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Minireview

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Intranuclear Trafficking: Organization and Assembly of Regulatory Machinery for Combinatorial Biological Control*

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The molecular logistics of nuclear regulatory processes necessitate temporal and spatial regulation of protein-protein and protein-DNA interactions in response to physiological cues. Biochemical, *in situ*, and *in vivo* genetic evidence demonstrates the requirement for intranuclear localization of regulatory complexes that functionally couple cellular responses to signals that mediate combinatorial control of gene expression. We have summarized evidence that subnuclear targeting of transcription factors mechanistically links gene expression with architectural organization and assembly of nuclear regulatory machinery for biological control. The compromised intranuclear targeting of regulatory proteins under pathological conditions provides options for the diagnosis and treatment of disease.

An Architectural Perspective of Combinatorial Gene Regulation

Components of nuclear architecture are functionally linked to the organization and sorting of regulatory information in a manner that permits selective utilization (1–10). The primary level of nuclear organization, the representation and ordering of genes and promoter elements, provides alternatives for biological control. The molecular organization of regulatory elements, the overlap of regulatory sequences within promoter domains, and the multipartite composition of regulatory complexes increase options for responsiveness. From context dependence of modularly organized promoter sequences and juxtaposition of regulatory domains, parameters of the protein-DNA and protein-protein interactions that dictate the combinatorial assembly and organization of multicomponent regulatory complexes are emerging. Chromatin structure and nucleosome organization reduce distances between regulatory sequences, facilitate cross-talk between promoter elements, and render elements competent for interactions with positive and negative regulatory factors (11). Evidence is emerging for a "histone code" that (through the post-translational modifications of the highly conserved N-terminal tails of histones) defines the activity of a gene promoter. In addition, CpG methylation of specific promoters selectively silences the expression of tissue-specific genes in a manner that supports competency for progenitor cell differentiation with both options and constraints (12, 13).

The components of higher order nuclear architecture, which include nuclear pores, the nuclear matrix, and intranuclear domains, contribute to the bidirectional nucleocytoplasmic exchange of regulatory information as well as to the subnuclear distribution and activities of gene regulatory factors (1, 10, 14). Nuclear localization sequences and export signals within the proteins are recognized by transport machinery that mediates translocation of these proteins between cytoplasm and the nucleus (15). An additional level of regulation is provided by post-translational modifications of nuclear proteins. For example, TEL, a putative tumor suppressor, is exported out of the nucleus when sumoylated, which in turn impairs its ability to repress transcription (16). Similarly, the nuclear translocation of bone morphogenetic protein/transforming growth factor β signal transducers, Smads, and their ability to affect transcription is regulated by phosphorylation (17). Recently, it has been shown that the association of actively transcribed genes with the nuclear pore complex and the nuclear transport factors contributes to transcriptional regulation. Similarly, newly transcribed RNA is exported out of the nucleus in a stringently regulated manner (18–20). Thus, the nuclear membrane controls the flow of regulatory information between the two compartments.

Compartmentalization of nuclear regulatory complexes is illustrated by focal organization of promyelocytic leukemia (PML)[1] bodies (21), Runx (Runt-related factor)/acute myelogenous leukemia (AML)/Cbfa (core binding factor α) domains (2, 6, 22), the nucleolus and chromosomes (5), as well as by the punctate intranuclear distribution of sites for replication (23–25), DNA repair (26), transcription (25, 27–35), steroid and polypeptide modulation of gene expression, and the processing of gene transcripts (36–38). It is necessary to design experiments that define mechanisms that direct genes and regulatory factors to sites within the nucleus where localization integrates regulatory parameters of gene expression and establishes microenvironments with boundaries between regulatory complexes that are required for fidelity of activity.

Nuclear Microenvironments: an Architectural Platform for Organization, Assembly, and Activity of Regulatory Machinery

Nuclear microenvironments that have been functionally as well as architecturally defined are promoter sites and subnuclear domains. Cognate binding sites of basal and tissue-specific transcription factors provide structural platforms to recruit and integrate components of the transcriptional regulatory machinery. Biochemical and *in situ* evidence demonstrates that replication and transcription machinery are compartmentalized as specialized, punctate subnuclear domains (9, 10, 39, 40). Regulatory proteins that function as molecular scaffolds organize nuclear microenvironments both at promoter sites and in subnuclear domains, thereby providing an architectural bridge between two classes of nuclear microenvironments.

