# CHAPTER VI

## SUMMARY AND FUTURE DIRECTIONS

Histone deacetylases are required enzymes for cell viability, but are also targeted by chemotherapeutic small molecule inhibitors in cancer. Uncovering the function of each individual HDAC is necessary to further understand how these enzymes contribute to normal cellular homeostasis through regulation of NRs and other transcription factors such as RUNX1, and how disruption of their activity by HDI may affect normal tissues when trying to eradicate cancer cells. The class I enzyme HDAC3 is required for embryogenesis in a knockout mouse model, demonstrating the importance of this enzyme for life. To by-pass embryonic lethality, a conditional knockout strategy was designed to first delete *Hdac3* in the bone marrow, as this organ is a target of HDI in treatment of leukemia.

The *Mx1-Cre* transgenic model allowed for inducible but transient deletion of *Hdac3*, revealing that loss of *Hdac3* affects stem and progenitor hematopoietic cells, but these populations can recover if *Hdac3* is not constantly deleted. In addition to bone marrow cells, *Mx1-Cre*, being regulated by the interferon response, was also expressed highly in the liver. Transient loss of *Hdac3* in the liver had an unexpected phenotype, which also could recover once *Hdac3* expression returned to the organ. Loss of *Hdac3* increased the hepatic amount of neutral lipid and decreased glycogen levels, identified by histochemical analysis. Individual hepatocytes also became hypertrophic, which correlated with increased organ size. As most drugs currently on the market must go

through the liver for metabolism and detoxification, this result is significant if deletion of *Hdac3* caused such a dramatic phenotype. To follow up with this interesting phenotype, a more specific conditional knockout strategy was employed to delete *Hdac3* only in the liver, starting during embryogenesis, using *Alb-Cre*. The effect of *Hdac3* loss was much more dramatic compared to the *Mx1-Cre* model. Complete deletion of *Hdac3* was observed as early at P17 using *Alb-Cre*, and the results of hepatic hypertrophy and imbalance between lipid and carbohydrate were replicated. Strikingly, the initial loss of *Hdac3* did not affect cell proliferation or induce apoptosis in normal hepatocytes, which differs from the phenotype of cell differentiation and apoptosis with HDAC3 knockdown in cancer cell lines.

Since Hdac3 is a key component of NR repressor complexes, and the liver is the major site of metabolism regulated by NRs, it was not surprising to find that many genes transcriptionally regulated by NRs were up-regulated due to loss of *Hdac3* in the liver. Surprisingly, Pparγ, whose expression is usually restricted to adipose tissue, was up-regulated, and specifically, the isoform *Pparγ2* transcript was increased, which also correlated with increased protein levels and increases in Pparγ target genes. Inhibition of Pparγ activity with a known Pparγ antagonist decreased the amount of lipid accumulation in the liver, demonstrating this NR contributed to the *Alb:Hdac3*$^{fl/-}$ phenotype. Many other signaling pathways were also misregulated due to loss of *Hdac3*, and inhibition of the Akt/PI3K/mTOR pathway with the mTOR inhibitor rapamycin *in vivo* partially reversed the lipid accumulation in the liver, further linking this important pathway to metabolic regulation.

The major enzymatic property of HDAC3 is to deacetylate specific lysine

residues on histone N-terminal tails, and loss of *Hdac3* in the liver demonstrated an overall global increase in histone acetylation, with more specific increases in H4K5, H4K8, and H4K12 residues. These increases were not only apparent at promoter regions of up-regulated genes, but also at regions of the genome, which were not generally affected at the transcriptional level. Global histone acetylation decreased the amount of heterochromatin in *Hdac3*-null nuclei, and this was hypothesized to create greater access to DNA by damage inducing agents, resulting in the accumulation of DNA damage. This hypothesis was supported by *in vitro* data in MEFs which demonstrated increased DNA damage and apoptosis when *Hdac3* was depleted (136). Indeed, *in vivo* data from *Hdac3*-null livers correlated with the *in vitro* data in that by P28, *Hdac3*-null hepatocytes had accumulated multiple sites of endogenously produced DNA damage. When damage was induced by a dose of non-lethal irradiation to whole animals, the livers of *Alb:Hdac3*$^{fl/-}$ mice accumulated a greater amount of DNA damage, which also took longer to repair. These data demonstrate that Hdac3 is required for proper genome maintenance.

The multiple insults to the liver, such as misregulated transcriptional activity by NRs and increased lipid metabolism, stimulated the development of phenotypes related to the liver diseases NAFLD, NASH, and cirrhosis as early as 8 weeks of age in *Alb:Hdac3*$^{fl/-}$ mice. Accompanied by endogenously produced DNA damage, these diseases quickly developed into HCC and resulted in death. Features of the mouse HCC phenotype mimicked the human disease, in relation to such aspects as similar biomarker expression. With most animal models, though, the *Alb:Hdac3*$^{fl/-}$ mice did not exactly recapitulate the human condition.

The data presented in this dissertation defines an important role for Hdac3 in liver homeostasis. Future work on the role of Hdac3 and hematopoiesis will require a more defined approach to studying the role of Hdac3 in specific cellular compartments of the hematopoietic system. *In vitro* data has established that function of Hdac3 is necessary for proper DNA repair, specifically non-homologous end joining (NHEJ) (S. Bhaskara, unpublished). NHEJ is the mechanism by which proper VDJ recombination occurs in B-cells, so it will be interesting to create a specific deletion of *Hdac3* in this cell lineage and analyze any effects on this cellular mechanism. Also, as demonstrated in Chapter III, the transcription factor RUNX1 requires binding to HDAC3 for proper repression of target genes. RUNX1 function has been well-defined in T-cell differentiation, so it will be important to identify any disruption of normal T-cell function in an *Hdac3*-specific knockout in the T-cell lineage, especially in regard to Runx1 transcriptional regulation.

The liver provides an additional model organ for the study of Hdac3 function, not only from a metabolic perspective, but from a proliferation point of view. Initially described in 1931, a 70% partial hepatectomy (PHx) can be performed on rodents, and within one week, the liver can regenerate the lost mass by initiating proliferation of quiescent hepatoctyes (reviewed in (452)). It is not true regeneration, as the lobes that are removed do not re-grow; instead, the remaining lobes go through a stage of hyperplasia to enlarge the remaining tissue until the correct liver:body mass ratio is achieved (453). Additionally, the initiation of proliferation is a synchronized process possibly regulated by circadian rhythm, occurring at a similar time in roughly 95% of hepatocytes within 24-48 hours post-surgery (454). This PHx model provides a platform in which to study the role Hdac3 plays in cell cycle regulation, although it may be

complicated based on the background of cellular damage that has already accumulated in *Hdac3*-null livers.

The DNA damage phenotype is an intriguing one, because how the damage occurs in the first place and why it persists over a longer period of time in *Alb:Hdac3*$^{fl/-}$ mice remains in question. One hypothesis is that the DNA damage occurs due to accumulation of ROS as a result of high levels of oxidative stress in *Hdac3*-null livers. *In vivo* treatment of *Alb:Hdac3*$^{fl/-}$ mice with antioxidants such as N-acetylcysteine or taurine, which can scavenge free radicals (455, 456), could possibly delay oxidative DNA damage and further complications such as NASH and HCC. Oxidative damage also leads to DNA lesions as a result of modification of DNA in the presence of ROS. These DNA adducts are usually excised by base excision repair or NER, and can be quantified either within the DNA strand before excision or as an excreted product in urine and feces after excision (457, 458).

The DNA repair pathways involved in the *Alb:Hdac3*$^{fl/-}$ model can be determined in a genetic approach by creating compound knockout mice lacking *Hdac3* in addition to genes involved in preventing genomic instability. One key regulator that is a likely factor in the *Alb:Hdac3*$^{fl/-}$ phenotype is p53. Mice deficient for *p53* expression survive, but develop lymphoma within 3 months of age (459). Crossing *p53*-null mice with *Alb:Hdac3*$^{fl/-}$ mice is hypothesized to accelerate the accumulation of DNA damage early on because cells cannot repair the endogenous DNA damage, thus accumulating mutations faster, possibly mimicking mice in later stages of HCC development. The status of *p53* expression in the *Alb:Hdac3*$^{fl/-}$ mice is currently under investigation, but the expression of p53-target miRNAs (460) decreases as development of HCC occurs (S.

Knutson and A. Summers, unpublished data), suggesting loss of *p53* may be occurring over time and contributing to liver cancer incidence.

Cellular hypertrophy, or degenerative ballooning, of hepatocytes is a histological hallmark of NASH, but the mechanism is currently unknown. It was hypothesized that activation of mTOR through the Akt signaling cascade was a mechanism for hepatocyte hypertrophy in *Hdac3*-null livers, but inhibition of mTOR with rapamycin did not prevent or diminish cellular enlargement (Figure 30). Alternatively, activated Wnt signaling or *c-Myc* overexpression have been linked to cellular hypertrophy (461-463), and also occur in the background of *Hdac3* loss in the liver (Figure 43 and Table 8, respectively). The liver is a good target for adenoviral expression of genes or siRNA through tail vein injection in mice (464), so it may be possible to deliver molecules of interest in an *in vivo* setting, and affect these candidate pathways to identify the mechanisms that regulate hepatocyte cell size.

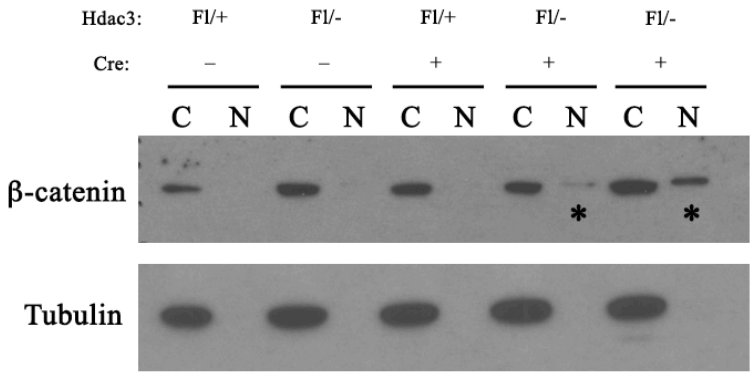


Figure 43. Presence of nuclear β-catenin in P28 *Alb:Hdac3*$^{fl/-}$ mice. Western blot analysis of β-catenin in cytoplasmic (C) and nuclear (N) liver lysate fractions from P28 mice of the indicated genotype. Astericks (*) denote lanes with nuclear β-catenin.

Oval cell activation in the liver has been a controversial topic in the field, due to the question of where the stem cells actually arise from (are they quiescent in liver, the hematopoietic system, or do hepatocytes de-differentiate?), and what changes or mutations lead them down the road to cancer development. The *Alb:Hdac3*$^{fl/-}$ model may be a beneficial model to study oval cell activation, as it occurs quickly and most likely under a period of hepatic stress. As new methods and markers are developed to study hepatic progenitor cells, these may be applied to the *Alb:Hdac3*$^{fl/-}$ mice as well.

Overall, an important biological function of Hdac3 in the liver is to act as a co-repressor for NRs which regulate metabolism in a mouse model. Long-term hepatic disruption of *Hdac3* has detrimental secondary phenotypes, which ultimately lead to HCC. The liver provides a good model organ system in which to study such areas as cell cycle regulation, DNA damage and repair, stem cell activation, and organ homeostasis, while also providing relevant data in regard to an important organ which may be affected by disease and drug treatment. The work presented in this dissertation has also helped to bridge the fields of cellular metabolism and cancer biology, and call into mind possible concern for long-term use of HDI on liver function.

## REFERENCES


1. Alberts, B., Johnson, A., Lewis, J., Raff, M., Roberts, K., Walter, P. (2002) *Molecular Biology of the Cell.* 4 ed. Garland Science.
2. Brown, R. (1833) Observations on the organs and mode of fecundation in Orchidae and Asclepiadeae. *Trans. Linn. Soc. (Lond.),* **16,** 685-743.
3. Schleiden, M.J. (1838) Beitrage zur Phytogenesis. *Muller's Arch. Anat. Physiol. Wiss. Med.***,** 136-176.
4. Schwann, T. (1839) *Mikroskopische Untersuchungen uber die Ubereinstimmung in der Struktur und dem Wachsthum der Thiere und Pflanzen*, Berlin.
5. Remak, R. (1852) *Arch. Anat. Physiol. wiss. Med.*
6. Flemming, W. (1965) Historical Paper. Contributions To The Knowledge Of The Cell And Its Vital Processes. *J Cell Biol,* **25,** SUPPL:1-69.
7. Flemming, W. (1879) Ueber das Verhalten des Kerns bei der Zellteilung und uber die Bedeutung mehrkerniger Zellen. *Virchow's Arch. Pathol. Anat.,* **77,** 1-28.
8. Kossel, A. (1884) Über einen peptoartigen Bestandteil des zellkerns. *Hoppe-Seyler's Z. Physiol. Chem.,* **8,** 511-515.
9. Kossel, A. (1928) *The Protamines and Histones*. Longmans Green and Co., London.
10. Moore, B., Roaf, H.E. and Webster, A. (1912) Direct Measurement of the Osmotic Pressure of Casein in Alkaline Solution. Experimental Proof that apparent impermeability of a Membrane to Ions is not due to the Properties of the Membrane but to the Colloid contained within the Membrane. *Biochem J,* **6,** 110-21.
11. Mirsky, A.E., and Pollister A. W. (1946) Chromosin, a desoxyribose nucleoprotein complex of the cell nucleus. *The Journal of General Physiology,* **30,** 117-148.
12. Mirsky, A.E. and Pollister, A.W. (1942) Nucleoproteins of Cell Nuclei. *Proc Natl Acad Sci U S A,* **28,** 344-52.
13. Stedman, E. (1950) Cell specificity of histones. *Nature,* **166,** 780-1.
14. Avery, O.T., MacLeod, C.M. and McCarty, M. (1979) Studies on the chemical nature of the substance inducing transformation of pneumococcal types. Inductions of transformation by a desoxyribonucleic acid fraction isolated from pneumococcus type III. *J Exp Med,* **149,** 297-326.
15. Daly, M.M., Mirsky, A.E. and Ris, H. (1951) The amino acid composition and some properties of histones. *J Gen Physiol,* **34,** 439-50.
16. Johns, E.W., Phillips, D.M., Simson, P. and Butler, J.A. (1960) Improved fractionations of arginine-rich histones from calf thymus. *Biochem J,* **77,** 631-6.
17. Hnilica, L., Johns, E.W. and Butler, J.A. (1962) Observations on the species and tissue specificity of histones. *Biochem J,* **82,** 123-9.
18. Luck, J.M., Rasmussen, P.S., Satake, K. and Tsvetikov, A.N. (1958) Further studies on the fractionation of calf thymus histone. *J Biol Chem,* **233,** 1407-14.
19. Rasmussen, P.S., Murray, K. and Luck, J.M. (1962) On the complexity of calf thymus histone. *Biochemistry,* **1,** 79-89.

