Journal of Cellular Biochemistry 104:1949–1952 (2008)

Nuclear Microenvironments in Cancer Series

VIEW POINTS

Nuclear Microenvironments and Cancer

Gary S. Stein,[1]* James R. Davie,[2] J. Randy Knowlton,[3] and Sayyed K. Zaidi[1]

[1]Department of Cell Biology, S3-310, University of Massachusetts Medical School, 55 Lake Ave. North, Worcester, Massachusetts 01655
[2]Manitoba Institute of Cell Biology, 675 McDermot Ave., Winnipeg, Manitoba, Canada R3E OV9
[3]Structural Biology and Molecular Applications, Division of Cancer Biology NCI/NIH, 5006 EPN, 6130 Executive Blvd., Bethesda, Maryland 20892

Abstract Nucleic acids and regulatory proteins are architecturally organized in nuclear microenvironments. The compartmentalization of regulatory machinery for gene expression, replication and repair, is obligatory for fidelity of biological control. Perturbations in the organization, assembly and integration of regulatory machinery have been functionally linked to the onset and progression of tumorigenesis. The combined application of cellular, molecular, biochemical and in vivo genetic approaches, together with structural biology, genomics, proteomics and bioinformatics, will likely lead to new approaches in cancer diagnostics and therapy. J. Cell. Biochem. 104: 1949–1952, 2008.

Recognizing the role of the nuclear microenvironment in tumor biology and pathology, the National Cancer Institute convened a Workshop to explore strategies for functionally dissecting the intranuclear compartmentalization of regulatory machinery. This meeting provided a forum for an assessment of our current understanding of the function of nuclear organization, cancer development and progression at the cellular and molecular levels as well as consideration of the strengths and limitations of emerging concepts and experimental approaches.

Regulatory machinery for transcription replication and repair is compartmentalized in microenvironments within the nucleus. The combinatorial components for biological control are organized and assembled into focal intranuclear domains. This architectural perspective of nuclear structure and function is consistent with our current understanding of the temporal and spatial elements of regulatory mechanisms that govern physiological processes. Equally relevant, changes in nuclear morphology and in the representation, organization, assembly and integration of regulatory signals are linked to perturbations in the stringent control of proliferation and differentiation that can lead to cancer.

Microenvironments within the nucleus are hierarchical with respect to organization, localization and complexity, providing architectural components for regulation at multiple levels. Regulatory scaffolding proteins that bind at sites of target gene promoters recruit combinations of coregulatory proteins for transcriptional regulation, chromatin remodeling, histone modifications and execution of key signaling pathways. Reflecting higher level nuclear organization, many transcription factors are organized in defined punctate subnuclear domains where concentrations are established that promote regulatory activity.

There was consensus that exploring the involvement of nuclear microenvironments in tumorigenesis requires new experimental strategies that challenge existing paradigms. The importance of combining molecular, cellular, biochemical and in vivo genetic approaches with structural biology, genomics, proteomics and

*Correspondence to: Gary S. Stein, PhD, 55 Lake Avenue North, Worcester, MA 01655.
E-mail: gary.stein@umassmed.edu
Received 2 June 2008; Accepted 2 June 2008
DOI 10.1002/jcb.21846

bioinformatics was emphasized. The rapid throughput, high resolution and quantitative options for understanding nuclear organization within the context of gene expression, replication and repair were considered. Specificity was a key consideration with respect to sequence, structure and signatures based on location. The synergy between multiple levels of nuclear organization to accommodate the integration of regulatory signals and configuration of regulatory networks was assessed in relation to nuclear localization. Trafficking of regulatory proteins to navigate the landscape of the cell nucleus was evaluated as a basis for establishing domains that support threshold concentrations of regulatory molecules for gene expression, replication and repair. Nuclear import signals, intranuclear trafficking signals and promoter recognition sequences were considered as components of a dynamic cellular response to cues that mediate gene activation and suppression.

Consideration was given to mechanisms for utilizing elements of nuclear structure to epigenetically sustain the capacity for execution of regulatory signals during interphase as well as for progeny cells to sustain the capacity for expression of cell growth and phenotypic genes following mitosis, despite the disassembly of nuclear structure during the process. The implications of retention of transcription factors within target gene loci of mitotic chromosomes as a mechanism for distribution of regulatory machinery during cell division in order to render cells transcriptionally competent when they emerge from mitosis were discussed. In a broader biological context, epigenetic control can be expanded from mechanisms that are based on DNA methylation and histone modifications to include transcription factor interactions with genes on mitotic chromosomes.

