

9 REFERENCES

- 1 Kornberg, R.D. Chromatin structure: a repeating unit of histones and DNA. *Science* **184**, 868-71 (1974).
- 2 Davey, C.A., Sargent, D.F., Luger, K., Maeder, A.W. & Richmond, T.J. Solvent-Mediated Interactions in the Structure of the Nucleosome Core Particle at 1.9 Å Resolution. *Journal of Molecular Biology* **319**, 1097-1113 (2002).
- 3 Luger, K. Structure and dynamic behavior of nucleosomes. *Current Opinion in Genetics & Development* **13**, 127-135 (2003).
- 4 Oudet, P., Gross-Bellard, M. & Chambon, P. Electron microscopic and biochemical evidence that chromatin structure is a repeating unit. *Cell* **4**, 281-300 (1975).
- 5 Thoma, F., Koller, T. & Klug, A. Involvement of histone H1 in the organization of the nucleosome and of the salt-dependent superstructures of chromatin. *J Cell Biol* **83**, 403-27 (1979).
- 6 Polo, S.E. & Almouzni, G. Chromatin assembly: a basic recipe with various flavours. *Current Opinion in Genetics & Development* **16**, 104-111 (2006).
- 7 Wells, D. & McBride, C. A comprehensive compilation and alignment of histones and histone genes. *Nucleic Acids Res* **17**, r311-46 (1989).
- 8 Wells, D. & Brown, D. Histone and histone gene compilation and alignment update. *Nucleic Acids Res* **19**, 2173-88 (1991).
- 9 Ramakrishnan, V. The histone fold: evolutionary questions. *Proc Natl Acad Sci U S A* **92**, 11328-30 (1995).
- 10 Nowak, S.J. & Corces, V.G. Phosphorylation of histone H3: a balancing act between chromosome condensation and transcriptional activation. *Trends Genet* **20**, 214-20 (2004).
- 11 Grunstein, M. Histone acetylation in chromatin structure and transcription. *Nature* **389**, 349-52 (1997).
- 12 Sterner, D.E. & Berger, S.L. Acetylation of histones and transcription-related factors. *Microbiol Mol Biol Rev* **64**, 435-59 (2000).
- 13 Zhang, Y. & Reinberg, D. Transcription regulation by histone methylation: interplay between different covalent modifications of the core histone tails. *Genes Dev* **15**, 2343-60 (2001).
- 14 Sims, I., Robert J., Nishioka, K. & Reinberg, D. Histone lysine methylation: a signature for chromatin function. *Trends in Genetics* **19**, 629-639 (2003).
- 15 Davie, J.R. & Murphy, L.C. Level of ubiquitinated histone H2B in chromatin is coupled to ongoing transcription. *Biochemistry* **29**, 4752-7 (1990).
- 16 Dhananjayan, S.C., Ismail, A. & Nawaz, Z. Ubiquitin and control of transcription. *Essays Biochem* **41**, 69-80 (2005).
- 17 Nathan, D., Sterner, D.E. & Berger, S.L. Histone modifications: Now summoning sumoylation. *Proc Natl Acad Sci U S A* **100**, 13118-20 (2003).
- 18 Adamietz, P. & Rudolph, A. ADP-ribosylation of nuclear proteins in vivo. Identification of histone H2B as a major acceptor for mono- and poly(ADP-ribose) in dimethyl sulfate-treated hepatoma AH 7974 cells. *J Biol Chem* **259**, 6841-6 (1984).
- 19 Liebich, H.M. *et al.* Non-enzymatic glycation of histones. *Biol Mass Spectrom* **22**, 121-3 (1993).
- 20 Hymes, J., Fleischhauer, K. & Wolf, B. Biotinylation of histones by human serum biotinidase: assessment of biotinyl-transferase activity in sera from normal individuals and children with biotinidase deficiency. *Biochem Mol Med* **56**, 76-83 (1995).
- 21 Wondrak, G.T., Cervantes-Laurean, D., Jacobson, E.L. & Jacobson, M.K. Histone carbonylation in vivo and in vitro. *Biochem J* **351 Pt 3**, 769-77 (2000).
- 22 Turner, B.M. Reading signals on the nucleosome with a new nomenclature for modified histones. *Nat Struct Mol Biol* **12**, 110-112 (2005).
- 23 Beck, H.C. *et al.* Quantitative proteomic analysis of post-translational modifications of human histones. *Mol Cell Proteomics* **5**, 1314-25 (2006).
- 24 Segal, E. *et al.* A genomic code for nucleosome positioning. *Nature* **442**, 772-8 (2006).
- 25 Pokholok, D.K. *et al.* Genome-wide Map of Nucleosome Acetylation and Methylation in Yeast. *Cell* **122**, 517-527 (2005).
- 26 Iyer, V. & Struhl, K. Poly(dA:dT), a ubiquitous promoter element that stimulates transcription via its intrinsic DNA structure. *Embo J* **14**, 2570-9 (1995).
- 27 Zhang, D.E. & Nelson, D.A. Histone acetylation in chicken erythrocytes. Rates of acetylation and evidence that histones in both active and potentially active chromatin are rapidly modified. *Biochem J* **250**, 233-40 (1988).
- 28 Duncan, M.R., Robinson, M.J. & Dell'Orco, R.T. Kinetics of histone hyperacetylation and deacetylation in human diploid fibroblasts. *Biochim Biophys Acta* **762**, 221-6 (1983).
- 29 Allfrey, V.G., Faulkner, R. & Mirsky, A.E. 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 (1964).
- 30 Lorch, Y., LaPointe, J.W. & Kornberg, R.D. Nucleosomes inhibit the initiation of transcription but allow chain elongation with the displacement of histones. *Cell* **49**, 203-10 (1987).
- 31 Han, M. & Grunstein, M. Nucleosome loss activates yeast downstream promoters in vivo. *Cell* **55**, 1137-45 (1988).
- 32 Durrin, L.K., Mann, R.K., Kayne, P.S. & Grunstein, M. Yeast histone H4 N-terminal sequence is required for promoter activation in vivo. *Cell* **65**, 1023-31 (1991).
- 33 Kouzarides, T. Chromatin modifications and their function. *Cell* **128**, 693-705 (2007).
- 34 Shogren-Knaak, M. *et al.* Histone H4-K16 Acetylation Controls Chromatin Structure and Protein Interactions. *Science* **311**, 844-847 (2006).
- 35 Byvoet, P., Shepherd, G.R., Hardin, J.M. & Noland, B.J. The distribution and turnover of labeled methyl groups in histone fractions of cultured mammalian cells. *Archives of Biochemistry and Biophysics* **148**, 558-567 (1972).

