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Architectural Genetic and Epigenetic Control of Regulatory Networks: Compartmentalizing Machinery for Transcription and Chromatin Remodeling in Nuclear Microenvironments

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Abstract

The regulatory machinery that governs genetic and epigenetic control of gene expression for biological processes and cancer is organized in nuclear microenvironments. Strategic placement of transcription factors at target gene promoters in punctate microenvironments of interphase nuclei supports scaffolding of co-regulatory proteins and the convergence as well as integration of regulatory networks. The organization and localization of regulatory complexes within the nucleus can provide signatures that are linked to regulatory activity. Retention of transcription factors at gene loci in mitotic chromosomes contributes to epigenetic control of cell fate and lineage commitment, as well as to persistence of transformed and tumor phenotypes. Mechanistic understanding of the architectural assembly of regulatory machinery can serve as a basis for treating cancer with high specificity and minimal off-target effects.

Keywords

gene expression; nuclear structure; histone

I. INTRODUCTION

Genetic and epigenetic regulation of gene expression is operative in biological control of proliferation, growth, and phenotype. Both regulatory mechanisms synergistically contribute to compromised gene expression that is functionally linked to transformation and tumorigenesis. There is growing recognition that regulatory machinery is compartmentalized in subnuclear domains in which the components for combinatorial control are organized and assembled.[1–12]

Clinical relevance is emerging from well-documented modifications in the localization of regulatory machinery that govern transcription, replication, and repair in cancer cell nuclei that provide new dimensions to diagnosis and therapy.[13,14] We review evidence that the architectural organization of genetic and epigenetic regulatory machinery is obligatory. We

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also emphasize strategies to mechanistically relate the focal organization of regulatory complexes with genetic and epigenetic parameters of control that are architecturally configured as integrated networks in the interphase nucleus (Fig. 1). In addition, we explore emerging indications that transcriptional machinery is retained at target gene loci of chromosomes during mitosis, epigenetically contributing to sustained competency for sustained expression of genes in progeny cells.

II. AN ARCHITECTURAL PERSPECTIVE OF GENETIC AND EPIGENETIC REGULATION

A. Promoter Architecture

Combinatorial control of transcription involves the organization and assembly of regulatory complexes mediated by protein-DNA and protein-protein interactions at strategic sites of target gene promoters.[15] The transcription factors bind to cognate regulatory sequences and provide scaffolds for recruitment and retention of co-regulatory proteins that include co-activators, co-repressors, steroid hormone receptors, and endpoints for signaling pathways. Transcription factor interactions with histone-modifying and chromatin-remodeling factors support the localization of epigenetic regulatory machinery for selectively influencing chromatin structure and nucleosome organization.[16,17] Although the biochemistry of these components to epigenetic regulation has been characterized to a significant extent, there is a requirement to mechanistically define the placement of the components for epigenetic control that mediate physiologically responsive transcriptional activation and suppression. However, a mechanistic explanation for the fidelity of localization at promoter sites is minimally understood. The cross-talk between histone modifications, DNA methylation, and selective representation of histone subgroups to epigenetic control necessitates clarification. Further biochemical modifications, both independently and combinatorially with consideration of context, should not be dismissed.

The changes that occur during development and differentiation, differences that are cell type specific, and modifications that are observed in diseases that include cancer are conserved. There seems to be retention of architectural regulatory mediators of epigenetic control at genomic sites that require access to factors to determine the extent to which the genes are actively transcribed or suppressed. This architecturally based epigenetic control is exerted at two levels, which include both cause and effect. The first is placement of the factors that are required for architecturally configuring and remodeling genomes, whereas the second is the consequential remodeling of genomic DNA to accommodate demands for transcription.