Modifications in architectural and functional organization of nucleoli, sites of ribosomal gene expression, are associated with tumorigenesis (41). Nucleolar disruption, which occurs under cellular stress, is required for the stabilization of p53. In normal cells, nucleolar stability sustains p53 levels and consequently its effects on cell proliferation (42). Another example is the relocalization of several proteins involved in insulin growth factor signaling; these nucleolar proteins are redistributed to the nucleus and cytoplasm as a function of myeloid differentiation (43). These findings point to

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[1] The abbreviations used are: PML, promyelocytic leukemia; AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; RAR, retinoic acid receptor; NMTS, nuclear matrix targeting signal.

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a broader involvement of a subnuclear compartment in multiple cellular activities.

Interphase chromatin is arranged in spatially separate chromosome territories, which are linked with gene activation or suppression during interphase as well as with chromosome condensation and segregation during cell division (44). The proximity of chromosomes may facilitate homolog pairing and contribute to chromosomal translocations (45, 46).

There is an increasing understanding of the redistribution of regulatory proteins and genes in response to cellular states and as a function of differentiation. The β-globin gene is associated with repressive chromatin near centromeres and is localized to nuclear periphery before differentiation of multipotent cells to the erythroid lineage. After differentiation, β-globin gene expression is greatly enhanced and is coupled with relocation of the gene to regions of the nucleus that are distant from centromeres and the nuclear periphery (47, 48). Similarly, Ikaros regulatory proteins first localize diffusely in the nucleoplasm and then initiate accumulation at centromeric loci during lymphoid differentiation. This movement coincides with the relocation and inactivation of Ikaros target genes that include CD8α and Rag (49, 50). Reorganization and chromatin decondensation of the *Hoxb* gene cluster has been observed upon transcriptional activation in response to retinoic acid signaling (51). Redistribution of the transcription factor C/EBPα during adipocyte differentiation and reorganization of subnuclear domains containing the pRB and BRCA1 tumor suppressors upon DNA damage are also coupled with biological control (26, 52). Thus, linkage of subnuclear distribution of regulatory proteins with control of gene expression is evident under a series of biological conditions.

Compartmentalization of the tissue-specific Runx transcription factors may accommodate constraints on control of phenotype-specific transcription in hematopoietic, bone, and gastrointestinal cells. The biological relevance for the intranuclear distribution of Runx-containing regulatory complexes is directly reflected by focal localization of Runx proteins within the nucleus for tissue-specific transcription (2, 3, 53) and by aberrant nuclear structure-gene expression interrelationships that are associated with perturbations in leukemia and skeletal disorders (7, 54). Low representation of Runx regulatory elements in the promoters of target genes and Runx transcription factors within the nucleus necessitates a subnuclear organization of nucleic acids and regulatory proteins that supports threshold concentrations for the activation and repression of gene expression.

The punctate subnuclear localization and nuclear matrix association of acute lymphoblastic leukemia-1 (ALL-1) (55), the glucocorticoid receptor (56), the estrogen receptor (57), the androgen receptor (35), and the thyroid hormone receptor (58) are consistent with compartmentalization and focal concentrations of regulatory machinery for biologically responsive integration of regulatory signals. A clinically relevant example of perturbations in regulatory activity that result from modifications in the intranuclear distribution of receptors is illustrated by PML bodies (59). Chromosomal translocations that involve the RAR locus are characteristic of promyelocytic leukemia, resulting in altered composition, number, and intranuclear localization of PML bodies; the changes are attributed to alterations in expression of RAR target genes. Chromosomal rearrangements at the ALL and AML loci similarly alter composition and subnuclear placement of regulatory complexes in nuclear microenvironments associated with tumor-related changes in gene regulatory mechanisms (60).

Scaffolding Proteins Functionally Configure and Organize Regulatory Complexes for Combinatorial Control

Transcription factors that function as scaffolds for interaction with co-regulatory proteins provide an architectural basis for biological control within nuclear microenvironments. Functional interrelationships between nuclear structure and gene expression are reflected by dual recognition of regulatory proteins, such as Runx and ALL-1 transcription factors, for interactions with both promoter elements and co-regulatory proteins.

