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Transcriptional Control Within the Three-Dimensional Context of Nuclear Architecture: Requirements for Boundaries and Direction

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Abstract Evidence is accruing that the architectural organization of nucleic acids and regulatory proteins within the cell nucleus support functional interrelationships between nuclear structure and gene expression. The punctate distribution of several transcription factors has provided several paradigms for pursuing mechanisms that direct these regulatory proteins to subnuclear sites where gene activation or suppression occurs. Sequences that are necessary and sufficient to direct regulatory proteins to transcriptionally active nuclear domains have been identified. Mutations that disrupt intranuclear targeting signals lead to modified subnuclear distribution of transcription factors and aberrant expression in tumor cells. J. Cell. Biochem. Suppls. 32/33:24–31, 1999. © 1999 Wiley-Liss, Inc.

Key words: AML/CBFA; gene expression; intranuclear targeting; subnuclear domains

Transcriptional control requires linkage of signaling pathways that exchange regulatory information between the nucleus and cytoplasm as well as within the cell nucleus. Gene promoters provide regulatory infrastructure by functioning as blueprints for responsiveness to the flow of cellular regulatory signals. Selective utilization of the information supports transient developmental and long-term phenotypic expression of genes. As the regulatory sequences and factors that activate or suppress transcription are identified and characterized, several fundamental paradoxes surface. How can a gene with a single promoter meet the selective requirements for expression under diverse biological circumstances? How, with a limited repertoire of promoter elements and cognate regulatory factors, can a threshold be attained to initiate or downregulate transcription in nuclei of intact cells? How are the regulatory activities that reside at independent promoter domains integrated?

There is increasing acceptance that components of nuclear architecture support the organization and sorting of regulatory information in a manner that facilitates selective utilization. The primary level of nuclear organization, the representation and ordering of genes and promoter elements, provides alternatives for physiological control. The modular arrangement of regulatory elements and overlap of regulatory sequences within promoter domains and the multipartite composition of regulatory complexes increases options for responsiveness. Chromatin structure and nucleosome organization reduces distances between regulatory sequences, facilitates crosstalk between promoter elements, and renders elements competent for interactions with positive and negative regulatory factors. The components of higher-order nuclear architecture that includes nuclear pores, the nuclear matrix and subnuclear domains contribute to the subnuclear distribution and activities of genes and regulatory factors.

There is emerging recognition that nuclear structure and function are causally interrelated. With accruing evidence for organization

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of nucleic acids and regulatory proteins into subnuclear domains that are associated with components of nuclear architecture, the perception of a dichotomy between nuclear architecture and control of gene expression is no longer justifiable. Rather, the challenges now being faced are to design experiments to define mechanisms that direct genes and regulatory factors to sites within the nucleus where localization integrates regulatory parameters of gene expression and establishes boundaries between regulatory complexes that are necessary for fidelity of regulatory activity.

In this article, we focus on the involvement of nuclear architecture in transcriptional control with the appreciation that there is compelling evidence for contributions of nuclear structure to the stringent regulation of DNA replication [Leonhardt et al., 1998; Ma et al., 1999; Wei et al., 1998; Lamond and Earnshaw, 1998], post-transcriptional processing of gene transcripts [Wei et al., 1999; Iborra et al., 1998; Carter et al., 1993; Clemson et al., 1996; Nickerson et al., 1995; Pombo and Cook, 1996; Chen et al., 1994; Jackson et al., 1998], as well as the import, retention and export of nucleic acids and regulatory proteins [Silver et al., 1984; Ullman et al., 1997].

LINKAGE OF NUCLEAR ARCHITECTURE WITH COMPONENTS OF GENE EXPRESSION: A CONCEPTUAL AND EXPERIMENTAL BASIS FOR BOUNDARIES AND DIRECTIONS

Evidence for Architectural Organization of Genes and Regulatory Factors

From an historical perspective, it was recognized at the beginning of the twentieth century that the genome is packaged as chromosomes, providing the first indication that regulatory information is organized as discrete structures within the cell nucleus. The observation that chromosomes are "decondensed" to "interphase chromatin" at the completion of mitosis strikingly indicated that remodeling of a prominent nuclear structure occurs during a biologically relevant transition. The reorganization of the nucleolus in a cell cycle-dependent manner similarly revealed the plasticity of ribosomal gene packaging. The unique organization of DNA in lampbrush and in polytene chromosomes exhibited specialized architectural features of gene organization to support specific requirements for gene expression under biological conditions. Chromosome fragmentation and reorganization in cancer, and more recently in neurological disorders, provided evidence for interrelationships between altered chromosome organization when fidelity of gene expression is compromised.