Although it is evident that the orchestration of a complex cohort of regulatory factors is required for genetic and epigenetic control of gene loci, there is much to be learned about rate-limiting obligatory relationships that are proactive and responsive. As a strategy to probe mechanisms that render genes competent for expression or suppression in a physiologically responsive manner, the concept of signatures rather than single molecular determinants of control is becoming increasingly informative. With accruing insight into multiple levels of molecular organization contributing combinatorial control of gene expression, the informational contribution provided by architectural organization is becoming increasingly evident.[18] The regulatory signatures that were once viewed as exclusive properties of nucleotide sequences in DNA have been extended to “codes” that are epigenetically based on histone modifications, [19,20] the selective use of histone subtypes, higher order genomic organization, and the configuration as well as localization of regulatory microenvironments within the cell nucleus.[2,12]

B. Nuclear Microenvironments

Regulatory machinery for biological control is not uniformly distributed throughout the nucleus. Rather, the nucleic acid and protein components of biological control are focally organized in specialized nuclear domains.[12,21] These nuclear microenvironments are illustrated by two nucleoli where the regulatory machinery for ribosomal gene expression resides, chromosome territories where genes are localized in interphase nuclei, and sites of active transcription, processing of gene transcriptions, replication, and repair.

High-resolution strategies that incorporate antibodies to regulatory factors and in situ hybridization for detection of genes and transcripts, together with sophisticated microscopy, biochemistry and molecular approaches, have permitted the identification and functional characterization of regulatory domains within the interphase nucleus. These are dynamic, rather than static, subnuclear compartments that exhibit exchange and turnover of components to regulatory complexes in a physiologically responsive manner.

The identification of intranuclear trafficking signals in transcription factors that include RUNX/AML, AML/ETO, and glucocorticoid, estrogen, and androgen receptors provides examples of regulatory proteins that can begin to be understood in relation to mechanisms that are linked to obligatory nuclear localization. Aberrant or abortive proliferation, differentiation, and/or development in vivo point to obligatory relationships between nuclear organization and biological control. Together with regulatory signals for nuclear import, retention, and DNA binding, it is becoming apparent that multiple components of control are operative in the focal assembly of machinery for gene expression in nuclear microenvironments.[18,22]

Sophisticated imaging and algorithms that define localization of regulatory machinery, in relation to an extensive series of regulatory parameters that are context-dependent, provide a basis for configuring a signature to characterize a component of control that is retained and conveyed to progeny cells during mitosis, thereby contributing an architectural dimension to epigenetic control. [23,24] The architectural features of focally organized regulatory complexes are further illustrated by genomic and proteomic analyses that provide insight into the complex cohort of signals that converge at nuclear domains where regulatory networks support the integration of cues to initiate, sustain, or down-regulate biological processes as well as changes that occur in cancer.[23–25]

III. EPIGENETIC RETENTION OF REGULATORY MACHINERY DURING MITOSIS

The retention of transcription factors at target gene loci of mitotic chromosomes establishes a dimension to epigenetic control of cell fate and lineage commitment that complements DNA methylation and histone modifications.[26] Osteogenic, myogenic, and adipogenic transcription factors have been shown to remain bound to promoter sequences during mitosis, supporting persistence of RNA polymerase-II-dependent and tissue-specific gene expression in progeny cells following cell division.[27–30] Ribosomal genes also retain phenotypic transcription factors in nuclear organizing regions of chromosomes and in the interphase nucleoli, reflecting epigenetic control of RNA polymerase-I-dependent transcription to support cell growth and protein synthesis postmitotically.[23,25] In addition to growing appreciation for epigenetic mechanisms, a potential obligatory relationship between cell cycle, growth, and phenotype is suggested.[12]

A fundamental question is the extent to which the cohort of co-regulatory proteins that are complexed with tissue-specific transcription factors are conveyed to progeny cells during mitosis. This architectural epigenetic component of control has implications for

understanding the requirements to reinitiate transcription of tissue-specific genes following completion of mitosis to sustain the cellular phenotype. Recent results indicate that RUNX transcription factors associated with ribosomal genes during mitosis retain UBF,[23] reflecting persistence of a principal RNA polymerase-I co-regulatory factor. Retention of TLE with RUNX during mitosis is another example of co-regulatory protein persistence.[27,28] An architectural epigenetic perspective of mitotic control that accounts for the full complement of DNA-binding transcription factors and co-regulatory proteins that are retained at target gene promoters in mitotic cells can provide an indication of the extent to which progeny cells are poised to express or suppress genes that are consistent with requirements for specialized structure and function.[2,12,31,32]