20. Butler, J.A., Johns, E.W. and Phillips, D.M. (1968) Recent investigations on histones and their functions. *Prog Biophys Mol Biol,* **18,** 209-44.
21. Johns, E.W. (1967) The electrophoresis of histones in polyacrylamide gel and their quantitative determination. *Biochem J,* **104,** 78-82.
22. DeLange, R.J., Fambrough, D.M., Smith, E.L. and Bonner, J. (1968) Calf and pea histone IV. I. Amino acid compositions and the identical COOH-terminal 19-residue sequence. *J Biol Chem,* **243,** 5906-13.
23. Iwai, K., Ishikawa, K. and Hayashi, H. (1970) Amino-acid sequence of slightly lysine-rich histone. *Nature,* **226,** 1056-8.
24. Iwai, K., Hayashi, H. and Ishikawa, K. (1972) Calf thymus lysine- and serine-rich histone. 3. Complete amino acid sequence and its implication for interactions of histones with DNA. *J Biochem,* **72,** 357-67.
25. DeLange, R.J., Hooper, J.A. and Smith, E.L. (1972) Complete amino-acid sequence of calf-thymus histone 3. *Proc Natl Acad Sci U S A,* **69,** 882-4.
26. Bustin, M. and Cole, R.D. (1969) A study of the multiplicity of lysine-rich histones. *J Biol Chem,* **244,** 5286-90.
27. Phillips, D.M.P., ed (1971) *Histones and Nucleohistones*. Plenum Press, London and New York.
28. Panyim, S., Chalkley, R., Spiker, S. and Oliver, D. (1970) Constant electrophoretic mobility of the cysteine-containing histone in plants and animals. *Biochim Biophys Acta,* **214,** 216-21.
29. DeLange, R.J. and Smith, E.L. (1971) Histones: structure and function. *Annu Rev Biochem,* **40,** 279-314.
30. Thomas, J.O. and Furber, V. (1976) Yeast chromatin structure. *FEBS Lett,* **66,** 274-80.
31. Goff, C.G. (1976) Histones of Neurospora crassa. *J Biol Chem,* **251,** 4131-8.
32. Felden, R.A., Sanders, M.M. and Morris, N.R. (1976) Presence of histones in Aspergillus nidulans. *J Cell Biol,* **68,** 430-9.
33. Heitz, E. (1928) Das Heterochromatin der Moose. *Jahrb Wiss Botanik,* **69,** 762-818.
34. Littau, V.C., Burdick, C.J., Allfrey, V.G. and Mirsky, S.A. (1965) The role of histones in the maintenance of chromatin structure. *Proc Natl Acad Sci U S A,* **54,** 1204-12.
35. Brown, S.W. and Nur, U. (1964) Heterochromatic Chromosomes In The Coccids. *Science,* **145,** 130-6.
36. Ohno, S., Kaplan, W.D. and Kinosita, R. (1959) Formation of the sex chromatin by a single X-chromosome in liver cells of Rattus norvegicus. *Exp Cell Res,* **18,** 415-8.
37. Lyon, M.F. (1961) Gene action in the X-chromosome of the mouse (Mus musculus L.). *Nature,* **190,** 372-3.
38. Barr, G.C. and Butler, J.A. (1963) Histones And Gene Function. *Nature,* **199,** 1170-2.
39. Frenster, J.H. (1965) A model of specific de-repression within interphase chromatin. *Nature,* **206,** 1269-70.
40. Comings, D.E. (1967) Histones of genetically active and inactive chromatin. *J Cell Biol,* **35,** 699-708.

41. Allfrey, V.G., Littau, V.C. and Mirsky, A.E. (1963) On the role of of histones in regulation ribonucleic acid synthesis in the cell nucleus. *Proc Natl Acad Sci U S A,* **49,** 414-21.
42. Pardon, J.F., Wilkins, M.H. and Richards, B.M. (1967) Super-helical model for nucleohistone. *Nature,* **215,** 508-9.
43. Richards, B.M. and Pardon, J.F. (1970) The molecular structure of nucleohistone (DNH). *Exp Cell Res,* **62,** 184-96.
44. Oudet, P., Gross-Bellard, M. and Chambon, P. (1975) Electron microscopic and biochemical evidence that chromatin structure is a repeating unit. *Cell,* **4,** 281-300.
45. Kornberg, R.D. (1974) Chromatin structure: a repeating unit of histones and DNA. *Science,* **184,** 868-71.
46. Kornberg, R.D. (1977) Structure of chromatin. *Annu Rev Biochem,* **46,** 931-54.
47. Kornberg, R.D. and Thomas, J.O. (1974) Chromatin structure; oligomers of the histones. *Science,* **184,** 865-8.
48. Richmond, T.J., Finch, J.T., Rushton, B., Rhodes, D. and Klug, A. (1984) Structure of the nucleosome core particle at 7 A resolution. *Nature,* **311,** 532-7.
49. Arents, G., Burlingame, R.W., Wang, B.C., Love, W.E. and Moudrianakis, E.N. (1991) The nucleosomal core histone octamer at 3.1 A resolution: a tripartite protein assembly and a left-handed superhelix. *Proc Natl Acad Sci U S A,* **88,** 10148-52.
50. Luger, K., Mader, A.W., Richmond, R.K., Sargent, D.F. and Richmond, T.J. (1997) Crystal structure of the nucleosome core particle at 2.8 A resolution. *Nature,* **389,** 251-60.
51. Davey, C.A., Sargent, D.F., Luger, K., Maeder, A.W. and Richmond, T.J. (2002) Solvent mediated interactions in the structure of the nucleosome core particle at 1.9 a resolution. *J Mol Biol,* **319,** 1097-113.
52. Lilley, D.M., Howarth, O.W., Clark, V.M., Pardon, J.F. and Richards, B.M. (1976) The existence of random coil N-terminal peptides - 'tails' - in native histone complexes. *FEBS Lett,* **62,** 7-10.
53. Weintraub, H. and Van Lente, F. (1974) Dissection of chromosome structure with trypsin and nucleases. *Proc Natl Acad Sci U S A,* **71,** 4249-53.
54. Moore, S.C. and Ausio, J. (1997) Major role of the histones H3-H4 in the folding of the chromatin fiber. *Biochem Biophys Res Commun,* **230,** 136-9.
55. Tse, C. and Hansen, J.C. (1997) Hybrid trypsinized nucleosomal arrays: identification of multiple functional roles of the H2A/H2B and H3/H4 N-termini in chromatin fiber compaction. *Biochemistry,* **36,** 11381-8.
56. Huang, R.C. and Bonner, J. (1962) Histone, a suppressor of chromosomal RNA synthesis. *Proc Natl Acad Sci U S A,* **48,** 1216-22.
57. Strahl, B.D. and Allis, C.D. (2000) The language of covalent histone modifications. *Nature,* **403,** 41-5.
58. Bernstein, B.E., Humphrey, E.L., Erlich, R.L., Schneider, R., Bouman, P., Liu, J.S., Kouzarides, T. and Schreiber, S.L. (2002) Methylation of histone H3 Lys 4 in coding regions of active genes. *Proc Natl Acad Sci U S A,* **99,** 8695-700.
59. Strahl, B.D., Grant, P.A., Briggs, S.D., Sun, Z.W., Bone, J.R., Caldwell, J.A., Mollah, S., Cook, R.G., Shabanowitz, J., Hunt, D.F. *et al.* (2002) Set2 is a

nucleosomal histone H3-selective methyltransferase that mediates transcriptional repression. *Mol Cell Biol,* **22,** 1298-306.
60. Santos-Rosa, H., Schneider, R., Bannister, A.J., Sherriff, J., Bernstein, B.E., Emre, N.C., Schreiber, S.L., Mellor, J. and Kouzarides, T. (2002) Active genes are tri-methylated at K4 of histone H3. *Nature,* **419,** 407-11.
61. Marvin, K.W., Yau, P. and Bradbury, E.M. (1990) Isolation and characterization of acetylated histones H3 and H4 and their assembly into nucleosomes. *J Biol Chem,* **265,** 19839-47.
62. Rea, S., Eisenhaber, F., O'Carroll, D., Strahl, B.D., Sun, Z.W., Schmid, M., Opravil, S., Mechtler, K., Ponting, C.P., Allis, C.D. *et al.* (2000) Regulation of chromatin structure by site-specific histone H3 methyltransferases. *Nature,* **406,** 593-9.
63. Rice, J.C., Briggs, S.D., Ueberheide, B., Barber, C.M., Shabanowitz, J., Hunt, D.F., Shinkai, Y. and Allis, C.D. (2003) Histone methyltransferases direct different degrees of methylation to define distinct chromatin domains. *Mol Cell,* **12,** 1591-8.
64. Barratt, M.J., Hazzalin, C.A., Cano, E. and Mahadevan, L.C. (1994) Mitogen-stimulated phosphorylation of histone H3 is targeted to a small hyperacetylation-sensitive fraction. *Proc Natl Acad Sci U S A,* **91,** 4781-5.
65. Anest, V., Hanson, J.L., Cogswell, P.C., Steinbrecher, K.A., Strahl, B.D. and Baldwin, A.S. (2003) A nucleosomal function for IkappaB kinase-alpha in NF-kappaB-dependent gene expression. *Nature,* **423,** 659-63.
66. Yamamoto, Y., Verma, U.N., Prajapati, S., Kwak, Y.T. and Gaynor, R.B. (2003) Histone H3 phosphorylation by IKK-alpha is critical for cytokine-induced gene expression. *Nature,* **423,** 655-9.
67. Nickel, B.E. and Davie, J.R. (1989) Structure of polyubiquitinated histone H2A. *Biochemistry,* **28,** 964-8.
68. Thorne, A.W., Sautiere, P., Briand, G. and Crane-Robinson, C. (1987) The structure of ubiquitinated histone H2B. *Embo J,* **6,** 1005-10.
69. Nathan, D., Ingvarsdottir, K., Sterner, D.E., Bylebyl, G.R., Dokmanovic, M., Dorsey, J.A., Whelan, K.A., Krsmanovic, M., Lane, W.S., Meluh, P.B. *et al.* (2006) Histone sumoylation is a negative regulator in Saccharomyces cerevisiae and shows dynamic interplay with positive-acting histone modifications. *Genes Dev,* **20,** 966-76.
70. Shiio, Y. and Eisenman, R.N. (2003) Histone sumoylation is associated with transcriptional repression. *Proc Natl Acad Sci U S A,* **100,** 13225-30.
71. Laribee, R.N., Fuchs, S.M. and Strahl, B.D. (2007) H2B ubiquitylation in transcriptional control: a FACT-finding mission. *Genes Dev,* **21,** 737-43.
72. Wang, H., Wang, L., Erdjument-Bromage, H., Vidal, M., Tempst, P., Jones, R.S. and Zhang, Y. (2004) Role of histone H2A ubiquitination in Polycomb silencing. *Nature,* **431,** 873-8.
73. Doyon, Y., Cayrou, C., Ullah, M., Landry, A.J., Cote, V., Selleck, W., Lane, W.S., Tan, S., Yang, X.J. and Cote, J. (2006) ING tumor suppressor proteins are critical regulators of chromatin acetylation required for genome expression and perpetuation. *Mol Cell,* **21,** 51-64.

74. Vogelauer, M., Rubbi, L., Lucas, I., Brewer, B.J. and Grunstein, M. (2002) Histone acetylation regulates the time of replication origin firing. *Mol Cell,* **10,** 1223-33.
75. Hendzel, M.J., Wei, Y., Mancini, M.A., Van Hooser, A., Ranalli, T., Brinkley, B.R., Bazett-Jones, D.P. and Allis, C.D. (1997) Mitosis-specific phosphorylation of histone H3 initiates primarily within pericentromeric heterochromatin during G2 and spreads in an ordered fashion coincident with mitotic chromosome condensation. *Chromosoma,* **106,** 348-60.
76. Wei, Y., Mizzen, C.A., Cook, R.G., Gorovsky, M.A. and Allis, C.D. (1998) Phosphorylation of histone H3 at serine 10 is correlated with chromosome condensation during mitosis and meiosis in Tetrahymena. *Proc Natl Acad Sci U S A,* **95,** 7480-4.
77. Dai, J., Sultan, S., Taylor, S.S. and Higgins, J.M. (2005) The kinase haspin is required for mitotic histone H3 Thr 3 phosphorylation and normal metaphase chromosome alignment. *Genes Dev,* **19,** 472-88.
78. Wei, Y., Yu, L., Bowen, J., Gorovsky, M.A. and Allis, C.D. (1999) Phosphorylation of histone H3 is required for proper chromosome condensation and segregation. *Cell,* **97,** 99-109.
79. Johansen, K.M. and Johansen, J. (2006) Regulation of chromatin structure by histone H3S10 phosphorylation. *Chromosome Res,* **14,** 393-404.
80. Barber, C.M., Turner, F.B., Wang, Y., Hagstrom, K., Taverna, S.D., Mollah, S., Ueberheide, B., Meyer, B.J., Hunt, D.F., Cheung, P. *et al.* (2004) The enhancement of histone H4 and H2A serine 1 phosphorylation during mitosis and S-phase is evolutionarily conserved. *Chromosoma,* **112,** 360-71.
81. Sanders, S.L., Portoso, M., Mata, J., Bahler, J., Allshire, R.C. and Kouzarides, T. (2004) Methylation of histone H4 lysine 20 controls recruitment of Crb2 to sites of DNA damage. *Cell,* **119,** 603-14.
82. Botuyan, M.V., Lee, J., Ward, I.M., Kim, J.E., Thompson, J.R., Chen, J. and Mer, G. (2006) Structural basis for the methylation state-specific recognition of histone H4-K20 by 53BP1 and Crb2 in DNA repair. *Cell,* **127,** 1361-73.
83. Bergink, S., Salomons, F.A., Hoogstraten, D., Groothuis, T.A., de Waard, H., Wu, J., Yuan, L., Citterio, E., Houtsmuller, A.B., Neefjes, J. *et al.* (2006) DNA damage triggers nucleotide excision repair-dependent monoubiquitylation of histone H2A. *Genes Dev,* **20,** 1343-52.
84. Wang, H., Zhai, L., Xu, J., Joo, H.Y., Jackson, S., Erdjument-Bromage, H., Tempst, P., Xiong, Y. and Zhang, Y. (2006) Histone H3 and H4 ubiquitylation by the CUL4-DDB-ROC1 ubiquitin ligase facilitates cellular response to DNA damage. *Mol Cell,* **22,** 383-94.
85. Kreimeyer, A., Wielckens, K., Adamietz, P. and Hilz, H. (1984) DNA repair-associated ADP-ribosylation in vivo. Modification of histone H1 differs from that of the principal acceptor proteins. *J Biol Chem,* **259,** 890-6.
86. Kreimeyer, A., Adamietz, P. and Hilz, H. (1985) Alkylation-induced mono(ADP-ribosyl)-histones H1 and H2B. Hydroxylamine-resistant linkage in hepatoma cells. *Biol Chem Hoppe Seyler,* **366,** 537-44.
87. Boulikas, T. (1989) DNA strand breaks alter histone ADP-ribosylation. *Proc Natl Acad Sci U S A,* **86,** 3499-503.

88. Hassa, P.O., Haenni, S.S., Elser, M. and Hottiger, M.O. (2006) Nuclear ADP-ribosylation reactions in mammalian cells: where are we today and where are we going? *Microbiol Mol Biol Rev,* **70,** 789-829.
89. O'Driscoll, M., Ruiz-Perez, V.L., Woods, C.G., Jeggo, P.A. and Goodship, J.A. (2003) A splicing mutation affecting expression of ataxia-telangiectasia and Rad3-related protein (ATR) results in Seckel syndrome. *Nat Genet,* **33,** 497-501.
90. Rogakou, E.P., Pilch, D.R., Orr, A.H., Ivanova, V.S. and Bonner, W.M. (1998) DNA double-stranded breaks induce histone H2AX phosphorylation on serine 139. *J Biol Chem,* **273,** 5858-68.
91. Thatcher, T.H. and Gorovsky, M.A. (1994) Phylogenetic analysis of the core histones H2A, H2B, H3, and H4. *Nucleic Acids Res,* **22,** 174-9.
92. Fillingham, J., Keogh, M.C. and Krogan, N.J. (2006) GammaH2AX and its role in DNA double-strand break repair. *Biochem Cell Biol,* **84,** 568-77.
93. Bassing, C.H., Chua, K.F., Sekiguchi, J., Suh, H., Whitlow, S.R., Fleming, J.C., Monroe, B.C., Ciccone, D.N., Yan, C., Vlasakova, K. *et al.* (2002) Increased ionizing radiation sensitivity and genomic instability in the absence of histone H2AX. *Proc Natl Acad Sci U S A,* **99,** 8173-8.
94. Celeste, A., Petersen, S., Romanienko, P.J., Fernandez-Capetillo, O., Chen, H.T., Sedelnikova, O.A., Reina-San-Martin, B., Coppola, V., Meffre, E., Difilippantonio, M.J. *et al.* (2002) Genomic instability in mice lacking histone H2AX. *Science,* **296,** 922-7.
95. Phillips, D.M. (1963) The presence of acetyl groups of histones. *Biochem J,* **87,** 258-63.
96. Allfrey, V.G., Faulkner, R. and Mirsky, A.E. (1964) Acetylation And Methylation Of Histones And Their Possible Role In The Regulation Of Rna Synthesis. *Proc Natl Acad Sci U S A,* **51,** 786-94.
97. Gershey, E.L., Vidali, G. and Allfrey, V.G. (1968) Chemical studies of histone acetylation. The occurrence of epsilon-N-acetyllysine in the f2a1 histone. *J Biol Chem,* **243,** 5018-22.
98. Brownell, J.E., Zhou, J., Ranalli, T., Kobayashi, R., Edmondson, D.G., Roth, S.Y. and Allis, C.D. (1996) Tetrahymena histone acetyltransferase A: a homolog to yeast Gcn5p linking histone acetylation to gene activation. *Cell,* **84,** 843-51.
99. Kleff, S., Andrulis, E.D., Anderson, C.W. and Sternglanz, R. (1995) Identification of a gene encoding a yeast histone H4 acetyltransferase. *J Biol Chem,* **270,** 24674-7.
100. Nagy, Z. and Tora, L. (2007) Distinct GCN5/PCAF-containing complexes function as co-activators and are involved in transcription factor and global histone acetylation. *Oncogene,* **26,** 5341-57.
101. Lafon, A., Chang, C.S., Scott, E.M., Jacobson, S.J. and Pillus, L. (2007) MYST opportunities for growth control: yeast genes illuminate human cancer gene functions. *Oncogene,* **26,** 5373-84.
102. Kimura, A., Matsubara, K. and Horikoshi, M. (2005) A decade of histone acetylation: marking eukaryotic chromosomes with specific codes. *J Biochem (Tokyo),* **138,** 647-62.
103. Lee, K.K. and Workman, J.L. (2007) Histone acetyltransferase complexes: one size doesn't fit all. *Nat Rev Mol Cell Biol,* **8,** 284-95.