Placement of Runx proteins at strategic promoter sites as molecular scaffolds results in protein-protein interactions and organization of machinery for a broad spectrum of regulatory requirements. These include histone modifications and chromatin remodeling that increase competency for transcription factor binding and facilitate cross-talk between proximal and upstream promoter regions. Regulatory cues from signaling pathways that activate or repress gene expression in a physiologically responsive manner are integrated. There is a stringent requirement for fidelity of Runx subnuclear targeting to recruit signaling proteins to transcriptionally active or suppressed subnuclear foci (61, 62). Similarly, intranuclear trafficking of Runx proteins has been functionally linked with the subnuclear localization and activity of TLE (transducin-like enhancer)/Groucho co-regulatory proteins (63). In addition, the Runx proteins are post-translationally modified (*e.g.* phosphorylated) to further influence their activity (64, 65). Recent documentation that ALL-1 is part of a stable complex that includes basal transcription factors, chromatin remodeling factors, and histone-modifying proteins indicates the scope of combinatorial control and illustrates the potential impact of leukemia-related chromosomal translocations on gene expression (66). These findings are consistent with nuclear matrix-associated proteins serving as a scaffold for interactions with co-regulatory proteins that contribute to biological control (Fig. 1).

Other examples of combinatorial control are provided by replication, repair, steroid hormone responsiveness, and chromatin remodeling. Scaffold association and permutations of regulatory proteins involved in replication and repair result in the assembly of focally organized multipartite complexes that functionally increase specificity (*e.g.* BRCA1 and proliferating cell nuclear antigen) (26, 67). Yet another biologically relevant example of combinatorial control is the focal assembly of regulatory machinery for glucocorticoid and estrogen-responsive gene expression (31, 32, 56, 57). Similarly, the combinatorial organization of regulatory complexes that are responsible for chromatin structure, nucleosome organization, and dynamics of chromatin remodeling illustrates the scaffolding for factors that establish competency for transcriptional activation and/or suppression (Fig. 2). Nuclear microenvironments are thereby organized by these molecular scaffolds on gene promoters and/or origins of DNA replication or double strand breaks as focal points, where threshold concentrations of regulatory macromolecules are attained for transient and long term biological control.

Intranuclear Trafficking, a Mechanism for Orchestrating Assembly of Regulatory Machinery in the Right Place at the Right Time

At least two trafficking signals appear to be required for subnuclear targeting of nuclear proteins; the first supports nuclear import (nuclear localization signal), and a second mediates residency in nuclear matrix-associated regulatory domains (nuclear matrix targeting signal (NMTS)).

There are numerous examples of functional linkage between deregulated nuclear import and/or retention of regulatory proteins and the onset and progression of tumorigenesis. These include fibroblast growth factor signaling (68), insulin growth factor signaling in hematopoiesis and leukemogenesis (43), translocation fusion proteins in myeloid leukemias (59), Rb (retinoblastoma protein) in osteosarcomas (69), ATRX (α-thalassemia syndrome protein) signaling in neurological abnormalities (70), and activated protein C/β-catenin signaling in colon cancer (71).

The punctate architectural association of Runx transcription factors that mediate tissue-specific transcription has permitted examination of mechanisms that localize regulatory proteins to transcriptionally active subnuclear domains (2, 3, 22, 53). Mutational analysis has established that association of Runx proteins with the nuclear matrix is independent of DNA binding and requires the NMTS. The NMTS is distinct from the nuclear localization signal, functions autonomously, and is necessary as well as sufficient to direct Runx factors to nuclear scaffold-associated sites where gene expression occurs (2, 3, 53). A definitive and comprehensive structural as well as functional characterization of punctately organized transcription sites remains to be established. A viable possibility is that multiple genes with associated regulatory proteins co-occupy these intranuclear foci.

There is a fundamental requirement for postmitotic restoration of nuclear organization and assembly of regulatory complexes. Progressive mitotic changes in the distribution of Runx foci and sequential reorganization of nuclear proteins involved in gene expression have recently been documented. The interphase subnuclear organization of Runx foci is selectively restored in telo-