The discovery 25 years ago that chromatin is organized into "beads-on-a-string" structures, designated nucleosomes that are structurally remodeled to accommodate requirements for transcription, further emphasized the extent to which architectural organization of genes is linked to functional activity. Characterization of higher-order chromatin organization also demonstrated the intricacies of gene packaging and chromatin remodeling that accommodate activation and suppression of expression [reviewed in Zlatanova and van Holde, 1992; Imbalzano, 1998; Ito et al., 1997; Giese et al., 1995]. Taken together, these findings establish interrelationships between structural properties of genes and chromosomes with competency for transcription. Equally important, the requirement for modifications that mediate regulation of chromosome and chromatin remodeling in response to a broad spectrum of conditions became apparent. The initial documentation that reversible post-translational modifications of histones that included acetylation and phosphorylation are associated with alterations in gene activity and with remodeling of chromosomes and chromatin provided a basis for exploring mechanisms that control chromosome, chromatin and nucleosome organization. The recent identification and characterization of proteins that catalyze histone acetylation, deacetylation, phosphorylation [reviewed in Davie and Chadee, 1998], as well as the SWI/SNF-related proteins [Peterson et al., 1998; Imbalzano, 1998; Kwon et al., 1994; Cote et al., 1994; Workman and Kingston, 1998] that facilitate chromatin remodeling, and potentially the accessibility of promoter sequences to regulatory factors, represent a new dimension in the control of the structure and activity of genes and promoter regulatory elements. Linkage of regulatory signaling pathways to enzyme activity that modulates gene, chromatin and chromosome organization can now be directly investigated. Additional levels of specificity are provided by structural modifications of gene promoters that influence competency for factor interactions. Simply stated, changes in the architectural properties of promoter elements determine effectiveness of gene regulatory se-

quences as substrates for interactions with regulatory factors. The regulatory and regulated components of chromatin remodeling and the rate-limiting steps in the relevant signaling cascades are being actively pursued and unquestionably will provide insight into gene regulatory mechanisms from structural and functional perspectives.

The Subnuclear Organization of Regulatory Proteins

There is longstanding and compelling evidence for the asymmetric organization of protein complexes within the nucleus. Coiled bodies [Smith et al., 1999], PML domains [Dyck et al., 1994; Grande et al., 1996], and SC35 domains [Carter et al., 1993; Clemson et al., 1996; Blencowe et al., 1994; Nickerson et al., 1995; Pombo and Cook, 1996] are examples of protein localization at specific intranuclear sites that have been associated with gene expression. Transactivation factors that include AML [Merriman et al., 1995; Zeng et al., 1997, 1998; Chen et al., 1998], ALL [Rogaia et al., 1997; Yano et al., 1997], steroid hormone receptors [Tang et al., 1998a; van Steensel et al., 1995; Htun et al., 1996; Stenoien et al., 1998], and RNA polymerase II [Kimura et al., 1999; Zeng et al., 1998; Wei et al., 1998] exhibit a punctate subnuclear distribution.

Colocalization of regulatory factors with RNA polymerase II and RNA transcripts strengthens linkages between the intranuclear organization of regulatory complexes and fidelity of gene expression [Ma et al., 1999; Wei et al., 1999; Zeng et al., 1998]. Qualitative and quantitative variations in the representation and subnuclear distribution of regulatory factors are correlative but substantive support for involvement of nuclear structure with transcriptional control. However, evidence for interrelationships between nuclear architecture and regulation of gene expression that is difficult to dismiss is provided by demonstrations that transformed and tumor cells exhibit striking modifications in the intranuclear distribution of transcription factors.

From a fundamental regulatory perspective, organization of sites of transcription as discrete nuclear domains [Wei et al., 1998; Lamond and Earnshaw, 1998; Jackson et al., 1998; Iborra et al., 1998] provides an architectural basis for intranuclear organization of regulatory factors that mediate transcriptional control. Association of transcription factors with the nuclear matrix also invokes nuclear architecture in gene regulation providing a scaffold for the organization of transcriptional regulatory machinery and foci with concentrations of factors that can support initiation of transcription. Yet it is essential to understand mechanisms that direct regulatory factors to subnuclear sites as well as parameters of the assembly, activation and remodeling of regulatory domains.

