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VIEWPOINT

Nuclear Structure and Function

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There is a growing awareness of functional interrelationships mediating nuclear structure and function. Historically, there was a perceived dichotomy between regulatory mechanisms supporting gene expression and components of nuclear architecture. However, this parochial view is rapidly changing. The emerging concept is that both transcription and DNA synthesis occur in association with structural parameters of the nucleus. Consequently, it has become increasingly evident that the cellular and molecular mechanisms which contribute to both the regulated and regulatory relationships of nuclear morphology and to the expression and replication of genes must be defined.

The Prospect articles which follow address several of the fundamental concepts that relate structure to function within the nucleus as well as experimental approaches that support the pursuit of control. Page constraints preclude comprehensive coverage of progress and prospects in this rapidly evolving discipline. Therefore, we have focused on representative examples of bidirectional interrelationships of nuclear structure and function within the context of the cellular phenotype. Emphasis is on the multiple levels of nuclear structure which impinge upon DNA replication and transcriptional control in intact cells and tissues. Compelling lines of evidence are presented for necessity but inadequacy of the linear organization of gene regulatory sequences to accommodate requirements for physiological responsiveness to homeostatic, developmental, and tissue-related signals. Chromatin structure, nucleosome organization and gene-nuclear matrix interactions are evaluated as a basis for rendering promoter sequences accessible to transcription factors supporting integration of activities at independent gene regulatory elements.

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The Prospect by Davie focuses on involvement of the nuclear matrix and chromatin structure in organizing DNA within the nucleus to accommodate requirements for modifications in gene expression. Mechanisms that may support both stable and transient interactions between chromatin and the nuclear matrix are presented. The involvement of nuclear matrix proteins in post-translational modifications of histones is discussed together with implications for histone modifications in control of chromatin-nuclear matrix interactions.

Mancini, He, and Brinkley explore participation of the nuclear matrix in remodelling of nuclear organization during mitotic division. Several lines of evidence are presented for incorporation of the nuclear matrix into the mitotic apparatus. These investigators reviewed data from their studies and others which is consistent with both facultative and constitutive nuclear matrix protein association within and in close proximity to the mitotic apparatus.

The sorting of regulatory information which mediates transcriptional activity of genes is a compelling question. Here, several lines of evidence point to the involvement of nuclear matrix proteins in modulating the recognition, transduction, amplification, and/or dampening of regulatory signals. Tawfic et al. address an association of protein kinase CK2 with the nuclear matrix and functional contributions to phosphorylation of both nuclear matrix and non-matrix nuclear proteins.

It is well documented that aberrations in the tumor suppressor p53 influences growth control, fidelity of DNA repair, and apoptosis. Therefore, it is particularly intriguing that a series of mutations, which abrogate the tumor suppression function of p53 and confer oncogenic properties to the regulatory factor, may modulate tumor progression by altering the activity of nuclear matrix attachment regions (see Prospect by Deppert).

The Prospects by Clemson and Lawrence, and by Huang and Spector, provide valuable insight

into the functional definitions of nuclear domains which support transcription and RNA processing. By combining high resolution in situ hybridization with immunofluorescence analysis, the localization of gene transcripts with respect to factors which support RNA synthesis and processing is being established. These in situ approaches are expanding our appreciation for nuclear compartmentalization that is linked to specialized functions.

The Prospect by Stein et al. explores contributions of chromatin structure, nucleosome organization, and the nuclear matrix to transcriptional control of cell growth and tissue-specific genes during differentiation. Involvement of nuclear architecture is evaluated in relation to cross-talk between promoter domains, gene localization, and the concentration and targeting of transcription factors.

Dijkwel and Hamlin evaluate the potential relationships of nuclear matrix attachment to initiation of DNA replication. These investigators present a balanced overview of mechanisms associated with genome replication in mammalian cells in relation to principal parameters of nuclear organization.

The Prospect by Berezney et al. emphasizes how many of the nuclear matrix proteins are likely involved in regulatory aspects of genomic function. By combining state-of-the-art 3-D microscopy with computer image analysis, precise structural information is being obtained about sites of DNA replication, transcription, and RNA splicing factors and how they may form higher levels of organization in the nucleus. Deciphering the role of specific nuclear matrix proteins at these sites of genomic function is a major direction for future research in this field.

It is apparent that evidence is increasing for dynamic modifications in nuclear structure which parallel modifications in gene expression. However, despite the emerging evidence for nuclear structure-gene expression interrelationships, a number of fundamental questions must be experimentally addressed. The complexities of nuclear organization are becoming increasingly apparent. Our awareness of nuclear domains that are dedicated to specific components of gene expression has evolved from considering the nucleolar localization of ribosomal RNA transcription as an exception, to defining a broad spectrum of nuclear domains within the context of support for expression of specific genes. There is a quest for understanding interrelationships between multiple components of nuclear structure with the subtleties in replication, transcription, and transcript processing. Among the challenges that we now face is the necessity to define functionally the cause and/or effect components of relationships between structural parameters of the nucleus associated with specific replicational or transcriptional regulatory mechanisms.

During the past several years there has been a rapid accrual in definitions of structures that are functionally linked to steps in transcriptional activation and RNA processing. However, many represent advances that have been descriptive at both the structural and molecular levels. We are now in a position to pursue biochemical determinants and functional consequences of activities associated with gene expression as it regulates, and is regulated by, components of nuclear architecture. Elucidation of rate-limiting regulatory components of nuclear structure-function interrelationships will provide insight into control of plasticity required for remodelling of nuclear structure in relation to transcriptional control. Here, physiologically responsive accommodations to modulations in gene expression include, but are not restricted to, changes in nucleosome placement, intranucleosomal properties as well as higher order nuclear organization.