104. Kikuchi, H., Takami, Y. and Nakayama, T. (2005) GCN5: a supervisor in all-inclusive control of vertebrate cell cycle progression through transcription regulation of various cell cycle-related genes. *Gene,* **347,** 83-97.
105. Yamauchi, T., Yamauchi, J., Kuwata, T., Tamura, T., Yamashita, T., Bae, N., Westphal, H., Ozato, K. and Nakatani, Y. (2000) Distinct but overlapping roles of histone acetylase PCAF and of the closely related PCAF-B/GCN5 in mouse embryogenesis. *Proc Natl Acad Sci U S A,* **97,** 11303-6.
106. Xu, W., Edmondson, D.G., Evrard, Y.A., Wakamiya, M., Behringer, R.R. and Roth, S.Y. (2000) Loss of Gcn5l2 leads to increased apoptosis and mesodermal defects during mouse development. *Nat Genet,* **26,** 229-32.
107. Waterborg, J.H. (2002) Dynamics of histone acetylation in vivo. A function for acetylation turnover? *Biochem Cell Biol,* **80,** 363-78.
108. Byvoet, P. (1968) Differences in turnover between histones and their acetyl N-terminal groups. *Biochim Biophys Acta,* **160,** 217-23.
109. Inoue, A. and Fujimoto, D. (1970) Histone deacetylase from calf thymus. *Biochim Biophys Acta,* **220,** 307-16.
110. Krieger, D.E., Levine, R., Merrifield, R.B., Vidali, G. and Allfrey, V.G. (1974) Chemical studies of histone acetylation. Substrate specificity of a histone deacetylase from calf thymus nuclei. *J Biol Chem,* **249,** 332-4.
111. Fujimoto, D. and Segawa, K. (1973) Enzymatic deacetylation of f2a2 histone. *FEBS Lett,* **32,** 59-61.
112. Kervabon, A., Mery, J. and Parello, J. (1979) Enzymatic deacetylation of a synthetic peptide fragment of histone H4. *FEBS Lett,* **106,** 93-6.
113. Brosch, G., Georgieva, E.I., Lopez-Rodas, G., Lindner, H. and Loidl, P. (1992) Specificity of Zea mays histone deacetylase is regulated by phosphorylation. *J Biol Chem,* **267,** 20561-4.
114. Taunton, J., Hassig, C.A. and Schreiber, S.L. (1996) A mammalian histone deacetylase related to the yeast transcriptional regulator Rpd3p. *Science,* **272,** 408-11.
115. Vidal, M. and Gaber, R.F. (1991) RPD3 encodes a second factor required to achieve maximum positive and negative transcriptional states in Saccharomyces cerevisiae. *Mol Cell Biol,* **11,** 6317-27.
116. Rundlett, S.E., Carmen, A.A., Kobayashi, R., Bavykin, S., Turner, B.M. and Grunstein, M. (1996) HDA1 and RPD3 are members of distinct yeast histone deacetylase complexes that regulate silencing and transcription. *Proc Natl Acad Sci U S A,* **93,** 14503-8.
117. Glozak, M.A., Sengupta, N., Zhang, X. and Seto, E. (2005) Acetylation and deacetylation of non-histone proteins. *Gene,* **363,** 15-23.
118. Yang, W.M., Inouye, C., Zeng, Y., Bearss, D. and Seto, E. (1996) Transcriptional repression by YY1 is mediated by interaction with a mammalian homolog of the yeast global regulator RPD3. *Proc Natl Acad Sci U S A,* **93,** 12845-50.
119. Yang, W.M., Yao, Y.L., Sun, J.M., Davie, J.R. and Seto, E. (1997) Isolation and characterization of cDNAs corresponding to an additional member of the human histone deacetylase gene family. *J Biol Chem,* **272,** 28001-7.
120. Hu, E., Chen, Z., Fredrickson, T., Zhu, Y., Kirkpatrick, R., Zhang, G.F., Johanson, K., Sung, C.M., Liu, R. and Winkler, J. (2000) Cloning and

characterization of a novel human class I histone deacetylase that functions as a transcription repressor. *J Biol Chem,* **275,** 15254-64.
121. Hodawadekar, S.C. and Marmorstein, R. (2007) Chemistry of acetyl transfer by histone modifying enzymes: structure, mechanism and implications for effector design. *Oncogene,* **26,** 5528-40.
122. Hassig, C.A., Tong, J.K., Fleischer, T.C., Owa, T., Grable, P.G., Ayer, D.E. and Schreiber, S.L. (1998) A role for histone deacetylase activity in HDAC1-mediated transcriptional repression. *Proc Natl Acad Sci U S A,* **95,** 3519-24.
123. Ahringer, J. (2000) NuRD and SIN3 histone deacetylase complexes in development. *Trends Genet,* **16,** 351-6.
124. Zhang, Y., Iratni, R., Erdjument-Bromage, H., Tempst, P. and Reinberg, D. (1997) Histone deacetylases and SAP18, a novel polypeptide, are components of a human Sin3 complex. *Cell,* **89,** 357-64.
125. Zhang, Y., Sun, Z.W., Iratni, R., Erdjument-Bromage, H., Tempst, P., Hampsey, M. and Reinberg, D. (1998) SAP30, a novel protein conserved between human and yeast, is a component of a histone deacetylase complex. *Mol Cell,* **1,** 1021-31.
126. Alland, L., David, G., Shen-Li, H., Potes, J., Muhle, R., Lee, H.C., Hou, H., Jr., Chen, K. and DePinho, R.A. (2002) Identification of mammalian Sds3 as an integral component of the Sin3/histone deacetylase corepressor complex. *Mol Cell Biol,* **22,** 2743-50.
127. Silverstein, R.A. and Ekwall, K. (2005) Sin3: a flexible regulator of global gene expression and genome stability. *Curr Genet,* **47,** 1-17.
128. Tong, J.K., Hassig, C.A., Schnitzler, G.R., Kingston, R.E. and Schreiber, S.L. (1998) Chromatin deacetylation by an ATP-dependent nucleosome remodelling complex. *Nature,* **395,** 917-21.
129. Xue, Y., Wong, J., Moreno, G.T., Young, M.K., Cote, J. and Wang, W. (1998) NURD, a novel complex with both ATP-dependent chromatin-remodeling and histone deacetylase activities. *Mol Cell,* **2,** 851-61.
130. Zhang, Y., LeRoy, G., Seelig, H.P., Lane, W.S. and Reinberg, D. (1998) The dermatomyositis-specific autoantigen Mi2 is a component of a complex containing histone deacetylase and nucleosome remodeling activities. *Cell,* **95,** 279-89.
131. Guschin, D., Wade, P.A., Kikyo, N. and Wolffe, A.P. (2000) ATP-Dependent histone octamer mobilization and histone deacetylation mediated by the Mi-2 chromatin remodeling complex. *Biochemistry,* **39,** 5238-45.
132. Yang, X.J. and Seto, E. (2008) The Rpd3/Hda1 family of lysine deacetylases: from bacteria and yeast to mice and men. *Nat Rev Mol Cell Biol,* **9,** 206-18.
133. Lagger, G., O'Carroll, D., Rembold, M., Khier, H., Tischler, J., Weitzer, G., Schuettengruber, B., Hauser, C., Brunmeir, R., Jenuwein, T. *et al.* (2002) Essential function of histone deacetylase 1 in proliferation control and CDK inhibitor repression. *Embo J,* **21,** 2672-81.
134. Zupkovitz, G., Tischler, J., Posch, M., Sadzak, I., Ramsauer, K., Egger, G., Grausenburger, R., Schweifer, N., Chiocca, S., Decker, T. *et al.* (2006) Negative and positive regulation of gene expression by mouse histone deacetylase 1. *Mol Cell Biol,* **26,** 7913-28.

135. Trivedi, C.M., Luo, Y., Yin, Z., Zhang, M., Zhu, W., Wang, T., Floss, T., Goettlicher, M., Noppinger, P.R., Wurst, W. *et al.* (2007) Hdac2 regulates the cardiac hypertrophic response by modulating Gsk3 beta activity. *Nat Med,* **13,** 324-31.
136. Bhaskara, S., Chyla, B.J., Amann, J.M., Knutson, S.K., Cortez, D., Sun, Z.W. and Hiebert, S.W. (2008) Deletion of histone deacetylase 3 reveals critical roles in S phase progression and DNA damage control. *Mol Cell,* **30,** 61-72.
137. Grozinger, C.M., Hassig, C.A. and Schreiber, S.L. (1999) Three proteins define a class of human histone deacetylases related to yeast Hda1p. *Proc Natl Acad Sci U S A,* **96,** 4868-73.
138. Kao, H.Y., Downes, M., Ordentlich, P. and Evans, R.M. (2000) Isolation of a novel histone deacetylase reveals that class I and class II deacetylases promote SMRT-mediated repression. *Genes Dev,* **14,** 55-66.
139. Zhou, X., Marks, P.A., Rifkind, R.A. and Richon, V.M. (2001) Cloning and characterization of a histone deacetylase, HDAC9. *Proc Natl Acad Sci U S A,* **98,** 10572-7.
140. Kao, H.Y., Lee, C.H., Komarov, A., Han, C.C. and Evans, R.M. (2002) Isolation and characterization of mammalian HDAC10, a novel histone deacetylase. *J Biol Chem,* **277,** 187-93.
141. Gao, L., Cueto, M.A., Asselbergs, F. and Atadja, P. (2002) Cloning and functional characterization of HDAC11, a novel member of the human histone deacetylase family. *J Biol Chem,* **277,** 25748-55.
142. Verdin, E., Dequiedt, F. and Kasler, H.G. (2003) Class II histone deacetylases: versatile regulators. *Trends Genet,* **19,** 286-93.
143. Lu, J., McKinsey, T.A., Nicol, R.L. and Olson, E.N. (2000) Signal-dependent activation of the MEF2 transcription factor by dissociation from histone deacetylases. *Proc Natl Acad Sci U S A,* **97,** 4070-5.
144. McKinsey, T.A., Zhang, C.L. and Olson, E.N. (2002) MEF2: a calcium-dependent regulator of cell division, differentiation and death. *Trends Biochem Sci,* **27,** 40-7.
145. Davis, F.J., Gupta, M., Camoretti-Mercado, B., Schwartz, R.J. and Gupta, M.P. (2003) Calcium/calmodulin-dependent protein kinase activates serum response factor transcription activity by its dissociation from histone deacetylase, HDAC4. Implications in cardiac muscle gene regulation during hypertrophy. *J Biol Chem,* **278,** 20047-58.
146. Linseman, D.A., Bartley, C.M., Le, S.S., Laessig, T.A., Bouchard, R.J., Meintzer, M.K., Li, M. and Heidenreich, K.A. (2003) Inactivation of the myocyte enhancer factor-2 repressor histone deacetylase-5 by endogenous Ca(2+) //calmodulin-dependent kinase II promotes depolarization-mediated cerebellar granule neuron survival. *J Biol Chem,* **278,** 41472-81.
147. McKinsey, T.A., Zhang, C.L. and Olson, E.N. (2001) Identification of a signal-responsive nuclear export sequence in class II histone deacetylases. *Mol Cell Biol,* **21,** 6312-21.
148. Grozinger, C.M. and Schreiber, S.L. (2000) Regulation of histone deacetylase 4 and 5 and transcriptional activity by 14-3-3-dependent cellular localization. *Proc Natl Acad Sci U S A,* **97,** 7835-40.

149. McKinsey, T.A., Zhang, C.L. and Olson, E.N. (2000) Activation of the myocyte enhancer factor-2 transcription factor by calcium/calmodulin-dependent protein kinase-stimulated binding of 14-3-3 to histone deacetylase 5. *Proc Natl Acad Sci U S A,* **97,** 14400-5.
150. Chang, S., McKinsey, T.A., Zhang, C.L., Richardson, J.A., Hill, J.A. and Olson, E.N. (2004) Histone deacetylases 5 and 9 govern responsiveness of the heart to a subset of stress signals and play redundant roles in heart development. *Mol Cell Biol,* **24,** 8467-76.
151. Vega, R.B., Matsuda, K., Oh, J., Barbosa, A.C., Yang, X., Meadows, E., McAnally, J., Pomajzl, C., Shelton, J.M., Richardson, J.A. *et al.* (2004) Histone deacetylase 4 controls chondrocyte hypertrophy during skeletogenesis. *Cell,* **119,** 555-66.
152. Chang, S., Young, B.D., Li, S., Qi, X., Richardson, J.A. and Olson, E.N. (2006) Histone deacetylase 7 maintains vascular integrity by repressing matrix metalloproteinase 10. *Cell,* **126,** 321-34.
153. Guardiola, A.R. and Yao, T.P. (2002) Molecular cloning and characterization of a novel histone deacetylase HDAC10. *J Biol Chem,* **277,** 3350-6.
154. Fischer, D.D., Cai, R., Bhatia, U., Asselbergs, F.A., Song, C., Terry, R., Trogani, N., Widmer, R., Atadja, P. and Cohen, D. (2002) Isolation and characterization of a novel class II histone deacetylase, HDAC10. *J Biol Chem,* **277,** 6656-66.
155. Tong, J.J., Liu, J., Bertos, N.R. and Yang, X.J. (2002) Identification of HDAC10, a novel class II human histone deacetylase containing a leucine-rich domain. *Nucleic Acids Res,* **30,** 1114-23.
156. Westendorf, J.J., Zaidi, S.K., Cascino, J.E., Kahler, R., van Wijnen, A.J., Lian, J.B., Yoshida, M., Stein, G.S. and Li, X. (2002) Runx2 (Cbfa1, AML-3) interacts with histone deacetylase 6 and represses the p21(CIP1/WAF1) promoter. *Mol Cell Biol,* **22,** 7982-92.
157. Zhang, Y., Li, N., Caron, C., Matthias, G., Hess, D., Khochbin, S. and Matthias, P. (2003) HDAC-6 interacts with and deacetylates tubulin and microtubules in vivo. *Embo J,* **22,** 1168-79.
158. Matsuyama, A., Shimazu, T., Sumida, Y., Saito, A., Yoshimatsu, Y., Seigneurin-Berny, D., Osada, H., Komatsu, Y., Nishino, N., Khochbin, S. *et al.* (2002) In vivo destabilization of dynamic microtubules by HDAC6-mediated deacetylation. *Embo J,* **21,** 6820-31.
159. Hubbert, C., Guardiola, A., Shao, R., Kawaguchi, Y., Ito, A., Nixon, A., Yoshida, M., Wang, X.F. and Yao, T.P. (2002) HDAC6 is a microtubule-associated deacetylase. *Nature,* **417,** 455-8.
160. Zhang, Y., Kwon, S., Yamaguchi, T., Cubizolles, F., Rousseaux, S., Kneissel, M., Cao, C., Li, N., Cheng, H.L., Chua, K. *et al.* (2008) Mice lacking histone deacetylase 6 have hyperacetylated tubulin but are viable and develop normally. *Mol Cell Biol,* **28,** 1688-701.
161. Gregoretti, I.V., Lee, Y.M. and Goodson, H.V. (2004) Molecular evolution of the histone deacetylase family: functional implications of phylogenetic analysis. *J Mol Biol,* **338,** 17-31.
162. Ivy, J.M., Klar, A.J. and Hicks, J.B. (1986) Cloning and characterization of four SIR genes of Saccharomyces cerevisiae. *Mol Cell Biol,* **6,** 688-702.

