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VIEWPOINT

Nuclear Structure and Cancer

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There is the emerging recognition that placement of regulatory components of gene expression must be temporarily and spatially coordinated to facilitate biological control. The consequences of breeches in nuclear structure-function relationships are observed in an expanding series of diseases. Compromised interrelationships of nuclear structure with gene expression are illustrated by the modified subnuclear organization of genes and regulatory factors in cancer. A common feature to all cancers is that they exhibit striking alterations in nuclear morphology as well as in the representation and intranuclear distribution of nucleic acids and regulatory proteins that are linked to aberrant replication, repair, and transcriptional control during the onset and progression of tumorigenesis.

It is becoming increasingly evident that control of replication and gene expression must be understood within the three-dimensional context of nuclear architecture. It is essential to mechanistically account for compartmentalization of replication and transcriptional machinery in microenvironments within the nucleus where regulatory signals can be integrated and threshold concentrations for protein/DNA and protein/protein interactions can be attained. Cancer-related perturbations in the composition, organization, assembly, activity, and intranuclear localization of transcriptional and replication complexes reflects obligatory criteria for stringent control.

This special issue of Journal of Cellular Biochemistry is dedicated to exploring concepts, experimental approaches, and novel insights into fundamental parameters of nuclear structure and function that relate to the organization and activities of nucleic acids and regulatory proteins within the nucleus. It is realistic to anticipate that mechanisms which organize genes as well as transcription and replication factors into functional complexes will provide novel options for cancer diagnosis and targeted therapies.

Current thinking about the organization of DNA in nuclear matrix-associated loop domains and the relevance of subnuclear compartmentalization for accuracy in transcription, replication, and competency for repair are evaluated [see articles by Bode et al.; Sotolongo and Ward]. Unbase paired region-binding proteins are addressed within the context of loop domain-mediated regulatory activities and modifications in tumors [see article by Galande and Kohwi-Shigematsu]. The growing appreciation for the requirement of fundamental interrelationships between nuclear and cyto-architecture as well as with the extracellular matrix for transduction of regulatory signals that modulate chromatin remodeling is presented. Emphasis is on alterations in cancer cells [see article by Spencer and Davie]. Recent advances in tumor-related perturbations in chromatin remodeling [see articles by Bresnick et al.] and rearrangements of chromatin domains in cancer cells [see articles by Vassetzky et al.; Singh et al.] are evaluated from the perspective of impact on the etiology of cancer.

Organization of the regulatory machinery for replication and transcription at subcellular sites necessitates mechanisms to direct factors to locations within the nucleus where activity occurs. Several articles focus on identification and characterization of intranuclear trafficking signals in transcription factors and modifications in the intranuclear targeting of regulatory proteins that are causally related to cancer [see articles by Jackson; Stein et al.; Leonhardt and Cardoso; Meyers and Hiebert; Stenoien et al.]. Consistent with observed changes in the intranuclear organization of regulatory proteins in tumor cells, there is compelling evidence for segregation of acentric chromosomes during tumor cell mitosis [see article by Kanda and Wahl].

The full complement of regulatory signals that mediate control of gene expression in conjunction with components of nuclear architecture remain to be defined. However, the

repertoire of nuclear matrix-associated signaling molecules that are targets for cancer-related modifications has been extended to include lectins [see articles by Chay and Pienta; Deppert et al.] and serine/threonine kinase CK2 [see article by Ahmed et al.]. One can be optimistic that there are viable applications of nuclear structure/function interrelationships to cancer diagnosis and therapy. Nuclear matrix proteins are providing tumor markers [see article by Davido and Getzenberg]. Cancer related disintegration of nuclear organization has been causally related to therapeutic outcome of radiation and thermal therapy [see article by Roti Roti et al.] and quantitative nuclear morphometry is providing a new generation of parameters for tumor diagnosis, staging, and monitoring of progression [see article by Veltri et al.].

Thus, relationships between subnuclear organization and activities of nucleic acids and regulatory proteins is being translated to increased understanding of fundamental biological control and changes that occur in cancer. A challenge we now face is to further define tumor-related changes in architectural organization of regulatory machinery for replication and transcription within the nucleus. Each step in the assembly and activity of regulatory complexes at intranuclear sites requires a complex and interdependent series of events. But, every component of nuclear biochemistry and morphology contributes to specificity for physiological responsiveness as well as potential targets for tumor diagnosis and therapies with high specificity and minimal toxicity.