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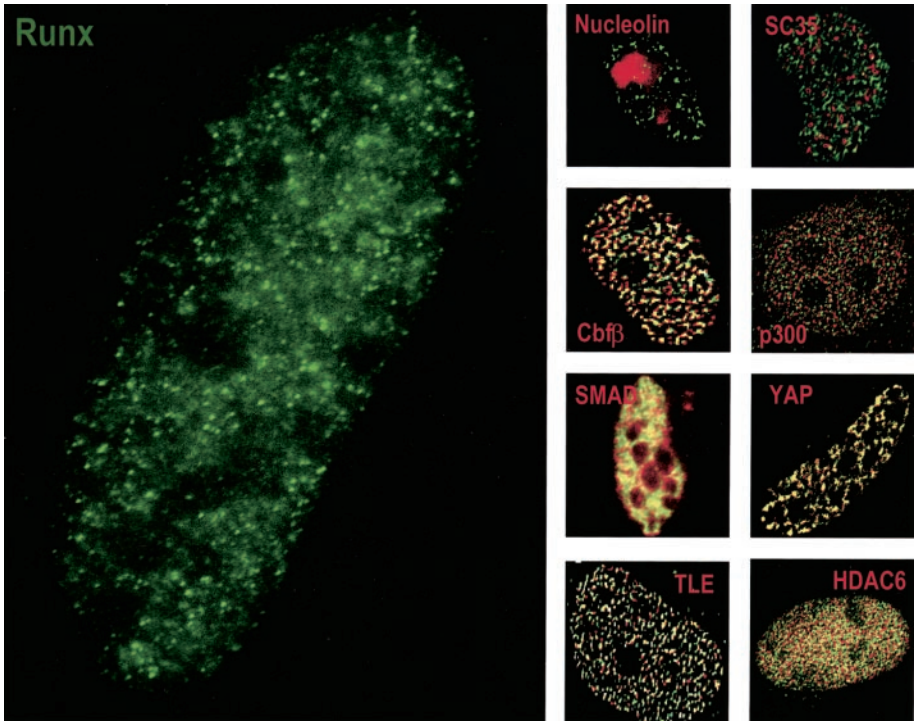

FIG. 1. **Runx proteins function as molecular scaffolds to organize regulatory complexes in the nucleus for combinatorial transcriptional control.** Runx transcription factors are examples of scaffold proteins that are required for lineage commitment and tissue-specific gene expression. Several proteins involved in chromatin remodeling, signal transducers, and factors required for cell cycle progression interact with Runx regulatory proteins. Runx proteins are organized as punctate sites within the nucleus. Many of these proteins are present in Runx nuclear microenvironments where activation or suppression of Runx-regulated genes takes place (*left panel*). Runx domains contain the heterodimeric partner Cbf*β*, histone acetyltransferase p300, co-repressors HDAC6 and TLE/Groucho, as well as signaling molecules Smad and Yes-associated protein (*YAP*) and several other proteins (*bottom right panels*). Runx nuclear microenvironments are however distinct from sites of ribosomal gene synthesis and RNA processing sites (*top right panels*). In all the images shown in this figure, Runx protein was visualized by a specific antibody followed by incubation with secondary antibodies conjugated with Alexa 488 fluorochromes. All other proteins were recognized by specific antibodies (indicated in each *panel*) followed by incubation with secondary antibodies conjugated with Alexa 568 fluorochromes.

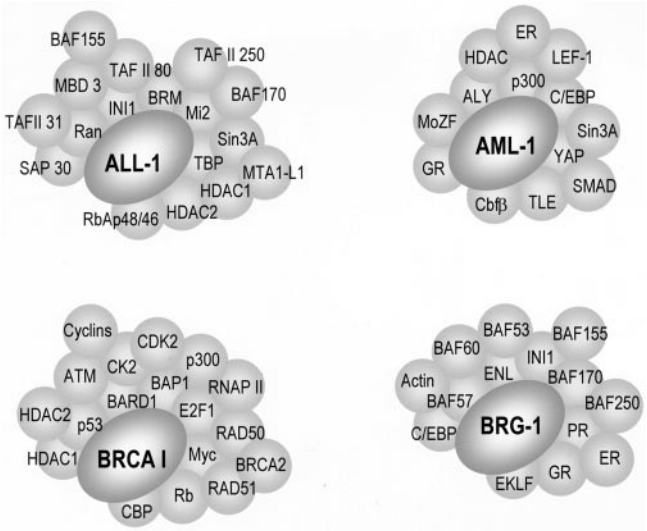

FIG. 2. **Scaffolding nuclear proteins support combinatorial control of gene expression and replication.** The ALL-1 and AML-1 transcription factors, BRCA1 DNA replication/repair protein, and Brg1 chromatin remodeling factor are paradigms for scaffold proteins that support the combinatorial assembly and integration of activity of regulatory proteins. The enzymology for transcription, chromatin remodeling, histone modification, and DNA methylation are non-inclusive examples of regulatory and co-regulatory proteins that are organized on AML and ALL scaffolds. These proteins, together with co-regulatory proteins, are depicted as multiprotein complexes that are assembled at nuclear microenvironments and are involved in transcription, replication, repair, and chromatin remodeling.

phase with equal partitioning of the protein into progeny nuclei (72). Several other proteins, such as ALL-1 (55), UBF-1 (upstream binding factor-1) (73), basonuclin (74), C/EBPβ (75), and TBP (TATA-binding protein) (76), exhibit similar mitotic trafficking. Mechanisms that control the observed association of regulatory proteins with mitotic chromosomes and/or the mitotic apparatus (55, 72–74, 76, 77) are only beginning to be elucidated. However, such trafficking of transcription factors provides the basis to understand postmitotic events that ensure fidelity of gene expression in progeny cells.