163. Brachmann, C.B., Sherman, J.M., Devine, S.E., Cameron, E.E., Pillus, L. and Boeke, J.D. (1995) The SIR2 gene family, conserved from bacteria to humans, functions in silencing, cell cycle progression, and chromosome stability. *Genes Dev,* **9,** 2888-902.
164. Frye, R.A. (1999) Characterization of five human cDNAs with homology to the yeast SIR2 gene: Sir2-like proteins (sirtuins) metabolize NAD and may have protein ADP-ribosyltransferase activity. *Biochem Biophys Res Commun,* **260,** 273-9.
165. Frye, R.A. (2000) Phylogenetic classification of prokaryotic and eukaryotic Sir2-like proteins. *Biochem Biophys Res Commun,* **273,** 793-8.
166. Lin, S.J., Defossez, P.A. and Guarente, L. (2000) Requirement of NAD and SIR2 for life-span extension by calorie restriction in Saccharomyces cerevisiae. *Science,* **289,** 2126-8.
167. Kaeberlein, M., McVey, M. and Guarente, L. (1999) The SIR2/3/4 complex and SIR2 alone promote longevity in Saccharomyces cerevisiae by two different mechanisms. *Genes Dev,* **13,** 2570-80.
168. Smith, J.S., Brachmann, C.B., Celic, I., Kenna, M.A., Muhammad, S., Starai, V.J., Avalos, J.L., Escalante-Semerena, J.C., Grubmeyer, C., Wolberger, C. *et al.* (2000) A phylogenetically conserved NAD+-dependent protein deacetylase activity in the Sir2 protein family. *Proc Natl Acad Sci U S A,* **97,** 6658-63.
169. Landry, J., Sutton, A., Tafrov, S.T., Heller, R.C., Stebbins, J., Pillus, L. and Sternglanz, R. (2000) The silencing protein SIR2 and its homologs are NAD-dependent protein deacetylases. *Proc Natl Acad Sci U S A,* **97,** 5807-11.
170. Vaquero, A., Scher, M.B., Lee, D.H., Sutton, A., Cheng, H.L., Alt, F.W., Serrano, L., Sternglanz, R. and Reinberg, D. (2006) SirT2 is a histone deacetylase with preference for histone H4 Lys 16 during mitosis. *Genes Dev,* **20,** 1256-61.
171. Lombard, D.B., Alt, F.W., Cheng, H.L., Bunkenborg, J., Streeper, R.S., Mostoslavsky, R., Kim, J., Yancopoulos, G., Valenzuela, D., Murphy, A. *et al.* (2007) Mammalian Sir2 homolog SIRT3 regulates global mitochondrial lysine acetylation. *Mol Cell Biol,* **27,** 8807-14.
172. Haigis, M.C., Mostoslavsky, R., Haigis, K.M., Fahie, K., Christodoulou, D.C., Murphy, A.J., Valenzuela, D.M., Yancopoulos, G.D., Karow, M., Blander, G. *et al.* (2006) SIRT4 inhibits glutamate dehydrogenase and opposes the effects of calorie restriction in pancreatic beta cells. *Cell,* **126,** 941-54.
173. Cheng, H.L., Mostoslavsky, R., Saito, S., Manis, J.P., Gu, Y., Patel, P., Bronson, R., Appella, E., Alt, F.W. and Chua, K.F. (2003) Developmental defects and p53 hyperacetylation in Sir2 homolog (SIRT1)-deficient mice. *Proc Natl Acad Sci U S A,* **100,** 10794-9.
174. Vakhrusheva, O., Smolka, C., Gajawada, P., Kostin, S., Boettger, T., Kubin, T., Braun, T. and Bober, E. (2008) Sirt7 Increases Stress Resistance of Cardiomyocytes and Prevents Apoptosis and Inflammatory Cardiomyopathy in Mice. *Circ Res*.
175. Mostoslavsky, R., Chua, K.F., Lombard, D.B., Pang, W.W., Fischer, M.R., Gellon, L., Liu, P., Mostoslavsky, G., Franco, S., Murphy, M.M. *et al.* (2006) Genomic instability and aging-like phenotype in the absence of mammalian SIRT6. *Cell,* **124,** 315-29.

176. Hahnen, E., Hauke, J., Trankle, C., Eyupoglu, I.Y., Wirth, B. and Blumcke, I. (2008) Histone deacetylase inhibitors: possible implications for neurodegenerative disorders. *Expert Opin Investig Drugs,* **17,** 169-84.
177. Li, N., Zhao, D., Kirschbaum, M., Zhang, C., Lin, C.L., Todorov, I., Kandeel, F., Forman, S. and Zeng, D. (2008) HDAC inhibitor reduces cytokine storm and facilitates induction of chimerism that reverses lupus in anti-CD3 conditioning regimen. *Proc Natl Acad Sci U S A,* **105,** 4796-801.
178. Berry, J.M., Cao, D.J., Rothermel, B.A. and Hill, J.A. (2008) Histone deacetylase inhibition in the treatment of heart disease. *Expert Opin Drug Saf,* **7,** 53-67.
179. Gray, S.G. and Dangond, F. (2006) Rationale for the use of histone deacetylase inhibitors as a dual therapeutic modality in multiple sclerosis. *Epigenetics,* **1,** 67-75.
180. Ylisastigui, L., Archin, N.M., Lehrman, G., Bosch, R.J. and Margolis, D.M. (2004) Coaxing HIV-1 from resting CD4 T cells: histone deacetylase inhibition allows latent viral expression. *Aids,* **18,** 1101-8.
181. Riggs, M.G., Whittaker, R.G., Neumann, J.R. and Ingram, V.M. (1977) n-Butyrate causes histone modification in HeLa and Friend erythroleukaemia cells. *Nature,* **268,** 462-4.
182. Vidali, G., Boffa, L.C., Bradbury, E.M. and Allfrey, V.G. (1978) Butyrate suppression of histone deacetylation leads to accumulation of multiacetylated forms of histones H3 and H4 and increased DNase I sensitivity of the associated DNA sequences. *Proc Natl Acad Sci U S A,* **75,** 2239-43.
183. Sealy, L. and Chalkley, R. (1978) The effect of sodium butyrate on histone modification. *Cell,* **14,** 115-21.
184. Tichonicky, L., Santana-Calderon, M.A., Defer, N., Giesen, E.M., Beck, G. and Kruh, J. (1981) Selective inhibition by sodium butyrate of glucocorticoid-induced tyrosine aminotransferase synthesis in hepatoma tissue-cultured cells. *Eur J Biochem,* **120,** 427-33.
185. Kruh, J. (1982) Effects of sodium butyrate, a new pharmacological agent, on cells in culture. *Mol Cell Biochem,* **42,** 65-82.
186. Miller, A.A., Kurschel, E., Osieka, R. and Schmidt, C.G. (1987) Clinical pharmacology of sodium butyrate in patients with acute leukemia. *Eur J Cancer Clin Oncol,* **23,** 1283-7.
187. Tsuji, N., Kobayashi, M., Nagashima, K., Wakisaka, Y. and Koizumi, K. (1976) A new antifungal antibiotic, trichostatin. *J Antibiot (Tokyo),* **29,** 1-6.
188. Yoshida, M., Nomura, S. and Beppu, T. (1987) Effects of trichostatins on differentiation of murine erythroleukemia cells. *Cancer Res,* **47,** 3688-91.
189. Yoshida, M., Kijima, M., Akita, M. and Beppu, T. (1990) Potent and specific inhibition of mammalian histone deacetylase both in vivo and in vitro by trichostatin A. *J Biol Chem,* **265,** 17174-9.
190. Grignani, F., De Matteis, S., Nervi, C., Tomassoni, L., Gelmetti, V., Cioce, M., Fanelli, M., Ruthardt, M., Ferrara, F.F., Zamir, I. *et al.* (1998) Fusion proteins of the retinoic acid receptor-alpha recruit histone deacetylase in promyelocytic leukaemia. *Nature,* **391,** 815-8.
191. Guidez, F., Ivins, S., Zhu, J., Soderstrom, M., Waxman, S. and Zelent, A. (1998) Reduced retinoic acid-sensitivities of nuclear receptor corepressor binding to

PML- and PLZF-RARalpha underlie molecular pathogenesis and treatment of acute promyelocytic leukemia. *Blood,* **91,** 2634-42.
192. He, L.Z., Guidez, F., Tribioli, C., Peruzzi, D., Ruthardt, M., Zelent, A. and Pandolfi, P.P. (1998) Distinct interactions of PML-RARalpha and PLZF-RARalpha with co-repressors determine differential responses to RA in APL. *Nat Genet,* **18,** 126-35.
193. Lin, R.J., Nagy, L., Inoue, S., Shao, W., Miller, W.H., Jr. and Evans, R.M. (1998) Role of the histone deacetylase complex in acute promyelocytic leukaemia. *Nature,* **391,** 811-4.
194. Fenrick, R., Amann, J.M., Lutterbach, B., Wang, L., Westendorf, J.J., Downing, J.R. and Hiebert, S.W. (1999) Both TEL and AML-1 contribute repression domains to the t(12;21) fusion protein. *Mol Cell Biol,* **19,** 6566-74.
195. Amann, J.M., Nip, J., Strom, D.K., Lutterbach, B., Harada, H., Lenny, N., Downing, J.R., Meyers, S. and Hiebert, S.W. (2001) ETO, a target of t(8;21) in acute leukemia, makes distinct contacts with multiple histone deacetylases and binds mSin3A through its oligomerization domain. *Mol Cell Biol,* **21,** 6470-83.
196. Wang, J., Wang, M. and Liu, J.M. (2004) Domains involved in ETO and human N-CoR interaction and ETO transcription repression. *Leuk Res,* **28,** 409-14.
197. Wang, L. and Hiebert, S.W. (2001) TEL contacts multiple co-repressors and specifically associates with histone deacetylase-3. *Oncogene,* **20,** 3716-25.
198. Giles, R.H., Peters, D.J. and Breuning, M.H. (1998) Conjunction dysfunction: CBP/p300 in human disease. *Trends Genet,* **14,** 178-83.
199. Halkidou, K., Gaughan, L., Cook, S., Leung, H.Y., Neal, D.E. and Robson, C.N. (2004) Upregulation and nuclear recruitment of HDAC1 in hormone refractory prostate cancer. *Prostate,* **59,** 177-89.
200. Wilson, A.J., Byun, D.S., Popova, N., Murray, L.B., L'Italien, K., Sowa, Y., Arango, D., Velcich, A., Augenlicht, L.H. and Mariadason, J.M. (2006) Histone deacetylase 3 (HDAC3) and other class I HDACs regulate colon cell maturation and p21 expression and are deregulated in human colon cancer. *J Biol Chem,* **281,** 13548-58.
201. Zhu, P., Martin, E., Mengwasser, J., Schlag, P., Janssen, K.P. and Gottlicher, M. (2004) Induction of HDAC2 expression upon loss of APC in colorectal tumorigenesis. *Cancer Cell,* **5,** 455-63.
202. Cress, W.D. and Seto, E. (2000) Histone deacetylases, transcriptional control, and cancer. *J Cell Physiol,* **184,** 1-16.
203. Muraoka, M., Konishi, M., Kikuchi-Yanoshita, R., Tanaka, K., Shitara, N., Chong, J.M., Iwama, T. and Miyaki, M. (1996) p300 gene alterations in colorectal and gastric carcinomas. *Oncogene,* **12,** 1565-9.
204. Magnaghi-Jaulin, L., Groisman, R., Naguibneva, I., Robin, P., Lorain, S., Le Villain, J.P., Troalen, F., Trouche, D. and Harel-Bellan, A. (1998) Retinoblastoma protein represses transcription by recruiting a histone deacetylase. *Nature,* **391,** 601-5.
205. Le Beau, M.M., Espinosa, R., 3rd, Neuman, W.L., Stock, W., Roulston, D., Larson, R.A., Keinanen, M. and Westbrook, C.A. (1993) Cytogenetic and molecular delineation of the smallest commonly deleted region of chromosome 5 in malignant myeloid diseases. *Proc Natl Acad Sci U S A,* **90,** 5484-8.

206. Mahlknecht, U., Bucala, R., Hoelzer, D. and Verdin, E. (1999) High resolution physical mapping of human HDAC3, a potential tumor suppressor gene in the 5q31 region. *Cytogenet Cell Genet,* **86,** 237-9.
207. Bolden, J.E., Peart, M.J. and Johnstone, R.W. (2006) Anticancer activities of histone deacetylase inhibitors. *Nat Rev Drug Discov,* **5,** 769-84.
208. Phiel, C.J., Zhang, F., Huang, E.Y., Guenther, M.G., Lazar, M.A. and Klein, P.S. (2001) Histone deacetylase is a direct target of valproic acid, a potent anticonvulsant, mood stabilizer, and teratogen. *J Biol Chem,* **276,** 36734-41.
209. Kim, T.Y., Bang, Y.J. and Robertson, K.D. (2006) Histone deacetylase inhibitors for cancer therapy. *Epigenetics,* **1,** 14-23.
210. Saito, A., Yamashita, T., Mariko, Y., Nosaka, Y., Tsuchiya, K., Ando, T., Suzuki, T., Tsuruo, T. and Nakanishi, O. (1999) A synthetic inhibitor of histone deacetylase, MS-27-275, with marked in vivo antitumor activity against human tumors. *Proc Natl Acad Sci U S A,* **96,** 4592-7.
211. Hu, E., Dul, E., Sung, C.M., Chen, Z., Kirkpatrick, R., Zhang, G.F., Johanson, K., Liu, R., Lago, A., Hofmann, G. *et al.* (2003) Identification of novel isoform-selective inhibitors within class I histone deacetylases. *J Pharmacol Exp Ther,* **307,** 720-8.
212. Furumai, R., Matsuyama, A., Kobashi, N., Lee, K.H., Nishiyama, M., Nakajima, H., Tanaka, A., Komatsu, Y., Nishino, N., Yoshida, M. *et al.* (2002) FK228 (depsipeptide) as a natural prodrug that inhibits class I histone deacetylases. *Cancer Res,* **62,** 4916-21.
213. Sasakawa, Y., Naoe, Y., Inoue, T., Sasakawa, T., Matsuo, M., Manda, T. and Mutoh, S. (2002) Effects of FK228, a novel histone deacetylase inhibitor, on human lymphoma U-937 cells in vitro and in vivo. *Biochem Pharmacol,* **64,** 1079-90.
214. Sandor, V., Bakke, S., Robey, R.W., Kang, M.H., Blagosklonny, M.V., Bender, J., Brooks, R., Piekarz, R.L., Tucker, E., Figg, W.D. *et al.* (2002) Phase I trial of the histone deacetylase inhibitor, depsipeptide (FR901228, NSC 630176), in patients with refractory neoplasms. *Clin Cancer Res,* **8,** 718-28.
215. Mie Lee, Y., Kim, S.H., Kim, H.S., Jin Son, M., Nakajima, H., Jeong Kwon, H. and Kim, K.W. (2003) Inhibition of hypoxia-induced angiogenesis by FK228, a specific histone deacetylase inhibitor, via suppression of HIF-1alpha activity. *Biochem Biophys Res Commun,* **300,** 241-6.
216. Kwon, H.J., Kim, M.S., Kim, M.J., Nakajima, H. and Kim, K.W. (2002) Histone deacetylase inhibitor FK228 inhibits tumor angiogenesis. *Int J Cancer,* **97,** 290-6.
217. Ruefli, A.A., Ausserlechner, M.J., Bernhard, D., Sutton, V.R., Tainton, K.M., Kofler, R., Smyth, M.J. and Johnstone, R.W. (2001) The histone deacetylase inhibitor and chemotherapeutic agent suberoylanilide hydroxamic acid (SAHA) induces a cell-death pathway characterized by cleavage of Bid and production of reactive oxygen species. *Proc Natl Acad Sci U S A,* **98,** 10833-8.
218. Nimmanapalli, R., Fuino, L., Stobaugh, C., Richon, V. and Bhalla, K. (2003) Cotreatment with the histone deacetylase inhibitor suberoylanilide hydroxamic acid (SAHA) enhances imatinib-induced apoptosis of Bcr-Abl-positive human acute leukemia cells. *Blood,* **101,** 3236-9.