Another question addressed in this workshop was the extent to which regulatory machinery is compartmentalized. There was extensive consideration regarding the focal placement of transcription factors, genes and sites for replication, repair and cell survival during interphase and mitosis. Linkage to persistence and progression of the transformed and tumor phenotype were emphasized. The strikingly reproducible presence and location of chromosomal territories in interphase nuclei was viewed as a basis for facilitating processes that include: the assembly of regulatory networks; crosstalk between genes and regulatory complexes that reside on independent chromosomes; and a predisposition for frequent chromosomal translocations that characterize certain tumors. Unquestionably, advances in high resolution microscopy and in situ analysis of genes, transcripts and regulatory factors has enabled this element of nuclear organization to become increasingly significant.

Our recognition of the complexity of nuclear organization is evolving. As a consequence, there is appreciation that multiple parameters of nuclear organization can serve as a major contributor to cell phenotype. Each signal that assigns location of regulatory complexes within the nucleus and each linkage of a nuclear microenvironment with a component of gene expression, replication or repair, can lead to transformation and tumorigenesis.

There is accruing evidence that a detailed understanding of nuclear organization can lead to new methods for tumor detection as well as a new source of drugable targets. Conventional chemotherapy is largely based on DNA structure. DNA methylation, chromatin structure and nucleosome organization serve as epigenetic targets for HDAC inhibitors and DNA methylase blockers. Targeting PML bodies with ATRA illustrates the feasibility of therapeutically reversing modifications in a tumor-related microenvironment that is sustained unless the PML patient relapses. These examples of selectively modifying changes in nuclear organization to treat cancer are "proofs of principal" for the value of dissecting the composition, organization and regulation of gene expression, replication and repair within the three dimensional context of nuclear architecture for novel approaches to detect and treat cancer.

The series of Prospect articles in this issue of Journal of Cellular Biochemistry, though by no means inclusive, conveys the challenges and approaches for nuclear microenvironments to enhance our appreciation for compromised regulatory mechanisms in tumor cells that can translate to therapy with high specificity and without "off-target" toxicity.

Participants in the National Cancer Institute Workshop on "The Nuclear Microenvironment and Cancer", February 8–10, 2006, Washington, D.C. and References.

Berezney, Ronald
Bushweller, John

Coffey, Donald
Cremer, Thomas
Davie, James
Ellisman, Mark
Getzenberg, Robert
Hager, Gordon
Hendzel, Michael
Imbalzano, Anthony
Knowlton, J. Randy
Livingston, David
Misteli, Tom
Pandolfi, Pier
Silver, Pamela
Singer, Robert
Spector, David
Stein, Gary
Tlsty, Thea
True, Lawrence
Woodcock, Christopher
Workman, Jerry
Zaidi, Sayyed K.

ACKNOWLEDGMENTS

The authors are appreciative of the editorial assistance of Betsy Bronstein with the preparation of the manuscript.

REFERENCES

Berman H, Zhang J, Crawford YG, Gauthier ML, Fordyce CA, McDermott KM, Sigaroudinia M, Kozakiewicz K, Tlsty TD. 2005. Genetic and epigenetic changes in mammary epithelial cells identify a subpopulation of cells involved in early carcinogenesis. Cold Spring Harb Symp Quant Biol 70:317–327.

Bernardi R, Pandolfi PP. 2007. Structure, dynamics and functions of promyelocytic leukaemia nuclear bodies. Nat Rev Mol Cell Biol 8(12):1006–1016.

Brown CR, Silver PA. 2007. Transcriptional regulation at the nuclear pore complex. Curr Opin Genet Dev 17(2):100–106.

Brown CR, Kennedy CJ, Delmar VA, Forbes DJ, Silver PA. 2008. Global histone acetylation induces functional genomic reorganization at mammalian nuclear pore complexes. Genes Dev 22(5):627–639.

Cannon GM Jr, Balasudramani M, Getzenberg RH. 2007. Characterization of nuclear matrix protein alterations associated with renal cell carcinoma. Urology 69(6):1227–1230.

Chen YC, Kappel C, Beaudouin J, Eils R, Spector DL. 2008. Live cell dynamics of PML nuclear bodies upon entry into and exit from mitosis. Mol Biol Cell [Epub ahead of print].

Coffey DS, Getzenberg RH, DeWeese TL. 2006. Hyperthermic biology and cancer therapies: A hypothesis for the "Lance Armstrong effect". JAMA 296(4):445–448.

Delcuve GP, He S, Davie JR. 2008. Mitotic partitioning of transcription factors. J Cell Biochem [Epub ahead of print].

Drobic B, Dunn KL, Espino PS, Davie JR. 2006. Abnormalities of chromatin in tumor cells. EXS 96:25–47.

Dundr M, Ospina JK, Sung MH, John S, Upender M, Ried T, Hager GL, Matera AG. 2007. Actin-dependent intranuclear repositioning of an active gene locus in vivo. J Cell Biol 179(6):1095–1103.