Consequences of Perturbations in Architectural Organization of Regulatory Complexes—Biological control requires stringent regulation of subcellular distribution and intranuclear placement of regulatory complexes. Consequently, perturbations in gene expression occur when the architectural organization of regulatory complexes is compromised.

The essential role of Runx2 in osteogenesis has provided a model to investigate the importance of fidelity of subnuclear localization for tissue differentiation. Mice homozygous for Runx2 lacking the NMTS (Runx2ΔC) do not form bone due to maturational arrest of osteoblasts. In a manner analogous with the human bone disorder, cleidocranial dysplasia, heterozygotes do not develop clavicles. These phenotypes are indistinguishable from those of the homozygous and heterozygous null mutants, indicating that the intranuclear targeting signal and its potential to integrate cellular regulatory information at sites within the nucleus are critical determinants for function (78). Similar observations have been documented for Runx1ΔC knock-in mice that exhibit a phenotype which is indistinguishable from mice in which the Runx1 gene has been ablated (79). These results suggest that the subnuclear localization of Runx factors in specific foci together with associated regulatory functions is essential for control of Runx-dependent genes involved in tissue differentiation during embryonic development.

Compromised subnuclear organization and activity of Runx1 hematopoietic regulatory protein in AML further emphasize the importance of subnuclear localization in biological control. A significant portion of chromosomal translocations in AML patients results in a chimeric protein, AML-ETO. This fusion protein exhibits multiple subnuclear targeting signals and organizes into nuclear microenvironments that are distinct from those of wild type Runx1 (7). Thus the pathology of AML can, at least in part, be described as compromised fidelity of Runx1 subnuclear targeting. Another example is provided by a chimeric protein, PML-RAR, which results from the fusion of PML and RAR genes. This chimeric protein results in the dispersal of PML bodies, nuclear microenvironments linked to apoptosis, and other stress-related cellular responses. Treatment of PML patients with retinoic acid results in the remission of leukemia accompanied with the restoration of PML bodies (59). Interestingly, AML-ETO results in the dispersal of PML bodies in a manner that is analogous to the intranuclear distribution of PML-RAR foci (60). Thus, the compromised intranuclear targeting of regulatory proteins under pathological conditions provides options for the diagnosis and treatment of human leukemias.

Functional Implications for Intranuclear Trafficking—Biochemical, *in situ* microscopic, and *in vivo* genetic evidence demonstrate the requirement for intranuclear placement of regulatory com-

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plexes, which is directly linked with cellular response to physiological cues and is essential for combinatorial control of gene expression. Subnuclear targeting of transcription factors and regulatory proteins provides a mechanistic link between the temporal-spatial regulation of gene expression and architectural organization of regulatory complexes within the nucleus. It also establishes the requirement for delivery of regulatory proteins to the right place at the right time.

However, several key questions remain to be elucidated. What are the biochemical and structural requirements to direct regulatory proteins to subnuclear sites? Is energy-dependent motor activity required for the movement of proteins within the nucleus? To what extent does targeting (the mobile fraction) and retention (the immobile fraction) of proteins contribute to focal placement of regulatory complexes within the nucleus? It is necessary to discriminate between regulatory complexes that are tethered to a scaffold and scaffolds that are composites of regulatory proteins. These two models for the architectural organization of regulatory complexes within the nucleus may not be mutually exclusive.

Although cellular and molecular components of nuclear structure-gene expression relationships are not fully understood, the well documented correlation of the onset and progression of tumorigenesis with the compromised intranuclear localization of regulatory complexes provides a viable platform for new dimensions to the diagnosis and treatment of human diseases. Mechanistic insight into gene regulatory processes within the three-dimensional context of nuclear architecture expands options for therapeutic targets and drug delivery to intranuclear sites of gene transcription, replication, and repair.