219. Butler, L.M., Zhou, X., Xu, W.S., Scher, H.I., Rifkind, R.A., Marks, P.A. and Richon, V.M. (2002) The histone deacetylase inhibitor SAHA arrests cancer cell growth, up-regulates thioredoxin-binding protein-2, and down-regulates thioredoxin. *Proc Natl Acad Sci U S A,* **99,** 11700-5.
220. Almenara, J., Rosato, R. and Grant, S. (2002) Synergistic induction of mitochondrial damage and apoptosis in human leukemia cells by flavopiridol and the histone deacetylase inhibitor suberoylanilide hydroxamic acid (SAHA). *Leukemia,* **16,** 1331-43.
221. Yang, G., Thompson, M.A., Brandt, S.J. and Hiebert, S.W. (2007) Histone deacetylase inhibitors induce the degradation of the t(8;21) fusion oncoprotein. *Oncogene,* **26,** 91-101.
222. Deroanne, C.F., Bonjean, K., Servotte, S., Devy, L., Colige, A., Clausse, N., Blacher, S., Verdin, E., Foidart, J.M., Nusgens, B.V. *et al.* (2002) Histone deacetylases inhibitors as anti-angiogenic agents altering vascular endothelial growth factor signaling. *Oncogene,* **21,** 427-36.
223. Itazaki, H., Nagashima, K., Sugita, K., Yoshida, H., Kawamura, Y., Yasuda, Y., Matsumoto, K., Ishii, K., Uotani, N., Nakai, H. *et al.* (1990) Isolation and structural elucidation of new cyclotetrapeptides, trapoxins A and B, having detransformation activities as antitumor agents. *J Antibiot (Tokyo),* **43,** 1524-32.
224. Kijima, M., Yoshida, M., Sugita, K., Horinouchi, S. and Beppu, T. (1993) Trapoxin, an antitumor cyclic tetrapeptide, is an irreversible inhibitor of mammalian histone deacetylase. *J Biol Chem,* **268,** 22429-35.
225. Furumai, R., Komatsu, Y., Nishino, N., Khochbin, S., Yoshida, M. and Horinouchi, S. (2001) Potent histone deacetylase inhibitors built from trichostatin A and cyclic tetrapeptide antibiotics including trapoxin. *Proc Natl Acad Sci U S A,* **98,** 87-92.
226. Park, J.H., Jung, Y., Kim, T.Y., Kim, S.G., Jong, H.S., Lee, J.W., Kim, D.K., Lee, J.S., Kim, N.K., Kim, T.Y. *et al.* (2004) Class I histone deacetylase-selective novel synthetic inhibitors potently inhibit human tumor proliferation. *Clin Cancer Res,* **10,** 5271-81.
227. Kim, B.S., Bae, E., Kim, Y.J., Ahn, K.S., Park, J., Rhee, J.Y., Lee, Y.Y., Kim, Y., Lee, D., Kim, B.K. *et al.* (2007) Combination of SK-7041, one of novel histone deacetylase inhibitors, and STI571-induced synergistic apoptosis in chronic myeloid leukemia. *Anticancer Drugs,* **18,** 641-7.
228. Emiliani, S., Fischle, W., Van Lint, C., Al-Abed, Y. and Verdin, E. (1998) Characterization of a human RPD3 ortholog, HDAC3. *Proc Natl Acad Sci U S A,* **95,** 2795-800.
229. Dangond, F., Hafler, D.A., Tong, J.K., Randall, J., Kojima, R., Utku, N. and Gullans, S.R. (1998) Differential display cloning of a novel human histone deacetylase (HDAC3) cDNA from PHA-activated immune cells. *Biochem Biophys Res Commun,* **242,** 648-52.
230. Dangond, F., Foerznler, D., Weremowicz, S., Morton, C.C., Beier, D.R. and Gullans, S.R. (1999) Cloning and expression of a murine histone deacetylase 3 (mHdac3) cDNA and mapping to a region of conserved synteny between murine chromosome 18 and human chromosome 5. *Mol Cell Biol Res Commun,* **2,** 91-6.

231. Mahlknecht, U., Hoelzer, D., Bucala, R. and Verdin, E. (1999) Cloning and characterization of the murine histone deacetylase (HDAC3). *Biochem Biophys Res Commun,* **263,** 482-90.
232. Yang, W.M., Tsai, S.C., Wen, Y.D., Fejer, G. and Seto, E. (2002) Functional domains of histone deacetylase-3. *J Biol Chem,* **277,** 9447-54.
233. Takami, Y. and Nakayama, T. (2000) N-terminal region, C-terminal region, nuclear export signal, and deacetylation activity of histone deacetylase-3 are essential for the viability of the DT40 chicken B cell line. *J Biol Chem,* **275,** 16191-201.
234. Longworth, M.S. and Laimins, L.A. (2006) Histone deacetylase 3 localizes to the plasma membrane and is a substrate of Src. *Oncogene,* **25,** 4495-500.
235. Escaffit, F., Vaute, O., Chevillard-Briet, M., Segui, B., Takami, Y., Nakayama, T. and Trouche, D. (2007) Cleavage and cytoplasmic relocalization of histone deacetylase 3 are important for apoptosis progression. *Mol Cell Biol,* **27,** 554-67.
236. Baek, S.H., Ohgi, K.A., Rose, D.W., Koo, E.H., Glass, C.K. and Rosenfeld, M.G. (2002) Exchange of N-CoR corepressor and Tip60 coactivator complexes links gene expression by NF-kappaB and beta-amyloid precursor protein. *Cell,* **110,** 55-67.
237. Guenther, M.G., Barak, O. and Lazar, M.A. (2001) The SMRT and N-CoR corepressors are activating cofactors for histone deacetylase 3. *Mol Cell Biol,* **21,** 6091-101.
238. Jeyakumar, M., Liu, X.F., Erdjument-Bromage, H., Tempst, P. and Bagchi, M.K. (2007) Phosphorylation of thyroid hormone receptor-associated nuclear receptor corepressor holocomplex by the DNA-dependent protein kinase enhances its histone deacetylase activity. *J Biol Chem,* **282,** 9312-22.
239. Zhang, X., Ozawa, Y., Lee, H., Wen, Y.D., Tan, T.H., Wadzinski, B.E. and Seto, E. (2005) Histone deacetylase 3 (HDAC3) activity is regulated by interaction with protein serine/threonine phosphatase 4. *Genes Dev,* **19,** 827-39.
240. Li, J., Wang, J., Wang, J., Nawaz, Z., Liu, J.M., Qin, J. and Wong, J. (2000) Both corepressor proteins SMRT and N-CoR exist in large protein complexes containing HDAC3. *Embo J,* **19,** 4342-50.
241. Guenther, M.G., Lane, W.S., Fischle, W., Verdin, E., Lazar, M.A. and Shiekhattar, R. (2000) A core SMRT corepressor complex containing HDAC3 and TBL1, a WD40-repeat protein linked to deafness. *Genes Dev,* **14,** 1048-57.
242. Yoon, H.G., Chan, D.W., Huang, Z.Q., Li, J., Fondell, J.D., Qin, J. and Wong, J. (2003) Purification and functional characterization of the human N-CoR complex: the roles of HDAC3, TBL1 and TBLR1. *Embo J,* **22,** 1336-46.
243. Wen, Y.D., Perissi, V., Staszewski, L.M., Yang, W.M., Krones, A., Glass, C.K., Rosenfeld, M.G. and Seto, E. (2000) The histone deacetylase-3 complex contains nuclear receptor corepressors. *Proc Natl Acad Sci U S A,* **97,** 7202-7.
244. Underhill, C., Qutob, M.S., Yee, S.P. and Torchia, J. (2000) A novel nuclear receptor corepressor complex, N-CoR, contains components of the mammalian SWI/SNF complex and the corepressor KAP-1. *J Biol Chem,* **275,** 40463-70.
245. Sande, S. and Privalsky, M.L. (1996) Identification of TRACs (T3 receptor-associating cofactors), a family of cofactors that associate with, and modulate the activity of, nuclear hormone receptors. *Mol Endocrinol,* **10,** 813-25.

246. Horlein, A.J., Naar, A.M., Heinzel, T., Torchia, J., Gloss, B., Kurokawa, R., Ryan, A., Kamei, Y., Soderstrom, M., Glass, C.K. *et al.* (1995) Ligand-independent repression by the thyroid hormone receptor mediated by a nuclear receptor co-repressor. *Nature,* **377,** 397-404.
247. Chen, J.D. and Evans, R.M. (1995) A transcriptional co-repressor that interacts with nuclear hormone receptors. *Nature,* **377,** 454-7.
248. Park, E.J., Schroen, D.J., Yang, M., Li, H., Li, L. and Chen, J.D. (1999) SMRTe, a silencing mediator for retinoid and thyroid hormone receptors-extended isoform that is more related to the nuclear receptor corepressor. *Proc Natl Acad Sci U S A,* **96,** 3519-24.
249. Ordentlich, P., Downes, M., Xie, W., Genin, A., Spinner, N.B. and Evans, R.M. (1999) Unique forms of human and mouse nuclear receptor corepressor SMRT. *Proc Natl Acad Sci U S A,* **96,** 2639-44.
250. Jepsen, K., Hermanson, O., Onami, T.M., Gleiberman, A.S., Lunyak, V., McEvilly, R.J., Kurokawa, R., Kumar, V., Liu, F., Seto, E. *et al.* (2000) Combinatorial roles of the nuclear receptor corepressor in transcription and development. *Cell,* **102,** 753-63.
251. Wong, C.W. and Privalsky, M.L. (1998) Transcriptional silencing is defined by isoform- and heterodimer-specific interactions between nuclear hormone receptors and corepressors. *Mol Cell Biol,* **18,** 5724-33.
252. Cohen, R.N., Putney, A., Wondisford, F.E. and Hollenberg, A.N. (2000) The nuclear corepressors recognize distinct nuclear receptor complexes. *Mol Endocrinol,* **14,** 900-14.
253. Aasland, R., Stewart, A.F. and Gibson, T. (1996) The SANT domain: a putative DNA-binding domain in the SWI-SNF and ADA complexes, the transcriptional co-repressor N-CoR and TFIIIB. *Trends Biochem Sci,* **21,** 87-8.
254. Boyer, L.A., Latek, R.R. and Peterson, C.L. (2004) The SANT domain: a unique histone-tail-binding module? *Nat Rev Mol Cell Biol,* **5,** 158-63.
255. Codina, A., Love, J.D., Li, Y., Lazar, M.A., Neuhaus, D. and Schwabe, J.W. (2005) Structural insights into the interaction and activation of histone deacetylase 3 by nuclear receptor corepressors. *Proc Natl Acad Sci U S A,* **102,** 6009-14.
256. Zhang, J., Kalkum, M., Chait, B.T. and Roeder, R.G. (2002) The N-CoR-HDAC3 nuclear receptor corepressor complex inhibits the JNK pathway through the integral subunit GPS2. *Mol Cell,* **9,** 611-23.
257. Johnson, C.A., White, D.A., Lavender, J.S., O'Neill, L.P. and Turner, B.M. (2002) Human class I histone deacetylase complexes show enhanced catalytic activity in the presence of ATP and co-immunoprecipitate with the ATP-dependent chaperone protein Hsp70. *J Biol Chem,* **277,** 9590-7.
258. Vermeulen, M., Carrozza, M.J., Lasonder, E., Workman, J.L., Logie, C. and Stunnenberg, H.G. (2004) In vitro targeting reveals intrinsic histone tail specificity of the Sin3/histone deacetylase and N-CoR/SMRT corepressor complexes. *Mol Cell Biol,* **24,** 2364-72.
259. Riester, D., Hildmann, C., Grunewald, S., Beckers, T. and Schwienhorst, A. (2007) Factors affecting the substrate specificity of histone deacetylases. *Biochem Biophys Res Commun,* **357,** 439-45.

260. Hartman, H.B., Yu, J., Alenghat, T., Ishizuka, T. and Lazar, M.A. (2005) The histone-binding code of nuclear receptor co-repressors matches the substrate specificity of histone deacetylase 3. *EMBO Rep,* **6,** 445-51.
261. Knutson, S.K., Chyla, B.J., Amann, J.M., Bhaskara, S., Huppert, S.S. and Hiebert, S.W. (2008) Liver-specific deletion of histone deacetylase 3 disrupts metabolic transcriptional networks. *Embo J,* **27,** 1017-28.
262. Thevenet, L., Mejean, C., Moniot, B., Bonneaud, N., Galeotti, N., Aldrian-Herrada, G., Poulat, F., Berta, P., Benkirane, M. and Boizet-Bonhoure, B. (2004) Regulation of human SRY subcellular distribution by its acetylation/deacetylation. *Embo J,* **23,** 3336-45.
263. Chuang, H.C., Chang, C.W., Chang, G.D., Yao, T.P. and Chen, H. (2006) Histone deacetylase 3 binds to and regulates the GCMa transcription factor. *Nucleic Acids Res,* **34,** 1459-69.
264. Gregoire, S., Xiao, L., Nie, J., Zhang, X., Xu, M., Li, J., Wong, J., Seto, E. and Yang, X.J. (2007) Histone deacetylase 3 interacts with and deacetylates myocyte enhancer factor 2. *Mol Cell Biol,* **27,** 1280-95.
265. Zeng, L., Xiao, Q., Margariti, A., Zhang, Z., Zampetaki, A., Patel, S., Capogrossi, M.C., Hu, Y. and Xu, Q. (2006) HDAC3 is crucial in shear- and VEGF-induced stem cell differentiation toward endothelial cells. *J Cell Biol,* **174,** 1059-69.
266. Chen, L., Fischle, W., Verdin, E. and Greene, W.C. (2001) Duration of nuclear NF-kappaB action regulated by reversible acetylation. *Science,* **293,** 1653-7.
267. Fu, J., Yoon, H.G., Qin, J. and Wong, J. (2007) Regulation of P-TEFb elongation complex activity by CDK9 acetylation. *Mol Cell Biol,* **27,** 4641-51.
268. Fischle, W., Dequiedt, F., Hendzel, M.J., Guenther, M.G., Lazar, M.A., Voelter, W. and Verdin, E. (2002) Enzymatic activity associated with class II HDACs is dependent on a multiprotein complex containing HDAC3 and SMRT/N-CoR. *Mol Cell,* **9,** 45-57.
269. Van Lint, C., Emiliani, S. and Verdin, E. (1996) The expression of a small fraction of cellular genes is changed in response to histone hyperacetylation. *Gene Expr,* **5,** 245-53.
270. Gray, S.G., Qian, C.N., Furge, K., Guo, X. and Teh, B.T. (2004) Microarray profiling of the effects of histone deacetylase inhibitors on gene expression in cancer cell lines. *Int J Oncol,* **24,** 773-95.
271. Peart, M.J., Smyth, G.K., van Laar, R.K., Bowtell, D.D., Richon, V.M., Marks, P.A., Holloway, A.J. and Johnstone, R.W. (2005) Identification and functional significance of genes regulated by structurally different histone deacetylase inhibitors. *Proc Natl Acad Sci U S A,* **102,** 3697-702.
272. Glaser, K.B., Staver, M.J., Waring, J.F., Stender, J., Ulrich, R.G. and Davidsen, S.K. (2003) Gene expression profiling of multiple histone deacetylase (HDAC) inhibitors: defining a common gene set produced by HDAC inhibition in T24 and MDA carcinoma cell lines. *Mol Cancer Ther,* **2,** 151-63.
273. Qiu, L., Burgess, A., Fairlie, D.P., Leonard, H., Parsons, P.G. and Gabrielli, B.G. (2000) Histone deacetylase inhibitors trigger a G2 checkpoint in normal cells that is defective in tumor cells. *Mol Biol Cell,* **11,** 2069-83.

