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Transcription Factor Mediated Epigenetic Control for Cell Fate and Lineage Commitment

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Abstract

Epigenetic control is required to maintain competency for activation and suppression of genes during cell division. Association of regulatory proteins with target gene loci during mitosis is a parameter of epigenetic control that sustains transcriptional regulatory machinery to perpetuate gene expression signatures in progeny cells. Mitotic retention of phenotypic regulatory factors with cell cycle, cell fate and tissue specific genes supports coordinate control that governs proliferation and differentiation for cell fate and lineage commitment.

Keywords

cell cycle; nuclear microenvironment; gene expression; chromatin; RUNX; intranuclear trafficking

Introduction

A fundamental process in biological control is the passage of regulatory information from parental to progeny cells during mitosis to support cell fate and lineage commitment. While the mitotic distribution of genes is mechanistically understood there is a requirement for epigenetic control to establish and sustain the activation and/or suppression of phenotypic genes during cell division. The traditional parameters of epigenetic control are DNA methylation and post translational modifications of histones. These non-genomic mechanisms convey regulatory cues that are configured as signatures based on specificity dictated by DNA structure and/or accessibility for protein/DNA and protein/protein interactions. Micro RNAs potentially provide another dimension to epigenetic modulation of biological control. Recent results suggest that association of regulatory proteins with target gene loci during mitosis is a parameter of epigenetic control that retains the regulatory machinery for transcriptional control to perpetuate expression of genes that determine cell specialization and identity. We will focus on several lines of support for mitotic persistence of phenotypic regulatory factors with cell cycle, cell growth and tissue-specific genes within the context of coordinating control of

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parameters that are required to govern proliferation and differentiation during development and tissue remodeling.

Organization and Association of Regulatory Machinery in Nuclear Microenvironments

Runx transcription factors provide a paradigm for the focal organization and assembly of transcriptional regulatory machinery in nuclear microenvironments. These lineage-specific master regulatory proteins (Zaidi et al., 2007; Stein et al., 2006; Zaidi et al., 2006; Li et al., 2005; Zaidi et al., 2005; Zaidi et al., 2004; Stein et al., 2004; Speck and Gilliland, 2002; Galindo et al., 2005; Barseguian et al., 2002; McNeil et al., 1999; Ito et al., 2005; Durst and Hiebert, 2004; Huang et al., 2008; Lian et al., 2004; Westendorf and Hiebert, 1999) control hematopoietic (Runx1), osteogenic (Runx2), and gastrointestinal/neural (Runx3) differentiation at two levels of nuclear organization. Activity is mediated by interactions with multiple sites of target gene promoters where they strategically provide scaffolds for the recruitment and integration of regulatory signals (e.g., TGF β , SRC), as well as the recruitment of histone modifying enzymes and chromatin remodeling factors (e.g., HATs, HDAC, SWI/SNF) to influence promoter accessibility and placement of a broad spectrum of coregulatory proteins that contribute to transcriptional activation and suppression. Relevance for promoter localization of Runx transcription factors has been provided by loss or decline of biological activity when promoter binding sites of target genes are mutated or when functional domains of the Runx transcription factors are selectively mutated (Gutierrez et al., 2004). Gene expression within the three dimensional context of nuclear architecture is additionally supported by the organization of Runx regulatory machinery in punctate intranuclear domains (Zeng et al., 1997; Zeng et al., 1998; Zaidi et al., 2001). Here the necessity for fidelity of location within the nucleus is supported by the identification of a Runx-specific intranuclear targeting signal that is required for the execution of regulatory signals, Runx-dependent histone modifications and chromatin remodeling and differentiation both *in vitro* and *in vivo* (Gutierrez et al., 2004; Choi et al., 2001; Gutierrez et al., 2007; Javed et al., 1999).