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REFERENCES

1. Berezney, R., Mortillaro, M., Ma, H., Meng, C., Samarabandu, J., Wei, X., Somanathan, S., Liou, W. S., Pan, S. J., and Cheng, P. C. (1996) *J. Cell. Biochem.* **62,** 223–226
2. Zeng, C., van Wijnen, A. J., Stein, J. L., Meyers, S., Sun, W., Shopland, L., Lawrence, J. B., Penman, S., Lian, J. B., Stein, G. S., and Hiebert, S. W. (1997) *Proc. Natl. Acad. Sci. U. S. A.* **94,** 6746–6751
3. Zeng, C., McNeil, S., Pockwinse, S., Nickerson, J. A., Shopland, L., Lawrence, J. B., Penman, S., Hiebert, S. W., Lian, J. B., van Wijnen, A. J., Stein, J. L., and Stein, G. S. (1998) *Proc. Natl. Acad. Sci. U. S. A.* **95,** 1585–1589
4. Lamond, A. I., and Earnshaw, W. C. (1998) *Science* **280,** 547–553
5. Ma, H., Siegel, A. J., and Berezney, R. (1999) *J. Cell Biol.* **146,** 531–542
6. McNeil, S., Guo, B., Stein, J. L., Lian, J. B., Bushmeyer, S., Seto, E., Atchison, M. L., Penman, S., van Wijnen, A. J., and Stein, G. S. (1998) *J. Cell. Biochem.* **68,** 500–510
7. McNeil, S., Zeng, C., Harrington, K. S., Hiebert, S., Lian, J. B., Stein, J. L., van Wijnen, A. J., and Stein, G. S. (1999) *Proc. Natl. Acad. Sci. U. S. A.* **96,** 14882–14887
8. Stein, G. S., van Wijnen, A. J., Stein, J. L., Lian, J. B., Montecino, M., Choi, J.-Y., Zaidi, K., and Javed, A. (2000) *J. Cell Sci.* **113,** 2527–2533
9. Gasser, S. M. (2002) *Science* **296,** 1412–1416
10. Misteli, T. (2000) *J. Cell Sci.* **113,** 1841–1849
11. Peterson, C. L., and Workman, J. L. (2000) *Curr. Opin. Genet. Dev.* **10,** 187–192
12. Fischle, W., Wang, Y., and Allis, C. D. (2003) *Nature* **425,** 475–479
13. Davie, J. K., and Dent, S. Y. (2004) *Curr. Top. Dev. Biol.* **59,** 145–163
14. Lemon, B., and Tjian, R. (2000) *Genes Dev.* **14,** 2551–2569
15. Mattaj, I. W., and Englmeier, L. (1998) *Annu. Rev. Biochem.* **67,** 265–306
16. Wood, L. D., Irvin, B. J., Nucifora, G., Luce, K. S., and Hiebert, S. W. (2003) *Proc. Natl. Acad. Sci. U. S. A.* **100,** 3257–3262
17. Xu, L., and Massague, J. (2004) *Nat. Rev. Mol. Cell. Biol.* **5,** 209–219
18. Casolari, J. M., Brown, C. R., Komili, S., West, J., Hieronymus, H., and Silver, P. A. (2004) *Cell* **117,** 427–439
19. Hieronymus, H., and Silver, P. A. (2003) *Nat. Genet.* **33,** 155–161
20. Kau, T. R., Way, J. C., and Silver, P. A. (2004) *Nat. Rev. Cancer* **4,** 106–117
21. Dyck, J. A., Maul, G. G., Miller, W. H., Chen, J. D., Kakizuka, A., and Evans, R. M. (1994) *Cell* **76,** 333–343
22. Harrington, K. S., Javed, A., Drissi, H., McNeil, S., Lian, J. B., Stein, J. L., van Wijnen, A. J., Wang, Y.-L., and Stein, G. S. (2002) *J. Cell Sci.* **115,** 4167–4176
23. Leonhardt, H., Rahn, H. P., and Cardoso, M. C. (1998) *J. Cell. Biochem. Suppl.* **30–31,** 243–249
24. Mahadevan, L. C., Willis, A. C., and Barratt, M. J. (1991) *Cell* **65,** 775–783
25. Cook, P. R. (1999) *Science* **284,** 1790–1795
26. Scully, R., and Livingston, D. M. (2000) *Nature* **408,** 429–432
27. Merriman, H. L., van Wijnen, A. J., Hiebert, S., Bidwell, J. P., Fey, E., Lian, J., Stein, J., and Stein, G. S. (1995) *Biochemistry* **34,** 13125–13132
28. Wei, X., Samarabandu, J., Devdhar, R. S., Siegel, A. J., Acharya, R., and Berezney, R. (1998) *Science* **281,** 1502–1505