MECHANISMS THAT TARGET REGULATORY FACTORS TO TRANSCRIPTIONALLY ACTIVE SUBNUCLEAR SITES

There has been extensive investigation of the exchange of regulatory information between the nucleus and cytoplasm. Both the morphology of nuclear pore complexes and mechanisms that mediate nuclear import and egress of nucleic acids, proteins and nucleoprotein complexes have been characterized. However, the intranuclear targeting of transcription factors is minimally understood. The recent observation that members of the AML transcription factors exhibit a punctate subnuclear distribution and are associated with the nuclear matrix provided the basis for experimentally addressing the targeting of regulatory proteins to architecturally-associated sites within the nucleus that support transcription [Zeng et al., 1997]. Biochemical and in situ immunofluorescence analysis of transcription factors established that a 31-amino acid segment, designated the nuclear matrix targeting signal (NMTS) near the C-terminus is necessary and sufficient to direct the regulatory proteins to a nuclear matrix-associated subnuclear site, where transcription occurs [Zeng et al., 1998; Zeng et al., 1997]. The NMTS functions autonomously and is independent of the DNA binding domain. Specificity of the intranuclear targeting signal in the AML transcription factors is indicated by a unique nucleotide sequence [Zeng et al., 1997]and a unique structure that was defined by x-ray crystallography [Tang et al., 1999; Tang et al., 1998b]. Specificity within the context of nuclear organization is supported by colocalization with activators and repressors of AML factor activity and the absence of colocalization with factors that have been shown to be functionally unrelated in biochemical assays. Targeting signals (Fig. 1) that have been characterized in the estrogen receptor and glucocorticoid receptor [Tang et al., 1998a; van Steensel et al., 1995;

Nuclear Matrix Targeting Signals in Gene Regulatory Factors

Protein name	Transcription factor class	Gene regulatory function	NMTS domain	Structural domains
AML1/CBFA2	Runt homology domain	Hematopoiesis	31 amino acids	ß strands connected by a U-shaped hinge
AML2/CBFA3	Runt homology domain	Intestinal development	27 amino acids	homologous to AML1 NMTS
AML3/CBFA1	Runt homology domain	Bone formation	37 amino acids	homologous to AML1 NMTS
YY1	Zn-finger domain	General	within 141 a.a.	region overlaps with Zn-finger DNA binding domain
PIT1	POU/homeodomain	Pituitary development	66 amino acids	helix-turn-helix DNA binding domain
GR	Ligand-dependent	Glucocorticoid signaling	bipartite	DNA binding domain/tau2 transactivation domain

Fig. 1. Nuclear matrix targeting signals in transcription factors. Nuclear matrix targeting signals (NMTS) have been identified in tissue-specific transcription factors (e.g., AML1/CBFA2, Pit1) [Zeng et al., 1997; Mancini et al., 1999], as well as other gene regulatory proteins (e.g., YY1, GR) [McNeil et al., 1998; Tang et al., 1998a]. Each of these proteins is representative of distinct classes of transcription factors with characteristic conserved protein domains (second column) and key roles in the biological regulation of gene expression (third column). The approximate sizes of the NMTS (fourth column) and their structural properties (fifth column) are indicated. The crystal structure of the AML1 NMTS represents the first three-dimensional structure of a signal peptide uniquely dedicated to subnuclear targeting [Tang et al., 1998b, 1999]. The remaining NMTS sequences appear to be embedded at least in part within different types of DNA binding modules.

Htun et al., 1996] or in the PIT1 [Stenoien et al., 1998] and YY1 [Guo et al., 1995; McNeil et al., 1998] transcription factors do not share sequence homology with the AML transcription factors. Each exhibits independent subnuclear distributions reinforcing specificity for intranuclear trafficking. Taken together, a series of trafficking signals have been identified that are responsible for directing regulatory factors to nonoverlapping sites within the cell nucleus. Collectively, these transcription factors provide coordinates for studying the intranuclear organization of gene regulatory complexes and the necessary components of structure, as well as multidirectional crosstalk that is requisite for biological control.

REQUIREMENTS FOR INCREASED UNDERSTANDING OF NUCLEAR STRUCTURE-GENE EXPRESSION INTERRELATIONSHIPS

There is now a significant body of evidence that the architectural organization of nucleic acids and regulatory proteins within the cell nucleus supports functional interrelationships between nuclear structure and gene expression. The punctate distribution of several transcription factors has provided paradigms for pursuing mechanisms that direct these regulatory proteins to specific subnuclear sites that support the activation or suppression of gene expression.

