

# **NUCLEAR STRUCTURE AND GENE EXPRESSION**

**(Part One of a Two-Part Series)**

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## **25 Years of Contributions to Characterizing Gene Expression and Replication within the Three-Dimensional Context of Nuclear Architecture**

During the last quarter of a century there have been incremental advances in understanding nuclear structure-function interrelationships. There is emerging recognition that the intranuclear distribution of nucleic acids and regulatory factors is linked to organization of architecturally associated, multicomponent complexes that support gene expression and replication.

The nuclear structure-function paradigm is built on a foundation that was initiated at the beginning of this century. At that time, it was first appreciated that regulatory information is packaged as chromosomes and that modifications in nuclear morphology accompany normal biological processes that include mitotic division as well as aberrant events that are associated with initiation and progression of tumorigenesis. Identification and characterization of the biochemical and molecular parameters of transcription and replication have strengthened appreciation for the central role of nuclear structure in biological control. Then, 25 years ago, two key observations provided a turning point in understanding gene regulatory mechanisms within the three-dimensional context of nuclear architecture. The discovery that DNA is packaged as repeating subunit "bead on string" structures designated nucleosomes (Kornberg, 1974; Olins and Olins, 1974), which are structurally remodeled to accommodate requirements for transcription (reviewed in Workman and Kingston, 1998; Zlatanova and van Holde, 1992; Montecino et al., 1994), emphasized the extent to which architectural organization of genes is linked to functional activity. An equivalently consequential observation in 1974 was the discovery of the nuclear matrix (Berezney and Coffey, 1974, 1975) that serves as a functional lattice for organization of genes and regulatory proteins (reviewed in Stein et al., 1997, 1999; Berezney et al., 1995; Penman, 1991).

The skepticism that initially accompanied the concept of architectural requirements for gene regulation and expression have given way to acceptance that components of nuclear architecture facilitate the organization of genes and regulatory factors at subnuclear sites. The challenges we now face are to characterize mechanisms that direct replication and transcription factors to specific sites within the nucleus and thereby be in the right place at the right time to participate in biological control. Equally important, it is becoming increasingly evident that modifications in the subnuclear organization of genes and regulatory factors accompany abrogated gene expression in cancer and neurological disorders.

This is the first of a two-part series that is dedicated to 25 years of progress in experimentally pursuing relationships between nuclear structure and function. There is confidence that increasing insight will be forthcoming into the architectural complexities of the cell nucleus that are required for genomic organization, function, and the integration of cellular regulatory signals that must be operative for physiological control in vivo.

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