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VIEWPOINT

Interrelationships of Nuclear Architecture With Gene Expression: Functional Encounters on a Long and Winding Road

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There is emerging recognition that gene regulatory mechanisms are functionally linked to nuclear architecture. It is increasingly evident that the expanding repertoire of gene promoter sequences and regulatory factors are necessary but insufficient for stringent transcriptional and posttranscriptional control. Rather, a growing body of evidence indicates that the physiologically responsive, multidirectional flow of regulatory information to support the activation and suppression of genes involves multiple components of nuclear structure and organization. Such interrelationships between nuclear structure and function are operative in the nuclear import of regulatory factors and in the processing and nuclear export of gene transcripts.

There are striking examples of linkage between nuclear architecture and control of gene expression at several levels. The representation and organization of promoter regulatory elements and cognate factors provide a blueprint for responsiveness to transient developmental and long-term phenotypic commitments to transcription. Chromatin structure and nucleosome organization facilitate accessibility of promoter sequences to regulatory factors and integrate activities at independent promoter elements. The nuclear matrix is involved in gene localization, the concentration and targeting of regulatory factors, and the processing of RNA transcripts. In a restricted sense, it is becoming apparent that there is a nonrandom nuclear distribution of nucleic acids and regulatory proteins. Gene replication and transcription occur in a series of subnuclear domains. In a broader biological context, the distinctions between nuclear structure and function are rapidly diminishing. This is to a large part based on compelling data that relate the spatial distribution of genes and gene transcripts with the intranuclear representation and concentration of regulatory factors.

In this Prospect series, we focus on recent advances in understanding the subnuclear compartmentalization of genes and cognate regulatory factors. A series of high-resolution approaches are discussed that permit assignment of regulatory activities to subnuclear domains that are biochemically and spatially defined. The identification of specific regions in proteins mediating transcription or replication is described; these regions are responsible for intranuclear trafficking to nuclear matrix-associated subnuclear sites that support gene expression and DNA synthesis. The functional coupling of nuclear structure with gene regulation and replication is thereby reinforced.

The Prospect by Schul, de Jong, and van Driel describes the characterization of genes and nuclear domains within the three-dimensional context of nuclear architecture. Implications for fidelity of nuclear organization to support gene expression are evaluated from the perspectives of biological and pathological features of control. The theme of aberrant nuclear architecture as a key component of the malignant phenotype is expanded in the Prospect by Nickerson.

Matera presents coiled bodies as a paradigm for interrelationships between a nuclear organelle and RNA processing that have been phylogenetically conserved. He proposes and provides viable support for a novel model of SNRNP biogenesis that predicts that SNRNPs regenerate their expression by returning to coiled bodies adjacent to sites of their synthesis. Nguyen and Karaplis address the distinctions between parathyroid hormone-related protein activities and signaling mechanisms within the contexts of normal or deregulated cellular function. The consequences of binding to cell surface G-

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protein coupled receptors compared with direct intracellular effects associated with translocation to the nucleus are evaluated.

Four Prospects consider the trafficking of regulatory factors within the nucleus. The objective is to provide an overview of experimental approaches being pursued to establish mechanisms that direct regulatory factors to nuclear domains that support replication and transcription. Emphasis is on identification of sequences within factors that are responsible for subnuclear partitioning and on components of nuclear architecture that facilitate the organization and functional activities of regulatory complexes.

There is compelling evidence for the involvement of nuclear architecture in the intricate signaling pathways that modulate gene expression. Even the most skeptical are inclined to accept examples that include but are not restricted to (1) a functional relationship of the composition and organization of nuclear pores with the physical and catalytic gating of informational macromolecule exchange between the nucleus and cytoplasm, (2) defined domains within the nucleus that facilitate the concentration and spatial alignment of regulatory molecules for control of DNA replication and gene expression, and (3) the functional interfacing of nucleosome structure and higher order chromatin organization with the recruitment, association and activities of transcription factors. Nonetheless, many fundamental questions remain to be resolved. What are the cause and effect components of mechanisms that bring about the colocalization of regulatory factors with structural elements within the nucleus? To what extent is the spatial subnuclear distribution of replication and transcription factors regulated or regulatory? What are the cellular and biochemical controls that support dynamic modifications in the intranuclear trafficking of regulatory factors to accommodate changes in gene expression?

A significant challenge is the resolution of mechanisms mediating modifications in nuclear architecture that accompany normal metabolic control and subtle as well as overt changes that occur in cancer and neurological disorders. Despite the formidable task, it is realistic to anticipate that insight will be forthcoming into associations of nuclear architecture with nucleic acids and factors that influence their activities. Such functional encounters that support the integration of regulatory information can now be pursued on the long and winding road where nuclear morphology interrelates with biological control.