It is becoming increasingly apparent that intranuclear trafficking of regulatory factors is a multistep process. We are only at the initial stages of understanding the complexities that control each component of the process that is responsible for targeting transcription factors to subnuclear sites. However, biochemical and in situ analysis have shown that at least two trafficking signals appear to be required for subnuclear targeting of AML transcription factors; the first supports nuclear import (nuclear localization signal) and a second mediates association with the nuclear matrix (nuclear matrix targeting signal). The multiplicity of determinants for nuclear localization and alternative splicing of AML messenger RNA may provide the requisite complexity to support targeting to specific sites within the nucleus in response to diverse biological conditions. Furthermore, because gene regulation by AML transcription factors involves contributions by other regulatory proteins such as CBFβ [Banerjee et al., 1996; Ogawa et al., 1993], ETS [Giese et al., 1995], and C/EBP [Zhang et al., 1996], AML may facilitate recruitment of these factors to nuclear matrix-associated sites.

There is growing appreciation for involvement of nuclear architecture in the dynamic and multidirectional exchange of gene transcripts and regulatory factors between the nucleus and cytoplasm, as well as between regions and structures within the nucleus. Targeting of regulatory factors to subnuclear sites that are dedicated to biological activity is not confined to transcription factors. It has been shown that DNA replication occurs at nuclear

matrix-associated foci [Berezney et al., 1996; Wei et al., 1998] and peptides have been identified that direct replication factors to sites within the nucleus where DNA synthesis occurs [Leonhardt et al., 1998].

It is difficult to separate nuclear structure and function arbitrarily or to distinguish the regulated and regulatory parameters of control. The challenges we now face are to further define the targeting of transcription factors and control that reside at the level of nuclear matrix-associated acceptor sites. Here it will be important to determine whether acceptor proteins are associated with a core filament structural lattice or whether a compositely organized matrix of regulatory factors that contribute to nuclear morphology is dynamically assembled. The result will unquestionably be further insight into fundamental processes that are involved with directing components of gene expression to specific regions within the nucleus.

It is premature to define an inclusive pathway to account mechanistically for all steps in the targeting of proteins to subnuclear sites where they participate in regulatory activity. However, findings suggest that parameters of nuclear architecture functionally interface with components of transcriptional control (Fig. 2).