29. Guo, B., Odgren, P. R., van Wijnen, A. J., Last, T. J., Nickerson, J., Penman, S., Lian, J. B., Stein, J. L., and Stein, G. S. (1995) *Proc. Natl. Acad. Sci. U. S. A.* **92,** 10526–10530
30. Ciejek, E. M., Tsai, M. J., and O'Malley, B. W. (1983) *Nature* **306,** 607–609
31. Htun, H., Barsony, J., Renyi, I., Gould, D. L., and Hager, G. L. (1996) *Proc. Natl. Acad. Sci. U. S. A.* **93,** 4845–4850
32. Stenoien, D., Sharp, Z. D., Smith, C. L., and Mancini, M. A. (1998) *J. Cell. Biochem.* **70,** 213–221
33. Kimura, H., Tao, Y., Roeder, R. G., and Cook, P. R. (1999) *Mol. Cell. Biol.* **19,** 5383–5392
34. Verschure, P. J., van Der Kraan, I., Manders, E. M., and van Driel, R. (1999) *J. Cell Biol.* **147,** 13–24
35. van Steensel, B., Jenster, G., Damm, K., Brinkmann, A. O., and van Driel, R. (1995) *J. Cell. Biochem.* **57,** 465–478
36. Misteli, T., and Spector, D. L. (1999) *Mol. Cell* **3,** 697–705
37. Smith, K. P., Moen, P. T., Wydner, K. L., Coleman, J. R., and Lawrence, J. B. (1999) *J. Cell Biol.* **144,** 617–629
38. Wagner, S., Chiosea, S., and Nickerson, J. A. (2003) *Proc. Natl. Acad. Sci. U. S. A.* **100,** 3269–3274
39. Stein, G. S., Montecino, M., van Wijnen, A. J., Stein, J. L., and Lian, J. B. (2000) *Cancer Res.* **60,** 2067–2076
40. DeFranco, D. B. (2002) *Mol. Endocrinol.* **16,** 1449–1455
41. Olson, M. O., Hingorani, K., and Szebeni, A. (2002) *Int. Rev. Cytol.* **219,** 199–266
42. Rubbi, C. P., and Milner, J. (2003) *EMBO J.* **22,** 6068–6077
43. Baserga, R., Peruzzi, F., and Reiss, K. (2003) *Int. J. Cancer* **107,** 873–877
44. Cremer, T., and Cremer, C. (2001) *Nat. Rev. Genet.* **2,** 292–301
45. Sachs, R. K., Chen, A. M., and Brenner, D. J. (1997) *Int. J. Radiat. Biol.* **71,** 1–19
46. Parada, L. A., McQueen, P. G., Munson, P. J., and Misteli, T. (2002) *Curr. Biol.* **12,** 1692–1697
47. Francastel, C., Magis, W., and Groudine, M. (2001) *Proc. Natl. Acad. Sci. U. S. A.* **98,** 12120–12125
48. Francastel, C., Schubeler, D., Martin, D. I., and Groudine, M. (2000) *Nat. Rev. Mol. Cell. Biol.* **1,** 137–143
49. Brown, K. E., Baxter, J., Graf, D., Merkenschlager, M., and Fisher, A. G. (1999) *Mol. Cell* **3,** 207–217
50. Brown, K. E., Guest, S. S., Smale, S. T., Hahm, K., Merkenschlager, M., and Fisher, A. G. (1997) *Cell* **91,** 845–854
51. Chambeyron, S., and Bickmore, W. A. (2004) *Genes Dev.* **18,** 1119–1130
52. Avni, D., Yang, H., Martelli, F., Hofmann, F., ElShamy, W. M., Ganesan, S., Scully, R., and Livingston, D. M. (2003) *Mol. Cell* **12,** 735–746
53. Zaidi, S. K., Javed, A., Choi, J.-Y., van Wijnen, A. J., Stein, J. L., Lian, J. B., and Stein, G. S. (2001) *J. Cell Sci.* **114,** 3093–3102
54. Barseguian, K., Lutterbach, B., Hiebert, S. W., Nickerson, J., Lian, J. B., Stein, J. L., van Wijnen, A. J., and Stein, G. S. (2002) *Proc. Natl. Acad. Sci. U. S. A.* **99,** 15434–15439
55. Ennas, M. G., Sorio, C., Greim, R., Nieddu, M., Scarpa, A., Orlandini, S., Croce, C. M., Fey, G. H., and Marschalek, R. (1997) *Cancer Res.* **57,** 2035–2041
56. McNally, J. G., Muller, W. G., Walker, D., Wolford, R., and Hager, G. L. (2000) *Science* **287,** 1262–1265