There are additional examples of regulatory proteins that remain associated with target genes during mitosis epigenetically "bookmarking" genes[33] for expression in progeny cells. Among these examples are the globin gene regulatory factor NF-E2[34,35] and HSF1,[36] extending architecture-mediated epigenetic control beyond phenotypic transcription factors.[37–42] However, as with other parameters of control, all transcription factors are not retained during cell division. The SP1-related regulatory proteins[43] and HMG[44] are two examples of factors that are genomically associated during interphase but not mitosis. Taken together, these observations provide a basis for a mechanism that can support commitment to lineages and/or specific phenotypes with a superimposed capability to modify parameters of control in a physiologically responsive manner.

In transformed and tumor cells, there is a similar requirement for retention of transcriptional competency to sustain a cancer phenotype. Retention of AML/ETO, transformation-fusion protein with RNA polymerase I and II target genes during mitosis epigenetically facilitates continued expression of genes that are conducive to transformation and/or tumor progression. It is realistic to anticipate that chromosomal retention of ALL[45] may similarly contribute to epigenetic persistence of tumor-related transcription. The cohorts of regulatory and co-regulatory proteins that remain associated with target genes in tumor cells may provide signatures for diagnosis and prognosis and combinatorial blueprints for therapeutic targets.

IV. AN ARCHITECTURAL GENETIC AND EPIGENETIC LANDSCAPE

Further refinement is required of the rules that govern functional relationships between nuclear organization and fidelity of genetic and epigenetic regulation to support biological control and that are compromised in transformed and tumor cells. We are beginning to mechanistically understand the organization of regulatory machinery at target gene promoters and in functionally organized subnuclear domains. The mitotic retention of regulatory proteins with genes transcribed by RNA polymerase I and II indicate that transcription factor-mediated epigenetic control contributes to cell fate, lineage commitment, and cross-talk between control of cell growth and phenotype. An emerging concept is that transcriptional control requires organization and assembly of regulatory machinery in nuclear microenvironments where threshold levels of rate-limiting factors can support activation and suppression of genes and the required convergence and integration of regulatory networks that determine transcriptional responsiveness (Fig. 1).

An architectural underpinning for genetic and epigenetic control is supported by the genomic scaffolding of biochemical mediators for transcription replication, chromatin structure, nucleosome organization, and DNA methylation during interphase and mitosis. Architectural signatures that reflect specificity of localization for regulatory domains and perturbations that occur in tumor cells may represent targets for the detection and treatment of tumors.

Combining high-resolution microscopy, in situ gene analysis, and transcription regulatory complexes with characterization of the mitotic and interphase chromosomal proteome can be instructive. We can anticipate new dimensions to understanding regulatory mechanisms operative in control of gene expression that can support requirements for epigenetically retaining components of control with the superimposed capabilities for accommodating requirements for dynamic responsiveness to a broad spectrum of regulatory cues.

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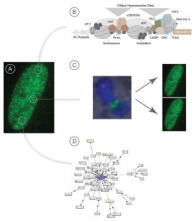

FIGURE 1.

An architectural perspective of genetic and epigenetic control in nuclear microenvironments. A schematic illustration of parameters to genetic and epigenetic control that are architecturally mediated. Panel (A) depicts a fluorescent micrograph showing the focal organization of RUNX regulatory machinery in nuclear microenvironments of the interphase nucleus. Using the RUNX transcription factors as a paradigm, the strategic localization of RUNX proteins at multiple sites of a target gene promoter are shown (B) where they strategically locate regulatory machinery that includes transcriptional co-activators and co-repressors, steroid hormone receptors, endpoints for signaling cascades and factors that contribute to epigenetic regulation by supporting histone modifications, chromatin remodeling and DNA methylation. Panel (C) illustrates the focal retention of RUNX transcription factors at target gene loci of chromosomes during mitosis, epigenetically conveying regulatory information for cell fate, lineage commitment and cell growth from parental to progeny cells. Panel (D) schematically depicts a RUNX regulatory network that supports the convergence and integration of regulatory signatures that contribute to RUNX-mediated biological control and RUNX control of aberrant gene expression in tumor cells.