Beyond the pivotal role for intranuclear organization of Runx regulatory complexes to support differentiation and development (e.g., osteogenesis and myeloid differentiation), there is a requirement for subnuclear localization of Runx proteins to initiate and sustain transformation and tumor progression. Localization of Runx2 within the nucleus is required for metastatic breast cancer and prostate cancer cells to form osteolytic lesions in bone (Javed et al., 2005). Competency for Runx1 intranuclear trafficking is necessary for myeloid differentiation and mutations that prevent intranuclear localization of Runx1 in myeloid progenitor cells results in a leukemic phenotype (Vraddi et al., 2005).

Despite the compelling evidence for a focal organization of regulatory machinery within the nucleus to support biological activity, as illustrated by Runx regulatory complexes, there are key parameters of control that are essential to be clarified. The model for focal organization of factors to establish threshold concentrations for interactions with coregulatory proteins and target genes remains to be formally demonstrated. Rate limiting constituents of regulatory complex formation must be determined. It is essential to discriminate between colocalization and functional interactions. Determinants for the turnover and modifications of components in regulatory complexes should be identified and characterized. The extent to which targeting and retention are the definitive determinants for focal formation and stability of regulatory domains is open ended. The involvement of intranuclear trafficking and dynamic self assembly in the organization and turnover of regulatory sites for gene expression should be further explored. Checkpoints that monitor the subnuclear distribution of regulatory factors and the sorting steps that ensure structural and functional fidelity of nuclear domains must be defined biochemically and mechanistically. However, there is growing support for informational

content to organization of nuclear domains that is illustrated by the subnuclear organization of Runx regulatory machinery.

Quantitative Signatures for Nuclear Localization of Regulatory Machinery

Recently, mathematical algorithms designated intranuclear informatics, have been developed to identify and assign unique quantitative signatures that define regulatory protein localization within the nucleus (Young et al., 2004). Quantitative parameters that can be assessed include nuclear size and variability in domain number, size, spatial randomness, and radial positioning. The significance and implications of intranuclear informatics can be shown by three distinct biological examples. Regulatory proteins with different activities can be subjected to intranuclear informatics analysis, which assigns each protein a unique architectural signature. The overlap between the architectural signatures of different proteins is often correlated to their functional overlap. Alternatively, the subnuclear organization of the protein domain can be linked with subnuclear targeting, biological function and disease. For example, Runx2, and its subnuclear targeting defective mutant (mSTD) show distinct architectural signatures, indicating that the biological activity of a protein can be defined and quantified as subnuclear organization. Finally, the data can be used to define functional conservation. This technique can be used to show that the post-mitotic restoration of the spatially ordered Runx subnuclear organization is functionally conserved. From the signatures that reflect regulatory protein localization within the nucleus and modifications that are associated with physiological responsiveness, transformation and tumorigenesis, a quantitative basis is provided for defining phenotype and detection/diagnosis of disease. It is also realistic to incorporate such signatures in strategies for novel dimensions to therapy.

The significance of focally organized regulatory complexes in nuclear microenvironments may reflect defined nuclear domains where threshold concentrations of regulatory factors for optimal formation of macromolecular complexes reside. The complexity of nuclear organization can support biological responsiveness by mediating the convergence and integration of signaling networks. Architectural signatures that are derived from mathematical algorithms such as intranuclear informatics have the potential to discriminate between intranuclear localization of proteins that are associated with subtle changes in biological control. Intranuclear informatics can be combined with proteomics (changes in protein-DNA and protein-protein interactions) and genomics (altered gene expression profiles) to attain comprehensive insight into nuclear structure-gene expression relationships that relate to both biology and pathology.

Architectural Parameters of Epigenetic Control

Runx proteins illustrate a key parameter of epigenetic control that supports physiological responsiveness. The location of Runx transcription factors at proximal and upstream sites of targeted gene promoters places histone-modifying and chromatin remodeling factors at regulatory domains which control basal and enhancer-mediated activity (Gutierrez et al., 2007; Javed et al., 1999; Gutierrez et al., 2004). Serving as scaffolds for assembling cohorts of regulatory factors that reconfigure chromatin organization and selectively modulate accessibility of promoter sequences to regulatory signals and proteins, an important component of biological control is provided that is based on a signature which does not depend on DNA sequences. This is an example of epigenetic regulatory information that establishes promoter landscape as architecturally assembled regulatory cues that can be conveyed to progeny cells during cell division. From a biological perspective such “epigenetic signatures” can sustain gene expression that establishes and ensures the persistence of phenotypes during development and tissue remodeling. Support is provided for transformation and tumor progression in a

manner where the tumor phenotype is retained as the cell population expands and the disease progresses.