274. Li, Y., Kao, G.D., Garcia, B.A., Shabanowitz, J., Hunt, D.F., Qin, J., Phelan, C. and Lazar, M.A. (2006) A novel histone deacetylase pathway regulates mitosis by modulating Aurora B kinase activity. *Genes Dev,* **20,** 2566-79.
275. Henderson, C., Mizzau, M., Paroni, G., Maestro, R., Schneider, C. and Brancolini, C. (2003) Role of caspases, Bid, and p53 in the apoptotic response triggered by histone deacetylase inhibitors trichostatin-A (TSA) and suberoylanilide hydroxamic acid (SAHA). *J Biol Chem,* **278,** 12579-89.
276. Yu, X., Guo, Z.S., Marcu, M.G., Neckers, L., Nguyen, D.M., Chen, G.A. and Schrump, D.S. (2002) Modulation of p53, ErbB1, ErbB2, and Raf-1 expression in lung cancer cells by depsipeptide FR901228. *J Natl Cancer Inst,* **94,** 504-13.
277. Narla, G., Heath, K.E., Reeves, H.L., Li, D., Giono, L.E., Kimmelman, A.C., Glucksman, M.J., Narla, J., Eng, F.J., Chan, A.M. *et al.* (2001) KLF6, a candidate tumor suppressor gene mutated in prostate cancer. *Science,* **294,** 2563-6.
278. Li, D., Yea, S., Li, S., Chen, Z., Narla, G., Banck, M., Laborda, J., Tan, S., Friedman, J.M., Friedman, S.L. *et al.* (2005) Kruppel-like factor-6 promotes preadipocyte differentiation through histone deacetylase 3-dependent repression of DLK1. *J Biol Chem,* **280,** 26941-52.
279. Bos, T.J., Monteclaro, F.S., Mitsunobu, F., Ball, A.R., Jr., Chang, C.H., Nishimura, T. and Vogt, P.K. (1990) Efficient transformation of chicken embryo fibroblasts by c-Jun requires structural modification in coding and noncoding sequences. *Genes Dev,* **4,** 1677-87.
280. Weiss, C., Schneider, S., Wagner, E.F., Zhang, X., Seto, E. and Bohmann, D. (2003) JNK phosphorylation relieves HDAC3-dependent suppression of the transcriptional activity of c-Jun. *Embo J,* **22,** 3686-95.
281. Gelmetti, V., Zhang, J., Fanelli, M., Minucci, S., Pelicci, P.G. and Lazar, M.A. (1998) Aberrant recruitment of the nuclear receptor corepressor-histone deacetylase complex by the acute myeloid leukemia fusion partner ETO. *Mol Cell Biol,* **18,** 7185-91.
282. Lai, A., Lee, J.M., Yang, W.M., DeCaprio, J.A., Kaelin, W.G., Jr., Seto, E. and Branton, P.E. (1999) RBP1 recruits both histone deacetylase-dependent and -independent repression activities to retinoblastoma family proteins. *Mol Cell Biol,* **19,** 6632-41.
283. Nicolas, E., Ait-Si-Ali, S. and Trouche, D. (2001) The histone deacetylase HDAC3 targets RbAp48 to the retinoblastoma protein. *Nucleic Acids Res,* **29,** 3131-6.
284. Fajas, L., Egler, V., Reiter, R., Hansen, J., Kristiansen, K., Debril, M.B., Miard, S. and Auwerx, J. (2002) The retinoblastoma-histone deacetylase 3 complex inhibits PPARgamma and adipocyte differentiation. *Dev Cell,* **3,** 903-10.
285. Robinson-Rechavi, M., Carpentier, A.S., Duffraisse, M. and Laudet, V. (2001) How many nuclear hormone receptors are there in the human genome? *Trends Genet,* **17,** 554-6.
286. Kininis, M. and Kraus, W.L. (2008) A global view of transcriptional regulation by nuclear receptors: gene expression, factor localization, and DNA sequence analysis. *Nucl Recept Signal,* **6,** e005.

287. Mangelsdorf, D.J., Thummel, C., Beato, M., Herrlich, P., Schutz, G., Umesono, K., Blumberg, B., Kastner, P., Mark, M., Chambon, P. *et al.* (1995) The nuclear receptor superfamily: the second decade. *Cell,* **83,** 835-9.
288. Fu, M., Rao, M., Bouras, T., Wang, C., Wu, K., Zhang, X., Li, Z., Yao, T.P. and Pestell, R.G. (2005) Cyclin D1 inhibits peroxisome proliferator-activated receptor gamma-mediated adipogenesis through histone deacetylase recruitment. *J Biol Chem,* **280,** 16934-41.
289. Pascual, G., Fong, A.L., Ogawa, S., Gamliel, A., Li, A.C., Perissi, V., Rose, D.W., Willson, T.M., Rosenfeld, M.G. and Glass, C.K. (2005) A SUMOylation-dependent pathway mediates transrepression of inflammatory response genes by PPAR-gamma. *Nature,* **437,** 759-63.
290. Ishizuka, T. and Lazar, M.A. (2003) The N-CoR/histone deacetylase 3 complex is required for repression by thyroid hormone receptor. *Mol Cell Biol,* **23,** 5122-31.
291. Li, J., Lin, Q., Wang, W., Wade, P. and Wong, J. (2002) Specific targeting and constitutive association of histone deacetylase complexes during transcriptional repression. *Genes Dev,* **16,** 687-92.
292. Zhu, Y., Qi, C., Korenberg, J.R., Chen, X.N., Noya, D., Rao, M.S. and Reddy, J.K. (1995) Structural organization of mouse peroxisome proliferator-activated receptor gamma (mPPAR gamma) gene: alternative promoter use and different splicing yield two mPPAR gamma isoforms. *Proc Natl Acad Sci U S A,* **92,** 7921-5.
293. Elbrecht, A., Chen, Y., Cullinan, C.A., Hayes, N., Leibowitz, M., Moller, D.E. and Berger, J. (1996) Molecular cloning, expression and characterization of human peroxisome proliferator activated receptors gamma 1 and gamma 2. *Biochem Biophys Res Commun,* **224,** 431-7.
294. Fajas, L., Auboeuf, D., Raspe, E., Schoonjans, K., Lefebvre, A.M., Saladin, R., Najib, J., Laville, M., Fruchart, J.C., Deeb, S. *et al.* (1997) The organization, promoter analysis, and expression of the human PPARgamma gene. *J Biol Chem,* **272,** 18779-89.
295. Zhu, Y., Alvares, K., Huang, Q., Rao, M.S. and Reddy, J.K. (1993) Cloning of a new member of the peroxisome proliferator-activated receptor gene family from mouse liver. *J Biol Chem,* **268,** 26817-20.
296. Werman, A., Hollenberg, A., Solanes, G., Bjorbaek, C., Vidal-Puig, A.J. and Flier, J.S. (1997) Ligand-independent activation domain in the N terminus of peroxisome proliferator-activated receptor gamma (PPARgamma). Differential activity of PPARgamma1 and -2 isoforms and influence of insulin. *J Biol Chem,* **272,** 20230-5.
297. Ren, D., Collingwood, T.N., Rebar, E.J., Wolffe, A.P. and Camp, H.S. (2002) PPARgamma knockdown by engineered transcription factors: exogenous PPARgamma2 but not PPARgamma1 reactivates adipogenesis. *Genes Dev,* **16,** 27-32.
298. Chawla, A., Schwarz, E.J., Dimaculangan, D.D. and Lazar, M.A. (1994) Peroxisome proliferator-activated receptor (PPAR) gamma: adipose-predominant expression and induction early in adipocyte differentiation. *Endocrinology,* **135,** 798-800.

299. Bishop-Bailey, D. and Wray, J. (2003) Peroxisome proliferator-activated receptors: a critical review on endogenous pathways for ligand generation. *Prostaglandins Other Lipid Mediat,* **71,** 1-22.
300. Xu, H.E., Lambert, M.H., Montana, V.G., Parks, D.J., Blanchard, S.G., Brown, P.J., Sternbach, D.D., Lehmann, J.M., Wisely, G.B., Willson, T.M. *et al.* (1999) Molecular recognition of fatty acids by peroxisome proliferator-activated receptors. *Mol Cell,* **3,** 397-403.
301. Forman, B.M., Tontonoz, P., Chen, J., Brun, R.P., Spiegelman, B.M. and Evans, R.M. (1995) 15-Deoxy-delta 12, 14-prostaglandin J2 is a ligand for the adipocyte determination factor PPAR gamma. *Cell,* **83,** 803-12.
302. Kliewer, S.A., Lenhard, J.M., Willson, T.M., Patel, I., Morris, D.C. and Lehmann, J.M. (1995) A prostaglandin J2 metabolite binds peroxisome proliferator-activated receptor gamma and promotes adipocyte differentiation. *Cell,* **83,** 813-9.
303. Lehmann, J.M., Moore, L.B., Smith-Oliver, T.A., Wilkison, W.O., Willson, T.M. and Kliewer, S.A. (1995) An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR gamma). *J Biol Chem,* **270,** 12953-6.
304. Berger, J., Bailey, P., Biswas, C., Cullinan, C.A., Doebber, T.W., Hayes, N.S., Saperstein, R., Smith, R.G. and Leibowitz, M.D. (1996) Thiazolidinediones produce a conformational change in peroxisomal proliferator-activated receptor-gamma: binding and activation correlate with antidiabetic actions in db/db mice. *Endocrinology,* **137,** 4189-95.
305. Willson, T.M., Cobb, J.E., Cowan, D.J., Wiethe, R.W., Correa, I.D., Prakash, S.R., Beck, K.D., Moore, L.B., Kliewer, S.A. and Lehmann, J.M. (1996) The structure-activity relationship between peroxisome proliferator-activated receptor gamma agonism and the antihyperglycemic activity of thiazolidinediones. *J Med Chem,* **39,** 665-8.
306. Moller, D.E. and Greene, D.A. (2001) Peroxisome proliferator-activated receptor (PPAR) gamma agonists for diabetes. *Adv Protein Chem,* **56,** 181-212.
307. Olefsky, J.M. and Saltiel, A.R. (2000) PPAR gamma and the treatment of insulin resistance. *Trends Endocrinol Metab,* **11,** 362-8.
308. Inzucchi, S.E., Maggs, D.G., Spollett, G.R., Page, S.L., Rife, F.S., Walton, V. and Shulman, G.I. (1998) Efficacy and metabolic effects of metformin and troglitazone in type II diabetes mellitus. *N Engl J Med,* **338,** 867-72.
309. Rangwala, S.M. and Lazar, M.A. (2004) Peroxisome proliferator-activated receptor gamma in diabetes and metabolism. *Trends Pharmacol Sci,* **25,** 331-6.
310. Arakawa, K., Ishihara, T., Aoto, M., Inamasu, M., Kitamura, K. and Saito, A. (2004) An antidiabetic thiazolidinedione induces eccentric cardiac hypertrophy by cardiac volume overload in rats. *Clin Exp Pharmacol Physiol,* **31,** 8-13.
311. Koenig, R.J. (1998) Thyroid hormone receptor coactivators and corepressors. *Thyroid,* **8,** 703-13.
312. Lazar, M.A. (1993) Thyroid hormone receptors: multiple forms, multiple possibilities. *Endocr Rev,* **14,** 184-93.
313. Viguerie, N. and Langin, D. (2003) Effect of thyroid hormone on gene expression. *Curr Opin Clin Nutr Metab Care,* **6,** 377-81.

314. Brent, G.A. (2000) Tissue-specific actions of thyroid hormone: insights from animal models. *Rev Endocr Metab Disord,* **1,** 27-33.
315. Tugwood, J.D., Issemann, I., Anderson, R.G., Bundell, K.R., McPheat, W.L. and Green, S. (1992) The mouse peroxisome proliferator activated receptor recognizes a response element in the 5' flanking sequence of the rat acyl CoA oxidase gene. *Embo J,* **11,** 433-9.
316. Kliewer, S.A., Umesono, K., Mangelsdorf, D.J. and Evans, R.M. (1992) Retinoid X receptor interacts with nuclear receptors in retinoic acid, thyroid hormone and vitamin D3 signalling. *Nature,* **355,** 446-9.
317. Kliewer, S.A., Umesono, K., Noonan, D.J., Heyman, R.A. and Evans, R.M. (1992) Convergence of 9-cis retinoic acid and peroxisome proliferator signalling pathways through heterodimer formation of their receptors. *Nature,* **358,** 771-4.
318. Kuhn, R., Schwenk, F., Aguet, M. and Rajewsky, K. (1995) Inducible gene targeting in mice. *Science,* **269,** 1427-9.
319. Postic, C. and Magnuson, M.A. (2000) DNA excision in liver by an albumin-Cre transgene occurs progressively with age. *Genesis,* **26,** 149-50.
320. Postic, C., Shiota, M., Niswender, K.D., Jetton, T.L., Chen, Y., Moates, J.M., Shelton, K.D., Lindner, J., Cherrington, A.D. and Magnuson, M.A. (1999) Dual roles for glucokinase in glucose homeostasis as determined by liver and pancreatic beta cell-specific gene knock-outs using Cre recombinase. *J Biol Chem,* **274,** 305-15.
321. Thomas, P.D., Campbell, M.J., Kejariwal, A., Mi, H., Karlak, B., Daverman, R., Diemer, K., Muruganujan, A. and Narechania, A. (2003) PANTHER: a library of protein families and subfamilies indexed by function. *Genome Res,* **13,** 2129-41.
322. Mi, H., Guo, N., Kejariwal, A. and Thomas, P.D. (2007) PANTHER version 6: protein sequence and function evolution data with expanded representation of biological pathways. *Nucleic Acids Res,* **35,** D247-52.
323. Zhu, M.Y., Hasty, A.H., Harris, C., Linton, M.F., Fazio, S. and Swift, L.L. (2005) Physiological relevance of apolipoprotein E recycling: studies in primary mouse hepatocytes. *Metabolism,* **54,** 1309-15.
324. van Wijnen, A.J., Stein, G.S., Gergen, J.P., Groner, Y., Hiebert, S.W., Ito, Y., Liu, P., Neil, J.C., Ohki, M. and Speck, N. (2004) Nomenclature for Runt-related (RUNX) proteins. *Oncogene,* **23,** 4209-10.
325. Gergen, J.P. and Wieschaus, E.F. (1985) The localized requirements for a gene affecting segmentation in Drosophila: analysis of larvae mosaic for runt. *Dev Biol,* **109,** 321-35.
326. Wheeler, J.C., VanderZwan, C., Xu, X., Swantek, D., Tracey, W.D. and Gergen, J.P. (2002) Distinct in vivo requirements for establishment versus maintenance of transcriptional repression. *Nat Genet,* **32,** 206-10.
327. Swantek, D. and Gergen, J.P. (2004) Ftz modulates Runt-dependent activation and repression of segment-polarity gene transcription. *Development,* **131,** 2281-90.
328. Zhang, D.E., Hetherington, C.J., Meyers, S., Rhoades, K.L., Larson, C.J., Chen, H.M., Hiebert, S.W. and Tenen, D.G. (1996) CCAAT enhancer-binding protein (C/EBP) and AML1 (CBF alpha2) synergistically activate the macrophage colony-stimulating factor receptor promoter. *Mol Cell Biol,* **16,** 1231-40.

329. Britos-Bray, M. and Friedman, A.D. (1997) Core binding factor cannot synergistically activate the myeloperoxidase proximal enhancer in immature myeloid cells without c-Myb. *Mol Cell Biol,* **17,** 5127-35.
330. Goetz, T.L., Gu, T.L., Speck, N.A. and Graves, B.J. (2000) Auto-inhibition of Ets-1 is counteracted by DNA binding cooperativity with core-binding factor alpha2. *Mol Cell Biol,* **20,** 81-90.
331. Gu, T.L., Goetz, T.L., Graves, B.J. and Speck, N.A. (2000) Auto-inhibition and partner proteins, core-binding factor beta (CBFbeta) and Ets-1, modulate DNA binding by CBFalpha2 (AML1). *Mol Cell Biol,* **20,** 91-103.
332. Cameron, E.R. and Neil, J.C. (2004) The Runx genes: lineage-specific oncogenes and tumor suppressors. *Oncogene,* **23,** 4308-14.
333. Aronson, B.D., Fisher, A.L., Blechman, K., Caudy, M. and Gergen, J.P. (1997) Groucho-dependent and -independent repression activities of Runt domain proteins. *Mol Cell Biol,* **17,** 5581-7.
334. Lutterbach, B. and Hiebert, S.W. (2000) Role of the transcription factor AML-1 in acute leukemia and hematopoietic differentiation. *Gene,* **245,** 223-35.
335. 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. *et al.* (2000) Groucho/TLE/R-esp proteins associate with the nuclear matrix and repress RUNX (CBF(alpha)/AML/PEBP2(alpha)) dependent activation of tissue-specific gene transcription. *J Cell Sci,* **113 (Pt 12),** 2221-31.
336. Nishimura, M., Fukushima-Nakase, Y., Fujita, Y., Nakao, M., Toda, S., Kitamura, N., Abe, T. and Okuda, T. (2004) VWRPY motif-dependent and -independent roles of AML1/Runx1 transcription factor in murine hematopoietic development. *Blood,* **103,** 562-70.
337. Taniuchi, I., Osato, M., Egawa, T., Sunshine, M.J., Bae, S.C., Komori, T., Ito, Y. and Littman, D.R. (2002) Differential requirements for Runx proteins in CD4 repression and epigenetic silencing during T lymphocyte development. *Cell,* **111,** 621-33.
338. Telfer, J.C., Hedblom, E.E., Anderson, M.K., Laurent, M.N. and Rothenberg, E.V. (2004) Localization of the domains in Runx transcription factors required for the repression of CD4 in thymocytes. *J Immunol,* **172,** 4359-70.
339. Gamou, T., Kitamura, E., Hosoda, F., Shimizu, K., Shinohara, K., Hayashi, Y., Nagase, T., Yokoyama, Y. and Ohki, M. (1998) The partner gene of AML1 in t(16;21) myeloid malignancies is a novel member of the MTG8(ETO) family. *Blood,* **91,** 4028-37.
340. Miyoshi, H., Kozu, T., Shimizu, K., Enomoto, K., Maseki, N., Kaneko, Y., Kamada, N. and Ohki, M. (1993) The t(8;21) translocation in acute myeloid leukemia results in production of an AML1-MTG8 fusion transcript. *Embo J,* **12,** 2715-21.
341. Miyoshi, H., Shimizu, K., Kozu, T., Maseki, N., Kaneko, Y. and Ohki, M. (1991) t(8;21) breakpoints on chromosome 21 in acute myeloid leukemia are clustered within a limited region of a single gene, AML1. *Proc Natl Acad Sci U S A,* **88,** 10431-4.