57. Stenoien, D. L., Patel, K., Mancini, M. G., Dutertre, M., Smith, C. L., O'Malley, B. W., and Mancini, M. A. (2001) *Nat. Cell Biol.* **3,** 15–23
58. Nicoll, J. B., Gwinn, B. L., Iwig, J. S., Garcia, P. P., Bunn, C. F., and Allison, L. A. (2003) *Mol. Cell. Endocrinol.* **205,** 65–77
59. Zelent, A., Guidez, F., Melnick, A., Waxman, S., and Licht, J. D. (2001) *Oncogene* **20,** 7186–7203
60. McNeil, S., Javed, A., Harrington, K. S., Lian, J. B., Stein, J. L., van Wijnen, A. J., and Stein, G. S. (2000) *J. Cell. Biochem.* **79,** 103–112
61. Zaidi, S. K., Sullivan, A. J., Medina, R., Ito, Y., van Wijnen, A. J., Stein, J. L., Lian, J. B., and Stein, G. S. (2004) *EMBO J.* **23,** 790–799
62. Zaidi, S. K., Sullivan, A. J., van Wijnen, A. J., Stein, J. L., Stein, G. S., and Lian, J. B. (2002) *Proc. Natl. Acad. Sci. U. S. A.* **99,** 8048–8053
63. Javed, A., Guo, B., Hiebert, S., Choi, J.-Y., Green, J., Zhao, S.-C., Osborne, M. A., Stifani, S., Stein, J. L., Lian, J. B., van Wijnen, A. J., and Stein, G. S. (2000) *J. Cell Sci.* **113,** 2221–2231
64. Wee, H. J., Huang, G., Shigesada, K., and Ito, Y. (2002) *EMBO Rep.* **3,** 967–974
65. Xiao, G., Jiang, D., Gopalakrishnan, R., and Franceschi, R. T. (2002) *J. Biol. Chem.* **277,** 36181–36187
66. Nakamura, T., Mori, T., Tada, S., Krajewski, W., Rozovskaia, T., Wassell, R., Dubois, G., Mazo, A., Croce, C. M., and Canaani, E. (2002) *Mol. Cell* **10,** 1119–1128
67. Hozak, P., Jackson, D. A., and Cook, P. R. (1994) *J. Cell Sci.* **107,** 2191–2202
68. Stachowiak, M. K., Fang, X., Myers, J. M., Dunham, S. M., Berezney, R., Maher, P. A., and Stachowiak, E. K. (2003) *J. Cell. Biochem.* **90,** 662–691
69. Pompetti, F., Rizzo, P., Simon, R. M., Freidlin, B., Mew, D. J., Pass, H. I., Picci, P., Levine, A. S., and Carbone, M. (1996) *J. Cell. Biochem.* **63,** 37–50
70. Berube, N. G., Jagla, M., Smeenk, C., De Repentigny, Y., Kothary, R., and Picketts, D. J. (2002) *Hum. Mol. Genet.* **11,** 253–261
71. Clevers, H. (2004) *Cancer Cell* **5,** 5–6
72. Zaidi, S. K., Young, D. W., Pockwinse, S. H., Javed, A., Lian, J. B., Stein, J. L., van Wijnen, A. J., and Stein, G. S. (2003) *Proc. Natl. Acad. Sci. U. S. A.* **100,** 14852–14857
73. Gebrane-Younes, J., Fomproix, N., and Hernandez-Verdun, D. (1997) *J. Cell Sci.* **110,** 2429–2440
74. Tseng, H., Biegel, J. A., and Brown, R. S. (1999) *J. Cell Sci.* **112,** 3039–3047
75. Tang, Q. Q., Otto, T. C., and Lane, M. D. (2003) *Proc. Natl. Acad. Sci. U. S. A.* **100,** 850–855
76. Chen, D., Hinkley, C. S., Henry, R. W., and Huang, S. (2002) *Mol. Biol. Cell* **13,** 276–284
77. Tang, L., Guo, B., Javed, A., Choi, J.-Y., Hiebert, S., Lian, J. B., van Wijnen, A. J., Stein, J. L., Stein, G. S., and Zhou, G. W. (1999) *J. Biol. Chem.* **274,** 33580–33586
78. Choi, J.-Y., Pratap, J., Javed, A., Zaidi, S. K., Xing, L., Balint, E., Dalamangas, S., Boyce, B., van Wijnen, A. J., Lian, J. B., Stein, J. L., Jones, S. N., and Stein, G. S. (2001) *Proc. Natl. Acad. Sci. U. S. A.* **98,** 8650–8655
79. North, T., Gu, T. L., Stacy, T., Wang, Q., Howard, L., Binder, M., Marin-Padilla, M., and Speck, N. A. (1999) *Development* **126,** 2563–2575

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