There has been an evolution in our appreciation for the informational content of epigenetic control. Initial approaches focused on the chromatin organization of candidate genes and the localization of enzymology for histone modifications in the proximity of sequences where chromatin structure supports a phenotype. Runx transcription factor interactions with basal, tissue defining and upstream enhancer sequences of the bone specific osteocalcin gene provide scaffolds for the placement of HATs and HDACs (Westendorf et al., 2002; Yang et al., 2007). This mechanism supports epigenetic control by a master regulatory factor that is required for skeletogenesis and bone remodeling. Similarly, there is a requirement for Runx-mediated epigenetic control of skeletal genes in metastatic breast cancer and prostate cancer cells that are functionally linked to formation of osteolytic or osteoblastic lesions in bone (Barnes et al., 2004; Barnes et al., 2003; Pratap et al., 2005).

Recently, genome-wide profiling strategies have been developed that permit a global assessment of parameters for chromatin organization (Liu et al., 2005; Hajkova et al., 2008). These global approaches provide complex but instructive signatures for epigenetic parameters of genome structure and organization. At the level of individual genes, the architectural context in which specific genes are embedded is revealed. Epigenetic control is not restricted to histone and chromatin signatures. DNA methylation is an additional, well documented, component of epigenetic regulatory mechanisms (Yoo and Jones, 2006). As with histone modifications, genome-wide profiling has enhanced understanding of epigenetic control that is functionally linked to biological regulation as well as to a broad spectrum of diseases that include cancer. Beyond the insight into regulatory mechanisms that are supported by histone modifications and DNA methylation, these components of epigenetic control serve as a basis for tumor diagnosis. Equally as relevant, HDAC inhibitors and DNA methylation inhibitors are being effectively used for cancer chemotherapy (Marks et al., 2004; Yoo and Jones, 2006).

Mitotic Retention and Segregation of Transcriptional Regulatory Machinery

Post-mitotic gene expression necessitates restoration of nuclear organization. Regulatory complexes must be assembled in progeny cells as they emerge from cell division. There is an immediate and stringent requirement for expression of cell cycle, cell growth, and phenotypic genes. Using the focal nuclear organization of Runx transcription factors as a “proof of principal”, immunofluorescence microscopy has directly shown that Runx transcription factors are focally retained on mitotic chromosomes and partitioned to progeny cells (Zaidi et al., 2003; Young et al., 2007a; Young et al., 2007b; Ali et al., 2008). The symmetrical localization of Runx transcription factors on mitotic chromosomes and confirmation by chromatin immunoprecipitation analysis, indicate that Runx transcription factors remain associated with target genes as cells progress to mitosis (Young et al., 2007a; Young et al., 2007b). Consequently the regulatory machinery for Runx control of gene expression remains in place during cell division rendering genes competent to reinitiate a program of transcription post-mitotically. The key question is the extent to which mitotic retention and segregation of regulatory proteins is a general regulatory mechanism. Several lines of evidence from gene expression profiling studies indicate mitotic retention of Runx transcription factors with more than 30 target gene promoters that are components of mechanisms which support multiple parameters of biological control (Young et al., 2007b). Association of regulatory factors that include SP1 (He and Davie, 2006), C/EBP, TBP, and TTF2 (Jiang et al., 2004; Segil et al., 1996; Tang et al., 2003) with chromosomes and/or genes during mitosis establishes the generality of this mechanism as a component of epigenetic control beyond histone modifications and DNA methylation.