342. Erickson, P.F., Robinson, M., Owens, G. and Drabkin, H.A. (1994) The ETO portion of acute myeloid leukemia t(8;21) fusion transcript encodes a highly evolutionarily conserved, putative transcription factor. *Cancer Res,* **54,** 1782-6.
343. Peterson, L.F. and Zhang, D.E. (2004) The 8;21 translocation in leukemogenesis. *Oncogene,* **23,** 4255-62.
344. Golub, T.R., Barker, G.F., Bohlander, S.K., Hiebert, S.W., Ward, D.C., Bray-Ward, P., Morgan, E., Raimondi, S.C., Rowley, J.D. and Gilliland, D.G. (1995) Fusion of the TEL gene on 12p13 to the AML1 gene on 21q22 in acute lymphoblastic leukemia. *Proc Natl Acad Sci U S A,* **92,** 4917-21.
345. Romana, S.P., Mauchauffe, M., Le Coniat, M., Chumakov, I., Le Paslier, D., Berger, R. and Bernard, O.A. (1995) The t(12;21) of acute lymphoblastic leukemia results in a tel-AML1 gene fusion. *Blood,* **85,** 3662-70.
346. Hiebert, S.W., Sun, W., Davis, J.N., Golub, T., Shurtleff, S., Buijs, A., Downing, J.R., Grosveld, G., Roussell, M.F., Gilliland, D.G. *et al.* (1996) The t(12;21) translocation converts AML-1B from an activator to a repressor of transcription. *Mol Cell Biol,* **16,** 1349-55.
347. Chakrabarti, S.R. and Nucifora, G. (1999) The leukemia-associated gene TEL encodes a transcription repressor which associates with SMRT and mSin3A. *Biochem Biophys Res Commun,* **264,** 871-7.
348. Guidez, F., Petrie, K., Ford, A.M., Lu, H., Bennett, C.A., MacGregor, A., Hannemann, J., Ito, Y., Ghysdael, J., Greaves, M. *et al.* (2000) Recruitment of the nuclear receptor corepressor N-CoR by the TEL moiety of the childhood leukemia-associated TEL-AML1 oncoprotein. *Blood,* **96,** 2557-61.
349. Fenrick, R., Wang, L., Nip, J., Amann, J.M., Rooney, R.J., Walker-Daniels, J., Crawford, H.C., Hulboy, D.L., Kinch, M.S., Matrisian, L.M. *et al.* (2000) TEL, a putative tumor suppressor, modulates cell growth and cell morphology of ras-transformed cells while repressing the transcription of stromelysin-1. *Mol Cell Biol,* **20,** 5828-39.
350. Liu, P., Tarle, S.A., Hajra, A., Claxton, D.F., Marlton, P., Freedman, M., Siciliano, M.J. and Collins, F.S. (1993) Fusion between transcription factor CBF beta/PEBP2 beta and a myosin heavy chain in acute myeloid leukemia. *Science,* **261,** 1041-4.
351. Lutterbach, B., Hou, Y., Durst, K.L. and Hiebert, S.W. (1999) The inv(16) encodes an acute myeloid leukemia 1 transcriptional corepressor. *Proc Natl Acad Sci U S A,* **96,** 12822-7.
352. Durst, K.L., Lutterbach, B., Kummalue, T., Friedman, A.D. and Hiebert, S.W. (2003) The inv(16) fusion protein associates with corepressors via a smooth muscle myosin heavy-chain domain. *Mol Cell Biol,* **23,** 607-19.
353. Jenuwein, T. and Allis, C.D. (2001) Translating the histone code. *Science,* **293,** 1074-80.
354. Lachner, M., O'Carroll, D., Rea, S., Mechtler, K. and Jenuwein, T. (2001) Methylation of histone H3 lysine 9 creates a binding site for HP1 proteins. *Nature,* **410,** 116-20.
355. Jacobs, S.A., Taverna, S.D., Zhang, Y., Briggs, S.D., Li, J., Eissenberg, J.C., Allis, C.D. and Khorasanizadeh, S. (2001) Specificity of the HP1 chromo domain for the methylated N-terminus of histone H3. *Embo J,* **20,** 5232-41.

356. Firestein, R., Cui, X., Huie, P. and Cleary, M.L. (2000) Set domain-dependent regulation of transcriptional silencing and growth control by SUV39H1, a mammalian ortholog of Drosophila Su(var)3-9. *Mol Cell Biol,* **20,** 4900-9.
357. Hiebert, S.W., Lutterbach, B. and Amann, J. (2001) Role of co-repressors in transcriptional repression mediated by the t(8;21), t(16;21), t(12;21), and inv(16) fusion proteins. *Curr Opin Hematol,* **8,** 197-200.
358. Reed-Inderbitzin, E., Moreno-Miralles, I., Vanden-Eynden, S.K., Xie, J., Lutterbach, B., Durst-Goodwin, K.L., Luce, K.S., Irvin, B.J., Cleary, M.L., Brandt, S.J. *et al.* (2006) RUNX1 associates with histone deacetylases and SUV39H1 to repress transcription. *Oncogene*.
359. Yokomizo, T., Ogawa, M., Osato, M., Kanno, T., Yoshida, H., Fujimoto, T., Fraser, S., Nishikawa, S., Okada, H., Satake, M. *et al.* (2001) Requirement of Runx1/AML1/PEBP2alphaB for the generation of haematopoietic cells from endothelial cells. *Genes Cells,* **6,** 13-23.
360. Mukouyama, Y., Chiba, N., Hara, T., Okada, H., Ito, Y., Kanamaru, R., Miyajima, A., Satake, M. and Watanabe, T. (2000) The AML1 transcription factor functions to develop and maintain hematogenic precursor cells in the embryonic aorta-gonad-mesonephros region. *Dev Biol,* **220,** 27-36.
361. Okuda, T., van Deursen, J., Hiebert, S.W., Grosveld, G. and Downing, J.R. (1996) AML1, the target of multiple chromosomal translocations in human leukemia, is essential for normal fetal liver hematopoiesis. *Cell,* **84,** 321-30.
362. Alcalay, M., Zangrilli, D., Pandolfi, P.P., Longo, L., Mencarelli, A., Giacomucci, A., Rocchi, M., Biondi, A., Rambaldi, A., Lo Coco, F. *et al.* (1991) Translocation breakpoint of acute promyelocytic leukemia lies within the retinoic acid receptor alpha locus. *Proc Natl Acad Sci U S A,* **88,** 1977-81.
363. Spear, B.T., Jin, L., Ramasamy, S. and Dobierzewska, A. (2006) Transcriptional control in the mammalian liver: liver development, perinatal repression, and zonal gene regulation. *Cell Mol Life Sci,* **63,** 2922-38.
364. Staudinger, J.L. and Lichti, K. (2008) Cell signaling and nuclear receptors: new opportunities for molecular pharmaceuticals in liver disease. *Mol Pharm,* **5,** 17-34.
365. Alaynick, W.A. (2008) Nuclear receptors, mitochondria and lipid metabolism. *Mitochondrion*.
366. Downes, M. and Liddle, C. (2008) Look who's talking: nuclear receptors in the liver and gastrointestinal tract. *Cell Metab,* **7,** 195-9.
367. Widmer, J., Fassihi, K.S., Schlichter, S.C., Wheeler, K.S., Crute, B.E., King, N., Nutile-McMenemy, N., Noll, W.W., Daniel, S., Ha, J. *et al.* (1996) Identification of a second human acetyl-CoA carboxylase gene. *Biochem J,* **316 (Pt 3),** 915-22.
368. Xu, F., Rychnovsky, S.D., Belani, J.D., Hobbs, H.H., Cohen, J.C. and Rawson, R.B. (2005) Dual roles for cholesterol in mammalian cells. *Proc Natl Acad Sci U S A,* **102,** 14551-6.
369. Clapham, J.C. and Arch, J.R. (2007) Thermogenic and metabolic antiobesity drugs: rationale and opportunities. *Diabetes Obes Metab,* **9,** 259-75.
370. Debeljak, N., Horvat, S., Vouk, K., Lee, M. and Rozman, D. (2000) Characterization of the mouse lanosterol 14alpha-demethylase (CYP51), a new

member of the evolutionarily most conserved cytochrome P450 family. *Arch Biochem Biophys,* **379,** 37-45.
371. Guan, H.P., Ishizuka, T., Chui, P.C., Lehrke, M. and Lazar, M.A. (2005) Corepressors selectively control the transcriptional activity of PPARgamma in adipocytes. *Genes Dev,* **19,** 453-61.
372. Fingar, D.C. and Blenis, J. (2004) Target of rapamycin (TOR): an integrator of nutrient and growth factor signals and coordinator of cell growth and cell cycle progression. *Oncogene,* **23,** 3151-71.
373. Hay, N. and Sonenberg, N. (2004) Upstream and downstream of mTOR. *Genes Dev,* **18,** 1926-45.
374. Mordier, S. and Iynedjian, P.B. (2007) Activation of mammalian target of rapamycin complex 1 and insulin resistance induced by palmitate in hepatocytes. *Biochem Biophys Res Commun,* **362,** 206-11.
375. Brown, N.F., Stefanovic-Racic, M., Sipula, I.J. and Perdomo, G. (2007) The mammalian target of rapamycin regulates lipid metabolism in primary cultures of rat hepatocytes. *Metabolism,* **56,** 1500-7.
376. Hernandez, R., Teruel, T. and Lorenzo, M. (2001) Akt mediates insulin induction of glucose uptake and up-regulation of GLUT4 gene expression in brown adipocytes. *FEBS Lett,* **494,** 225-31.
377. Luo, J., Su, F., Chen, D., Shiloh, A. and Gu, W. (2000) Deacetylation of p53 modulates its effect on cell growth and apoptosis. *Nature,* **408,** 377-81.
378. Ashburner, B.P., Westerheide, S.D. and Baldwin, A.S., Jr. (2001) The p65 (RelA) subunit of NF-kappaB interacts with the histone deacetylase (HDAC) corepressors HDAC1 and HDAC2 to negatively regulate gene expression. *Mol Cell Biol,* **21,** 7065-77.
379. Juan, L.J., Shia, W.J., Chen, M.H., Yang, W.M., Seto, E., Lin, Y.S. and Wu, C.W. (2000) Histone deacetylases specifically down-regulate p53-dependent gene activation. *J Biol Chem,* **275,** 20436-43.
380. Shimazu, T., Komatsu, Y., Nakayama, K.I., Fukazawa, H., Horinouchi, S. and Yoshida, M. (2006) Regulation of SV40 large T-antigen stability by reversible acetylation. *Oncogene,* **25,** 7391-400.
381. Picard, F., Kurtev, M., Chung, N., Topark-Ngarm, A., Senawong, T., Machado De Oliveira, R., Leid, M., McBurney, M.W. and Guarente, L. (2004) Sirt1 promotes fat mobilization in white adipocytes by repressing PPAR-gamma. *Nature,* **429,** 771-6.
382. Tontonoz, P., Hu, E. and Spiegelman, B.M. (1994) Stimulation of adipogenesis in fibroblasts by PPAR gamma 2, a lipid-activated transcription factor. *Cell,* **79,** 1147-56.
383. Yu, S., Matsusue, K., Kashireddy, P., Cao, W.Q., Yeldandi, V., Yeldandi, A.V., Rao, M.S., Gonzalez, F.J. and Reddy, J.K. (2003) Adipocyte-specific gene expression and adipogenic steatosis in the mouse liver due to peroxisome proliferator-activated receptor gamma1 (PPARgamma1) overexpression. *J Biol Chem,* **278,** 498-505.
384. Zhang, Y.L., Hernandez-Ono, A., Siri, P., Weisberg, S., Conlon, D., Graham, M.J., Crooke, R.M., Huang, L.S. and Ginsberg, H.N. (2006) Aberrant hepatic expression of PPARgamma2 stimulates hepatic lipogenesis in a mouse model of

obesity, insulin resistance, dyslipidemia, and hepatic steatosis. *J Biol Chem,* **281,** 37603-15.
385. Inoguchi, T., Li, P., Umeda, F., Yu, H.Y., Kakimoto, M., Imamura, M., Aoki, T., Etoh, T., Hashimoto, T., Naruse, M. *et al.* (2000) High glucose level and free fatty acid stimulate reactive oxygen species production through protein kinase C--dependent activation of NAD(P)H oxidase in cultured vascular cells. *Diabetes,* **49,** 1939-45.
386. Carlsson, C., Borg, L.A. and Welsh, N. (1999) Sodium palmitate induces partial mitochondrial uncoupling and reactive oxygen species in rat pancreatic islets in vitro. *Endocrinology,* **140,** 3422-8.
387. Ono, H., Shimano, H., Katagiri, H., Yahagi, N., Sakoda, H., Onishi, Y., Anai, M., Ogihara, T., Fujishiro, M., Viana, A.Y. *et al.* (2003) Hepatic Akt activation induces marked hypoglycemia, hepatomegaly, and hypertriglyceridemia with sterol regulatory element binding protein involvement. *Diabetes,* **52,** 2905-13.
388. Haga, S., Ogawa, W., Inoue, H., Terui, K., Ogino, T., Igarashi, R., Takeda, K., Akira, S., Enosawa, S., Furukawa, H. *et al.* (2005) Compensatory recovery of liver mass by Akt-mediated hepatocellular hypertrophy in liver-specific STAT3-deficient mice. *J Hepatol,* **43,** 799-807.
389. Jacinto, E., Loewith, R., Schmidt, A., Lin, S., Ruegg, M.A., Hall, A. and Hall, M.N. (2004) Mammalian TOR complex 2 controls the actin cytoskeleton and is rapamycin insensitive. *Nat Cell Biol,* **6,** 1122-8.
390. Loewith, R., Jacinto, E., Wullschleger, S., Lorberg, A., Crespo, J.L., Bonenfant, D., Oppliger, W., Jenoe, P. and Hall, M.N. (2002) Two TOR complexes, only one of which is rapamycin sensitive, have distinct roles in cell growth control. *Mol Cell,* **10,** 457-68.
391. Marks, P.A., Richon, V.M., Breslow, R. and Rifkind, R.A. (2001) Histone deacetylase inhibitors as new cancer drugs. *Curr Opin Oncol,* **13,** 477-83.
392. Sanyal, A.J. (2005) Mechanisms of Disease: pathogenesis of nonalcoholic fatty liver disease. *Nat Clin Pract Gastroenterol Hepatol,* **2,** 46-53.
393. Funahashi, T. and Matsuzawa, Y. (2007) Metabolic syndrome: clinical concept and molecular basis. *Ann Med,* **39,** 482-94.
394. Ford, E.S. (2005) Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the U.S. *Diabetes Care,* **28,** 2745-9.
395. Hamaguchi, M., Kojima, T., Takeda, N., Nakagawa, T., Taniguchi, H., Fujii, K., Omatsu, T., Nakajima, T., Sarui, H., Shimazaki, M. *et al.* (2005) The metabolic syndrome as a predictor of nonalcoholic fatty liver disease. *Ann Intern Med,* **143,** 722-8.
396. Sanyal, A.J., Campbell-Sargent, C., Mirshahi, F., Rizzo, W.B., Contos, M.J., Sterling, R.K., Luketic, V.A., Shiffman, M.L. and Clore, J.N. (2001) Nonalcoholic steatohepatitis: association of insulin resistance and mitochondrial abnormalities. *Gastroenterology,* **120,** 1183-92.
397. Powell, E.E., Cooksley, W.G., Hanson, R., Searle, J., Halliday, J.W. and Powell, L.W. (1990) The natural history of nonalcoholic steatohepatitis: a follow-up study of forty-two patients for up to 21 years. *Hepatology,* **11,** 74-80.

