, and the regulation of chromatin structure is provided by recent reports that actin-related proteins are components of chromatin remodeling complexes (62, 145–147). It has been suggested that these actin-related and actin-binding proteins may provide a basis for interactions between chromatin remodeling complexes and cytoskeletal structures involving actin. This suggestion is further supported by observations that both human SWI/SNF complexes and the *Drosophila* BRM complexes not only contain an actin-related protein (BAF 53 in human cells and BAP 55 in *Drosophila*) but also contain actin (145, 147). Furthermore, regions of BAF that contact myosin, proliferin, and other actin-binding proteins are similar to actin (145). The possibility can therefore be considered that such interactions are important for SWI/SNF function.

Linkages of Aberrant Nuclear Organization with Modified Gene Expression in Cancer. Interrelationships of nuclear structure with gene expression are illustrated by the modified subnuclear organization of genes and regulatory factors in cancer (Fig. 1). Transformed and tumor cells exhibit striking alterations in nuclear morphology as well as in the representation and intranuclear distribution of nucleic acids and regulatory factors. In both leukemias and solid tumors, there are modifications in components of nuclear architecture that are involved in control of gene expression. Examples include mutations of the AML, ALL, and PML loci in leukemias that accompany changes in gene expression and the subnuclear organization of encoded transcription factors. In colon tumor cells, modifications in the subnuclear distribution of the APC factor are observed (148). These factors are associated with nuclear architecture, and the alterations in relationships with nuclear architecture appear to be related to changes in gene control. Identification of nuclear import signals in transcription factors and the recent characterization of intranuclear targeting signals that direct regulatory proteins to subnuclear domains that support transcription reinforce linkages between nuclear structure and aberrant transcriptional control. These observations provide an opportunity to develop high-resolution *in situ* immunofluorescence analysis to diagnose and stage tumors and to monitor remission, relapse, and effectiveness of treatment. There is a potential for developing therapeutics that are directed to subnuclear sites that support specific components of gene expression.

Alterations in nuclear organization are the hallmarks of cancer cells. The gene locus encoding the AML transcription factor is frequently the target of chromosomal translocations in human leukemia. Replacement of the chromosome 21-encoded intranuclear trafficking signal by a targeting signal from chromosome 8 redirects the t(8;21) translocation-fusion protein to unique subnuclear sites. Thus, intranuclear targeting of the AML transcription factor may be abrogated because of gene rearrangements in leukemic cells. Fidelity of transcriptional control may involve the localization of gene-regulatory proteins to the correct subnuclear region (149).

PML bodies are another example of nuclear structures that are associated with the nuclear matrix and modified in leukemia cells (52). In normal cells, the PML protein resides in discrete PML bodies. However, in promyelocytic leukemic cells, the PML protein is genetically rearranged and dispersed throughout the nucleus (52, 150). A further example of chromosomal translocations involving a locus encoding a nuclear matrix-associated transcription factor occurs in acute lymphocytic leukemia (ALL/MLL). Recently, a translocation has been described in which the ALL/MLL protein is fused with a HAT. This chimeric protein may promote leukemia by modifying histone acetylation of specific genomic regions. Consequential modifications in the intranuclear distribution of factors encoded by the rearranged ALL locus occur (151–153), although the chimeric transcription factors remain nuclear matrix associated (154). Hence, these results suggest that perturbations in subnuclear location of regulatory proteins may be related to modifications in gene expression that are linked to leukemias. Additionally, tumor-associated modifications have been observed in nuclear domains that support the processing of transcripts, the intranuclear organization of Rb and DNA replication foci, and the nucleocytoplasmic shuttling of p53 that has been functionally linked to association of Mdm2 with the nucleolus (155–157).

Perspectives and Future Directions

It is well documented that components of nuclear architecture contribute both structurally and enzymatically to control of gene expression. The historic distinction between morphology and functional activity has given way to acceptance that the organization of nucleic acids and regulatory proteins within the cell nucleus is linked to biological control and aberrant gene expression that occurs during the onset and progression of cancer. A road map of regulatory events that mediate transcriptional control within the three-dimensional context of nuclear architecture has been established. A bidirectional exchange of gene transcripts and regulatory factors between the nucleus and cytoplasm as well as between regions and structures within the nucleus has been defined. Responsiveness to a broad spectrum of signaling pathways is being pursued experimentally along with mechanisms that target regulatory factors to subnuclear sites where the machinery for gene expression is assembled, rendered operative, and/or suppressed. However, it would be naive to anticipate a single target for tumor-related alterations in the organization of genes, transcripts, and regulatory machinery. Rather, the challenge we now face is to experimentally define the mechanisms that mediate each component of gene regulation in relation to nuclear structure-function relationships. There is growing recognition that placement of regulatory components of gene expression must be temporally and spatially coordinated to optimally support biological control. The consequences of breaches in nuclear structure-function interrelationships that have been observed in an extensive series of tumors provide options for high-resolution diagnosis and targeted therapies.

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