Efroni S, Duttagupta R, Cheng J, Dehghani H, Hoeppner DJ, Dash C, Basett-Jones DP, Le Grice S, McKay RD, Buetow KH, Gingeras TR, Misteli T, Meshorer E. 2008. Global transcription in pluripotent embryonic stem cells. Cell Stem Cell 2(5):437–447.

Erfurth FE, Popovic R, Grembecka J, Cierpicki T, Theisler C, Xia ZB, Stuart T, Diaz MO, Bushweller JH, Zeleznik-Le NJ. 2008. MLL protects CpG clusters from methylation within the Hoxa9 gene, maintaining transcript expression. Proc Natl Acad Sci USA [Epub ahead of print].

Garduno E, Wong-Barnum M, Volkmann N, Ellisman MH. 2008. Segmentation of electron tomographic data sets using fuzzy set theory principles. J Struct Biol [Epub ahead of print].

Gevry N, Chan HM, Laflamme L, Livingston DM, Gaudreau L. 2007. p21 transcription is regulated by differential localization of histone H2A. Z Genes Dev 21(15):1869–1881.

Ghosh RP, Horowitz-Scherer RA, Nikitina T, Gierasch LM, Woodcock CL. 2008. Rett syndrome-causing mutations in human MECP2 result in diverse structural changes that impact folding and DNA interactions. J Biol Chem [Epub ahead of print].

Gieni RS, Chan GK, Hendzel MJ. 2008. Epigenetics regulate centromere formation and kinetochore function. J Cell Biochem [Epub ahead of print].

Gorski SA, Snyder SK, John S, Grummt I, Misteli T. 2008. Modulation of RNA polymerase assembly dynamics in transcriptional regulation. Mol Cell 30(4):486–497.

Grasser F, Neusser M, Fiegler H, Thormeyer T, Cremer M, Carter NP, Cremer T, Muller S. 2008. Replication-timing-correlated spatial chromatin arrangements in cancer and in primate interphase nuclei. J Cell Sci 121:1876–1886.

Gu W, Wells AL, Pan F, Singer RH. 2008. Feedback regulation between ZBP1 and beta-catenin mRNAs in breast cancer cells. Mol Cell Biol [Epub ahead of print].

Guidi CJ, Mudhasani R, Hoover K, Koff A, Leav I, Imbalzano AN, Jones SN. 2006. Functional interaction of the retinoblastoma nad Ini1/Snf5 tumor suppressors in cell growth and pituitary tumorigenesis. Cancer Res 66(16):8076–8082.

Houston SI, McManus KJ, Adams MM, Sims JK, Carpenter PB, Hendzel MJ, Rice JC. 2008. Catalytic function of the PR-Set7 histone H4 lysine 20 monomethyltransferase is essential for mitotic entry and genomic stability. J Biol Chem [Epub ahead of print].

Ito K, Bernardi R, Morotti A, Matsuoka S, Saglio G, Ikeda Y, Rosenblatt J, Avigan DE, Teruya Feldstein J, Pandolfi PP. 2008. PML targeting eradicates quiescent leukaemia-initiating cells. Nature [Epub ahead of print].

John S, Sabo PJ, Johnson TA, Sung MH, Biddie SC, Lightman SL, Voss TC, Davis SR, Meltzer PS, Stamatoyannopoulos JA, Hager GL. 2008. Interaction of the

glucocorticoid receptor with the chromatin landscape. Mol Cell 29(5):611–624.

Knowlton JR, Bubunenko M, Andrykovitch M, Guo W, Routzahn KM, Waugh DS, Court DL, Ji X. 2003. A spring-loaded state of NusG in its functional cycle is suggested by X-ray crystallography and site-directed mutants. Biochemistry 42(8):2275–2281.

Kumaran RI, Thakar R, Spector DL. 2008. Chromatin dynamics and gene positioning. Cell 132(6):929–934.

Liu Y, Chen W, Gaudet J, Cheney MD, Roudaia L, Cierpicki T, Klet RC, Hartman K, Laue TM, Speck NA, Bushweller JH. 2007. Structural basis for recognition of SMRT/N-CoR by the MYND domain and its contribution to AML1/ETO's activity. Cancer Cell 11(6):483–497.

Marfella CG, Imbalzano AN. 2007. The Chd family of chromatin remodelers. Mutat Res 618(1–2):30–40.

Martone ME, Tran J, Wong WW, Sargis J, Fong L, Larson S, Lamont SP, Gupta A, Ellisman MH. 2007. The cell centered database project: An update on building community resources for managing and sharing 3D imaging data. J Struct Biol 161(3):220–231.

McBryant SJ, Krause C, Woodcock CL, Hansen JC. 2008. The silent information regulator 3 protein, SIR3p, binds to chromatin fibers and assembles a hypercondensed chromatin architecture in the presence of salt. Mol Cell Biol 28(11):3563–3572.