398. Wanless, I.R. and Lentz, J.S. (1990) Fatty liver hepatitis (steatohepatitis) and obesity: an autopsy study with analysis of risk factors. *Hepatology,* **12,** 1106-10.
399. Chitturi, S., Abeygunasekera, S., Farrell, G.C., Holmes-Walker, J., Hui, J.M., Fung, C., Karim, R., Lin, R., Samarasinghe, D., Liddle, C. *et al.* (2002) NASH and insulin resistance: Insulin hypersecretion and specific association with the insulin resistance syndrome. *Hepatology,* **35,** 373-9.
400. Reddy, J.K. and Rao, M.S. (2006) Lipid metabolism and liver inflammation. II. Fatty liver disease and fatty acid oxidation. *Am J Physiol Gastrointest Liver Physiol,* **290,** G852-8.
401. Mendez-Sanchez, N., Arrese, M., Zamora-Valdes, D. and Uribe, M. (2007) Current concepts in the pathogenesis of nonalcoholic fatty liver disease. *Liver Int,* **27,** 423-33.
402. Day, C.P. and James, O.F. (1998) Steatohepatitis: a tale of two "hits"? *Gastroenterology,* **114,** 842-5.
403. Tilg, H. and Diehl, A.M. (2000) Cytokines in alcoholic and nonalcoholic steatohepatitis. *N Engl J Med,* **343,** 1467-76.
404. Schulze-Osthoff, K., Bakker, A.C., Vanhaesebroeck, B., Beyaert, R., Jacob, W.A. and Fiers, W. (1992) Cytotoxic activity of tumor necrosis factor is mediated by early damage of mitochondrial functions. Evidence for the involvement of mitochondrial radical generation. *J Biol Chem,* **267,** 5317-23.
405. Chavin, K.D., Yang, S., Lin, H.Z., Chatham, J., Chacko, V.P., Hoek, J.B., Walajtys-Rode, E., Rashid, A., Chen, C.H., Huang, C.C. *et al.* (1999) Obesity induces expression of uncoupling protein-2 in hepatocytes and promotes liver ATP depletion. *J Biol Chem,* **274,** 5692-700.
406. Robertson, G., Leclercq, I. and Farrell, G.C. (2001) Nonalcoholic steatosis and steatohepatitis. II. Cytochrome P-450 enzymes and oxidative stress. *Am J Physiol Gastrointest Liver Physiol,* **281,** G1135-9.
407. Friedman, S.L. (2004) Mechanisms of disease: Mechanisms of hepatic fibrosis and therapeutic implications. *Nat Clin Pract Gastroenterol Hepatol,* **1,** 98-105.
408. Osterreicher, C.H., Stickel, F. and Brenner, D.A. (2007) Genomics of liver fibrosis and cirrhosis. *Semin Liver Dis,* **27,** 28-43.
409. Bataller, R. and Brenner, D.A. (2005) Liver fibrosis. *J Clin Invest,* **115,** 209-18.
410. Gines, P., Cardenas, A., Arroyo, V. and Rodes, J. (2004) Management of cirrhosis and ascites. *N Engl J Med,* **350,** 1646-54.
411. El-Serag, H.B. and Rudolph, K.L. (2007) Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology,* **132,** 2557-76.
412. Raoul, J.L. (2008) Natural history of hepatocellular carcinoma and current treatment options. *Semin Nucl Med,* **38,** S13-8.
413. Anthony, P.P. (2001) Hepatocellular carcinoma: an overview. *Histopathology,* **39,** 109-18.
414. Wong, C.M. and Ng, I.O. (2008) Molecular pathogenesis of hepatocellular carcinoma. *Liver Int,* **28,** 160-74.
415. Guan, X.Y., Fang, Y., Sham, J.S., Kwong, D.L., Zhang, Y., Liang, Q., Li, H., Zhou, H. and Trent, J.M. (2000) Recurrent chromosome alterations in hepatocellular carcinoma detected by comparative genomic hybridization. *Genes Chromosomes Cancer,* **29,** 110-6.

416. Marchio, A., Pineau, P., Meddeb, M., Terris, B., Tiollais, P., Bernheim, A. and Dejean, A. (2000) Distinct chromosomal abnormality pattern in primary liver cancer of non-B, non-C patients. *Oncogene,* **19,** 3733-8.
417. Wong, N., Lai, P., Pang, E., Fung, L.F., Sheng, Z., Wong, V., Wang, W., Hayashi, Y., Perlman, E., Yuna, S. *et al.* (2000) Genomic aberrations in human hepatocellular carcinomas of differing etiologies. *Clin Cancer Res,* **6,** 4000-9.
418. Rao, U.N., Gollin, S.M., Beaves, S., Cieply, K., Nalesnik, M. and Michalopoulos, G.K. (2001) Comparative genomic hybridization of hepatocellular carcinoma: correlation with fluorescence in situ hybridization in paraffin-embedded tissue. *Mol Diagn,* **6,** 27-37.
419. Thorgeirsson, S.S. and Grisham, J.W. (2002) Molecular pathogenesis of human hepatocellular carcinoma. *Nat Genet,* **31,** 339-46.
420. Wiemann, S.U., Satyanarayana, A., Tsahuridu, M., Tillmann, H.L., Zender, L., Klempnauer, J., Flemming, P., Franco, S., Blasco, M.A., Manns, M.P. *et al.* (2002) Hepatocyte telomere shortening and senescence are general markers of human liver cirrhosis. *Faseb J,* **16,** 935-42.
421. Plentz, R.R., Park, Y.N., Lechel, A., Kim, H., Nellessen, F., Langkopf, B.H., Wilkens, L., Destro, A., Fiamengo, B., Manns, M.P. *et al.* (2007) Telomere shortening and inactivation of cell cycle checkpoints characterize human hepatocarcinogenesis. *Hepatology,* **45,** 968-76.
422. Plentz, R.R., Caselitz, M., Bleck, J.S., Gebel, M., Flemming, P., Kubicka, S., Manns, M.P. and Rudolph, K.L. (2004) Hepatocellular telomere shortening correlates with chromosomal instability and the development of human hepatoma. *Hepatology,* **40,** 80-6.
423. Farazi, P.A., Glickman, J., Jiang, S., Yu, A., Rudolph, K.L. and DePinho, R.A. (2003) Differential impact of telomere dysfunction on initiation and progression of hepatocellular carcinoma. *Cancer Res,* **63,** 5021-7.
424. Roskams, T. (2006) Liver stem cells and their implication in hepatocellular and cholangiocarcinoma. *Oncogene,* **25,** 3818-22.
425. Anstee, Q.M. and Goldin, R.D. (2006) Mouse models in non-alcoholic fatty liver disease and steatohepatitis research. *Int J Exp Pathol,* **87,** 1-16.
426. Sato, M., Suzuki, S. and Senoo, H. (2003) Hepatic stellate cells: unique characteristics in cell biology and phenotype. *Cell Struct Funct,* **28,** 105-12.
427. Roskams, T.A., Libbrecht, L. and Desmet, V.J. (2003) Progenitor cells in diseased human liver. *Semin Liver Dis,* **23,** 385-96.
428. Roskams, T., Yang, S.Q., Koteish, A., Durnez, A., DeVos, R., Huang, X., Achten, R., Verslype, C. and Diehl, A.M. (2003) Oxidative stress and oval cell accumulation in mice and humans with alcoholic and nonalcoholic fatty liver disease. *Am J Pathol,* **163,** 1301-11.
429. Zatloukal, K., Stumptner, C., Fuchsbichler, A., Fickert, P., Lackner, C., Trauner, M. and Denk, H. (2004) The keratin cytoskeleton in liver diseases. *J Pathol,* **204,** 367-76.
430. Germain, L., Goyette, R. and Marceau, N. (1985) Differential cytokeratin and alpha-fetoprotein expression in morphologically distinct epithelial cells emerging at the early stage of rat hepatocarcinogenesis. *Cancer Res,* **45,** 673-81.

431. Fuchs, E. and Weber, K. (1994) Intermediate filaments: structure, dynamics, function, and disease. *Annu Rev Biochem,* **63,** 345-82.
432. Wu, P.C., Lai, V.C., Fang, J.W., Gerber, M.A., Lai, C.L. and Lau, J.Y. (1999) Hepatocellular carcinoma expressing both hepatocellular and biliary markers also expresses cytokeratin 14, a marker of bipotential progenitor cells. *J Hepatol,* **31,** 965-6.
433. Van Eyken, P., Sciot, R., Paterson, A., Callea, F., Kew, M.C. and Desmet, V.J. (1988) Cytokeratin expression in hepatocellular carcinoma: an immunohistochemical study. *Hum Pathol,* **19,** 562-8.
434. Ding, S.J., Li, Y., Tan, Y.X., Jiang, M.R., Tian, B., Liu, Y.K., Shao, X.X., Ye, S.L., Wu, J.R., Zeng, R. *et al.* (2004) From proteomic analysis to clinical significance: overexpression of cytokeratin 19 correlates with hepatocellular carcinoma metastasis. *Mol Cell Proteomics,* **3,** 73-81.
435. Yao, D.F., Dong, Z.Z. and Yao, M. (2007) Specific molecular markers in hepatocellular carcinoma. *Hepatobiliary Pancreat Dis Int,* **6,** 241-7.
436. Pang, R.W. and Poon, R.T. (2007) From molecular biology to targeted therapies for hepatocellular carcinoma: the future is now. *Oncology,* **72 Suppl 1,** 30-44.
437. Cillo, U., Navaglia, F., Vitale, A., Molari, A., Basso, D., Bassanello, M., Brolese, A., Zanus, G., Montin, U., D'Amico, F. *et al.* (2004) Clinical significance of alpha-fetoprotein mRNA in blood of patients with hepatocellular carcinoma. *Clin Chim Acta,* **347,** 129-38.
438. Soresi, M., Magliarisi, C., Campagna, P., Leto, G., Bonfissuto, G., Riili, A., Carroccio, A., Sesti, R., Tripi, S. and Montalto, G. (2003) Usefulness of alpha-fetoprotein in the diagnosis of hepatocellular carcinoma. *Anticancer Res,* **23,** 1747-53.
439. Yao, D., Jiang, D., Huang, Z., Lu, J., Tao, Q., Yu, Z. and Meng, X. (2000) Abnormal expression of hepatoma specific gamma-glutamyl transferase and alteration of gamma-glutamyl transferase gene methylation status in patients with hepatocellular carcinoma. *Cancer,* **88,** 761-9.
440. Khandwala, H.M., McCutcheon, I.E., Flyvbjerg, A. and Friend, K.E. (2000) The effects of insulin-like growth factors on tumorigenesis and neoplastic growth. *Endocr Rev,* **21,** 215-44.
441. Rogler, C.E., Yang, D., Rossetti, L., Donohoe, J., Alt, E., Chang, C.J., Rosenfeld, R., Neely, K. and Hintz, R. (1994) Altered body composition and increased frequency of diverse malignancies in insulin-like growth factor-II transgenic mice. *J Biol Chem,* **269,** 13779-84.
442. Katyal, S., Oliver, J.H., 3rd, Peterson, M.S., Ferris, J.V., Carr, B.S. and Baron, R.L. (2000) Extrahepatic metastases of hepatocellular carcinoma. *Radiology,* **216,** 698-703.
443. Sandgren, E.P., Luetteke, N.C., Palmiter, R.D., Brinster, R.L. and Lee, D.C. (1990) Overexpression of TGF alpha in transgenic mice: induction of epithelial hyperplasia, pancreatic metaplasia, and carcinoma of the breast. *Cell,* **61,** 1121-35.
444. Sandgren, E.P., Quaife, C.J., Pinkert, C.A., Palmiter, R.D. and Brinster, R.L. (1989) Oncogene-induced liver neoplasia in transgenic mice. *Oncogene,* **4,** 715-24.

445. Singh, M. and Kumar, V. (2003) Transgenic mouse models of hepatitis B virus-associated hepatocellular carcinoma. *Rev Med Virol,* **13,** 243-53.
446. Koike, K. (2002) Hepatocarcinogenesis in hepatitis viral infection: lessons from transgenic mouse studies. *J Gastroenterol,* **37 Suppl 13,** 55-64.
447. Day, C. (2007) Metabolic syndrome, or What you will: definitions and epidemiology. *Diab Vasc Dis Res,* **4,** 32-8.
448. Su, W.H., Chao, C.C., Yeh, S.H., Chen, D.S., Chen, P.J. and Jou, Y.S. (2007) OncoDB.HCC: an integrated oncogenomic database of hepatocellular carcinoma revealed aberrant cancer target genes and loci. *Nucleic Acids Res,* **35,** D727-31.
449. Xu, X.R., Huang, J., Xu, Z.G., Qian, B.Z., Zhu, Z.D., Yan, Q., Cai, T., Zhang, X., Xiao, H.S., Qu, J. *et al.* (2001) Insight into hepatocellular carcinogenesis at transcriptome level by comparing gene expression profiles of hepatocellular carcinoma with those of corresponding noncancerous liver. *Proc Natl Acad Sci U S A,* **98,** 15089-94.
450. Chen, X., Cheung, S.T., So, S., Fan, S.T., Barry, C., Higgins, J., Lai, K.M., Ji, J., Dudoit, S., Ng, I.O. *et al.* (2002) Gene expression patterns in human liver cancers. *Mol Biol Cell,* **13,** 1929-39.
451. Kusano, N., Shiraishi, K., Kubo, K., Oga, A., Okita, K. and Sasaki, K. (1999) Genetic aberrations detected by comparative genomic hybridization in hepatocellular carcinomas: their relationship to clinicopathological features. *Hepatology,* **29,** 1858-62.
452. Taub, R. (2004) Liver regeneration: from myth to mechanism. *Nat Rev Mol Cell Biol,* **5,** 836-47.
453. Hata, S., Namae, M. and Nishina, H. (2007) Liver development and regeneration: from laboratory study to clinical therapy. *Dev Growth Differ,* **49,** 163-70.
454. Matsuo, T., Yamaguchi, S., Mitsui, S., Emi, A., Shimoda, F. and Okamura, H. (2003) Control mechanism of the circadian clock for timing of cell division in vivo. *Science,* **302,** 255-9.
455. Aruoma, O.I., Halliwell, B., Hoey, B.M. and Butler, J. (1989) The antioxidant action of N-acetylcysteine: its reaction with hydrogen peroxide, hydroxyl radical, superoxide, and hypochlorous acid. *Free Radic Biol Med,* **6,** 593-7.
456. Aruoma, O.I., Halliwell, B., Hoey, B.M. and Butler, J. (1988) The antioxidant action of taurine, hypotaurine and their metabolic precursors. *Biochem J,* **256,** 251-5.
457. Cadet, J., D'Ham, C., Douki, T., Pouget, J.P., Ravanat, J.L. and Sauvaigo, S. (1998) Facts and artifacts in the measurement of oxidative base damage to DNA. *Free Radic Res,* **29,** 541-50.
458. Otteneder, M., Scott Daniels, J., Voehler, M. and Marnett, L.J. (2003) Development of a method for determination of the malondialdehyde-deoxyguanosine adduct in urine using liquid chromatography-tandem mass spectrometry. *Anal Biochem,* **315,** 147-51.
459. Donehower, L.A., Harvey, M., Slagle, B.L., McArthur, M.J., Montgomery, C.A., Jr., Butel, J.S. and Bradley, A. (1992) Mice deficient for p53 are developmentally normal but susceptible to spontaneous tumours. *Nature,* **356,** 215-21.
460. Hermeking, H. (2007) p53 enters the microRNA world. *Cancer Cell,* **12,** 414-8.

461. Apte, U., Zeng, G., Muller, P., Tan, X., Micsenyi, A., Cieply, B., Dai, C., Liu, Y., Kaestner, K.H. and Monga, S.P. (2006) Activation of Wnt/beta-catenin pathway during hepatocyte growth factor-induced hepatomegaly in mice. *Hepatology,* **44,** 992-1002.
462. Tan, X., Behari, J., Cieply, B., Michalopoulos, G.K. and Monga, S.P. (2006) Conditional deletion of beta-catenin reveals its role in liver growth and regeneration. *Gastroenterology,* **131,** 1561-72.
463. Iritani, B.M. and Eisenman, R.N. (1999) c-Myc enhances protein synthesis and cell size during B lymphocyte development. *Proc Natl Acad Sci U S A,* **96,** 13180-5.
464. Kozarsky, K. (2001) Gene delivery to the liver. *Curr Protoc Hum Genet,* **Chapter 13,** Unit 13 10.