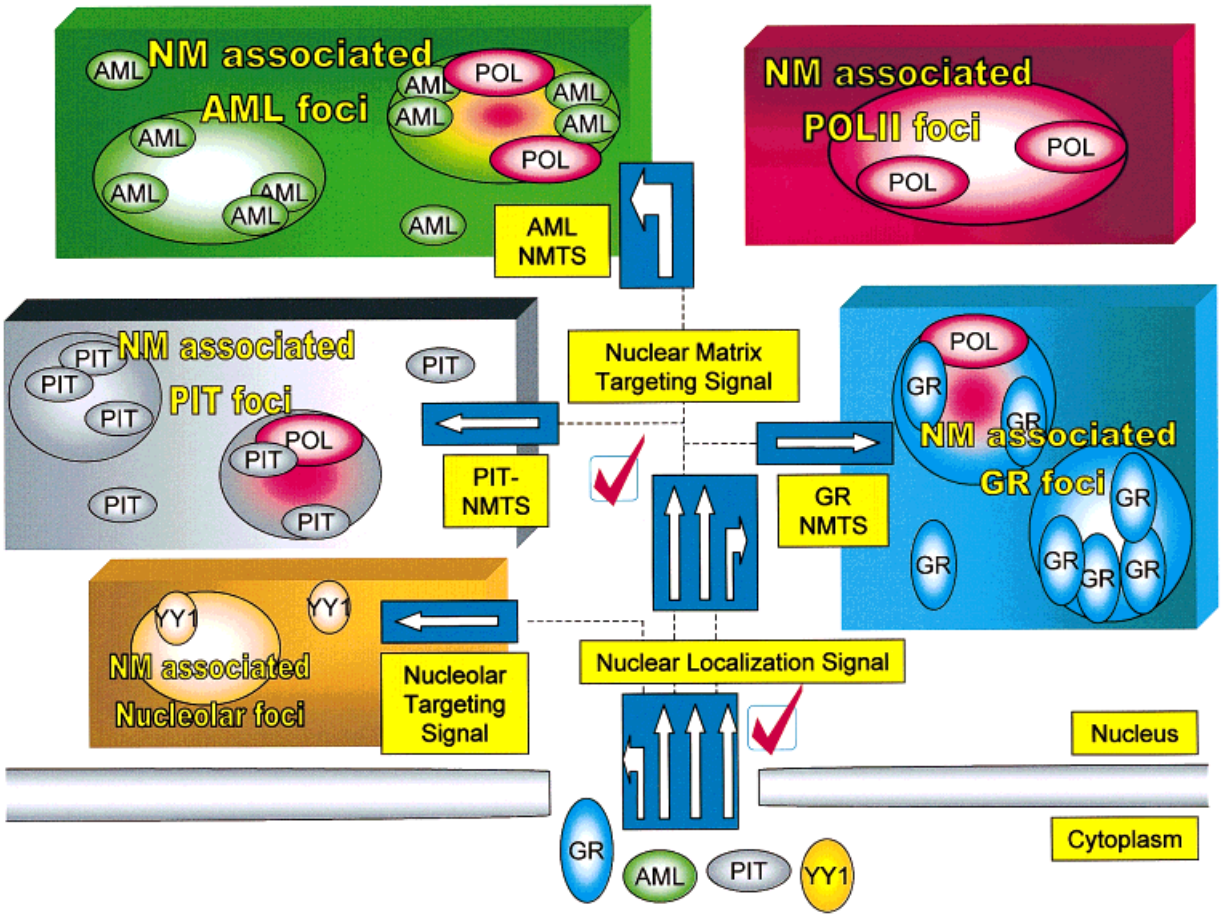

Fig. 2. Subnuclear targeting of transcription factors to gene regulatory sites. Transcription factors are imported into the nucleus using nuclear localization signals (NLS) that are structurally and functionally similar. Upon nuclear entry, regulatory factors are directed to subnuclear domains by intranuclear targeting signals (e.g., nuclear matrix targeting signal [NMTS]) (indicated in yellow boxes) that are structurally and functionally unique to specific transcription factors. Schematically illustrated is the trafficking (blue boxes with white arrows) of the transcription factors AML (small green ovals), GR (small blue ovals), PIT (small gray ovals), YY1 (small orange ovals) to nuclear matrix-associated foci (large ovals), where genes are transcribed or repressed. Transcriptionally active domains containing RNA polymerase II are highlighted in red. Checkpoints designated in red indicate regulatory stages in nuclear import and subnuclear trafficking during which sorting and surveillance mechanisms are operative. The transcription factors indicated in the diagram represent paradigms for defining mechanisms that mediate sorting of regulatory proteins within the nucleus.

The involvement of nuclear matrix-associated transcription factors with recruitment of regulatory components to modulate transcription remains to be defined. The diversity of targeting signals must be established to evaluate the extent to which regulatory discrimination is mediated by encoded intranuclear trafficking signals. It will also be imperative to define, both biochemically and mechanistically, the checkpoints that are operative during subnuclear distribution of regulatory factors and the editing steps that are invoked to ensure the structural and functional fidelity of nuclear domains where replication and expression of genes occur. There is emerging recognition that placement of regulatory components of gene expression must be temporally and spatially coordinated to mediate biological control optimally. The consequences of breaches in nuclear structure-function interrelationships are observed in an expanding series of diseases that include cancer and neurological disorders. As the repertoire of architecturally associated factors and cofactors that modulate regulatory activity expand, there is increasing confidence in contributions of nuclear organization to transcriptional activity. Defining structure-function interrelationships is not an obstacle to controlling gene expression in vivo. Rather, mechanisms are emerging that use nuclear structure to organize nucleic acids and regulatory proteins in a manner that facilitates regulation of genes. It is difficult to dismiss the necessity for further characterization of mechanisms that direct regulatory proteins to specific sites within the nucleus and thereby be in the right place at the right time to participate in transcriptional control. Here, the boundaries between subnuclear domains are important to establish threshold concentrations of regulatory factors to support the isolation as well as integration of activities that accommodate specific biological requirements for expression of genes.

It is no longer justifiable to equate transcriptional control that can be reconstituted under cell free conditions with the activation and suppression of genes of nuclei of intact cells. Although components of regulatory mechanisms can be dissected in vitro, the biochemical and architectural complexities of the intact cell are necessary for the full complement of regulatory factors and integration of signaling mechanisms, to be operative for physiologically responsive control.

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