Pascal LE, Oudes AJ, Petersen TW, Goo YA, Walashek LS, True LD, Liu AY. 2007. Molecular and cellular characterization of ABCG2 in the prostate. BMC Urol 7:6.

Pascal LE, True LD, Campbell DS, Deutsch EW, Risk M, Coleman IM, Eichner LJ, Nelson PS, Liu AY. 2008. Correlation of mRNA and protein levels: Cell type-specific gene expression of cluster designation antigens in the prostate. BMC Genomics 9(1):246.

Pliss A, Koberna K, Vecerova J, Malinsky J, Masata M, Fialova M, Raska I, Berezney R. 2005. Spatio-temporal dynamics at rDNA foci: Global switching between DNA replication and transcription. J Cell Biochem 94(3):554–565.

Pujana MA, Han JD, Starita LM, Stevens KN, Tewari M, Ahn JS, Rennert G, Moreno V, Kirchhoff T, Gold B, Assmann V, Elshamy WM, Rual JF, Levine D, Rozek LS, Gelman RS, Gunsalus KC, Greenberg RA, Sobhian B, Bertin N, Venkatesan K, Ayivi-Guedehoussou N, Sole X, Hernandez P, Lazaro C, Nathanson KL, Weber BL, Cusick ME, Hill DE, Offit K, Livingston DV, Gruber SB, Parvin JD, Vidal M. 2007. Network modeling links breast cancer susceptibility and centrosome dysfunction. Nat Genet 39(11):1338–1349.

Rodriguez AJ, Czaplinski K, Condeelis JS, Singer RH. 2008. Mechanisms and cellular roles of local protein synthesis in mammalian cells. Curr Opin Cell Biol 20(2):144–149.

Ronneberger O, Baddeley D, Scheipl F, Verveer PJ, Burkhardt H, Cremer C, Fahrmeir L, Cremer T, Joffe B. 2008. Spatial quantitative analysis of fluorescently labeled nuclear structures: Problems, methods, pitfalls. Chromosome Res 16(3):523–562.

Somanathan S, Stachowiak EK, Siegel AJ, Stachowiak MK, Berezney R. 2003. Nuclear matrix bound fibroblast growth factor receptor is associated with splicing factor rich and transcriptionally active nuclear speckles. J Cell Biochem 90(4):856–869.

Suganuma T, Pattenden SG, Workman JL. 2008. Diverse functions of WD40 repeat proteins in histone recognition. Genes Dev 22(10):1265–1268.

Takaha N, Resar LM, Vindivich D, Coffey DS. 2004. High mobility group protein HMG1(Y) enhances tumor cell growth, invasion, and matrix metalloproteinase-2 expression in prostate cancer cells. Prostate 60(2):160–170.

Tlsty TD, Coussens LM. 2006. Tumor stroma and regulation of cancer development. Annu Rev Pathol 1:119–150.

Walgenbach-Brunagel G, Burger B, Leman ES, Walgenbach KJ, Tolba R, Heukamp L, Hirner A, Getzenberg RH. 2008. The use of colon cancer associated nuclear antigen CCSA-2 for the blood based detection of colon cancer. J Cell Biochem 104(1):286–294.

Weake VM, Workman JL. 2008. Histone ubiquitination: Triggering gene activity. Mol Cell 29(6):653–663.

Whitby FG, Masters EI, Kramer L, Knowlton JR, Yao Y, Wang CC, Hill CP. 2000. Structural basis for the activation of 20S proteasomes by 11S regulators. Nature 408(6808):115–120.

Young DW, Hassan MQ, Pratap J, Galindo M, Zaidi SK, Lee S, Yang X, Xie R, Javed A, Underwood J, Furcinitti P, Imbalzano AN, Penman S, Nickerson JA, Montecino M, Lian JB, Stein JL, van Wijnen AJ, Stein GS. 2007. Mitotic occupancy and lineage-specific transcriptional control of rRNA genes by Runx2. Nature 445(25):442–446.

Zaidi SK, Young DW, Pockwinse S, Javed A, Lian JB, Stein JL, van Wijnen AJ, Stein GS. 2003. Mitotic partitioning and selective reorganization of tissue-specific transcription factors in progeny cells. Proc Natl Acad Sci USA 100(25):14852–14857.

Zaidi SK, Young DW, Javed A, Pratap J, Montecino M, van Wijnen AJ, Lian JB, Stein JL, Stein GS. 2007. Nuclear microenvironments in biological control and cancer. Nature Rev Cancer 7:454–463.

Zaidi SK, Pande S, Pratap J, Gaur T, Grigoriu S, Ali SA, Stein JL, Lian JB, van Wijnen AJ, Stein GS. 2007. Runx2 deficiency and defective subnuclear targeting bypass senescence to promote immortalization and tumorigenic potential. Proc Natl Acad Sci USA 104(50):19861–19866.