Despite the compelling evidence for mitotic retention of transcription factors as a parameter of epigenetic control, there are numerous fundamental questions that must be resolved. How is association of transcription factors with target genes compatible with the global repression of genes during mitosis? Are transcription factors alone or transcription factors that are complexed with cohorts of co-regulatory proteins retained at target genes and conveyed to progeny cells? Are unique mechanisms in place to support association of transcription factors with target genes that are compatible with conformational properties of genes that are associated with chromatin condensation and decondensation during the entry and exit from mitosis? Are gene-associated regulatory proteins determinants for formation of interphase chromosomal territories? Resolution of these questions should reveal additional dimensions to nuclear structure – gene expression relationships that relate to epigenetic control.

Transcription Factor-Medicate Epigenetic Control Coordinates Regulation of Proliferation, Cell Growth, and Phenotype

Several lines of evidence support association of transcription factors and co-regulatory proteins with RNA polymerase I and RNA polymerase II target genes during mitosis (Zaidi et al., 2003; Young et al., 2007a; Young et al., 2007b). Involvement in epigenetic control of gene expression for cell fate and lineage commitment is suggested by mitotic retention of tissue-specific regulatory proteins with promoters that are functionally linked to the establishment and maintenance of cell phenotype (Young et al., 2007b; Ali et al., 2008). In addition to mitotic retention of phenotypic genes, regulatory factors remain associated with genes that encode key components of signaling pathways, cell cycle control, and growth control (Young et al., 2007b). Occupancy of ribosomal gene promoters with key regulatory factors indicates that a major component of the regulatory machinery for protein synthesis is poised for resumption of expression when cells emerge from mitosis.

Recent results implicate phenotypic transcription factors in epigenetically mediating coordinate regulation of proliferation, cell cycle, and growth control. The Runx2 skeletal transcription factor associates with promoters of genes that support tissue-specific gene expression and expression of cell cycle regulatory genes that are transcribed by RNA polymerase II (Zaidi et al., 2003). In addition, Runx2 controls DNA polymerase I-mediated ribosomal gene transcription (Young et al., 2007a). During mitosis Runx2 resides at large discrete foci at nucleolar organizing regions where the ribosomal genes are located. The Runx2-UBF foci transition to nucleoli at sites of ribosomal RNA synthesis during interphase (Figure4). Functional studies directly establish Runx control of ribosomal gene transcription and protein synthesis (Young et al., 2007a). Similarly, the hematopoietic Runx1 and gastrointestinal/neural Runx3 transcription factors co-localize with ribosomal genes during mitosis and interphase to regulate protein synthesis. A similar mechanism is operative for control of ribosomal genes by MyoD during myogenesis and by C/EBP during adipogenesis (Ali et al., 2008).

Interrelationships between epigenetic control of tissue-specific genes, cell cycle and growth control appear to be operative in sustaining the transformed phenotype. The translocation of fusion protein AML/ETO associates with ribosomal genes during interphase and mitosis and contributes ribosomal gene expression and regulation of protein synthesis. Taken together, these findings are consistent with a critical molecular link between cell fate, proliferation and growth control.

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DNA Methylation

Histone Modifications

Mitotic Retention

Figure 1. Mechanisms of epigenetic maintenance of gene expression

Cells have adapted several mechanisms for transmitting regulatory information from one to the next progeny epigenetically. DNA methylation of CpG islands present in several gene promoters is a well studied and well understood mechanisms by which cells silence developmental genes, often irreversibly. Several tumor suppressor genes have also been shown to have methylated promoter regulatory regions that results in silencing of these genes and lead to cellular transformation. Similarly, post-translational modifications of the amino-terminal tails of nucleosomal histones play a pivotal role in controlled regulation of gene expression. The 'histone code' defines transcriptional state of a gene and allows expression or suppression of the locus in a physiological manner. Recently association of phenotypic transcription factors on nucleolar organizing regions (NORs – RNA Pol I responsive genes) and elsewhere (RNA Pol II responsive genes) on the mitotic chromosomes presents a novel mechanism to epigenetically convey regulatory information from one progeny to the next for lineage commitment and maintenance.