- 36 Jenuwein, T. & Allis, C.D. Translating the histone code. *Science* **293**, 1074-80 (2001).
- 37 Ahmad, K. & Henikoff, S. Epigenetic Consequences of Nucleosome Dynamics. *Cell* **111**, 281-284 (2002).
- 38 Bannister, A.J., Schneider, R. & Kouzarides, T. Histone Methylation: Dynamic or Static? *Cell* **109**, 801-806 (2002).
- 39 Ng, H.H., Robert, F., Young, R.A. & Struhl, K. Targeted Recruitment of Set1 Histone Methylase by Elongating Pol II Provides a Localized Mark and Memory of Recent Transcriptional Activity. *Molecular Cell* **11**, 709-719 (2003).
- 40 Rea, S. *et al.* Regulation of chromatin structure by site-specific histone H3 methyltransferases. *Nature* **406**, 593-599 (2000).
- 41 Shi, Y. *et al.* Histone demethylation mediated by the nuclear amine oxidase homolog LSD1. *Cell* **119**, 941-53 (2004).
- 42 Tsukada, Y. *et al.* Histone demethylation by a family of JmjC domain-containing proteins. *Nature* **439**, 811-6 (2006).
- 43 Heard, E. *et al.* Methylation of histone H3 at Lys-9 is an early mark on the X chromosome during X inactivation. *Cell* **107**, 727-38 (2001).
- 44 Boggs, B.A. *et al.* Differentially methylated forms of histone H3 show unique association patterns with inactive human X chromosomes. *Nat Genet* **30**, 73-6 (2002).
- 45 Mermoud, J.E., Popova, B., Peters, A.H., Jenuwein, T. & Brockdorff, N. Histone H3 lysine 9 methylation occurs rapidly at the onset of random X chromosome inactivation. *Curr Biol* **12**, 247-51 (2002).
- 46 Peters, A.H. *et al.* Histone H3 lysine 9 methylation is an epigenetic imprint of facultative heterochromatin. *Nat Genet* **30**, 77-80 (2002).
- 47 Grewal, S.I.S. & Elgin, S.C.R. Heterochromatin: new possibilities for the inheritance of structure. *Current Opinion in Genetics & Development* **12**, 178-187 (2002).
- 48 Jackson, J.P., Lindroth, A.M., Cao, X. & Jacobsen, S.E. Control of CpNpG DNA methylation by the KRYPTONITE histone H3 methyltransferase. *Nature* **416**, 556-60 (2002).
- 49 Tamaru, H. & Selker, E.U. A histone H3 methyltransferase controls DNA methylation in *Neurospora crassa*. *Nature* **414**, 277-83 (2001).
- 50 Lehnertz, B. *et al.* Suv39h-mediated histone H3 lysine 9 methylation directs DNA methylation to major satellite repeats at pericentric heterochromatin. *Curr Biol* **13**, 1192-200 (2003).
- 51 Nishioka, K. *et al.* PR-Set7 is a nucleosome-specific methyltransferase that modifies lysine 20 of histone H4 and is associated with silent chromatin. *Mol Cell* **9**, 1201-13 (2002).
- 52 Heard, E. & Disteche, C.M. Dosage compensation in mammals: fine-tuning the expression of the X chromosome. *Genes Dev.* **20**, 1848-1867 (2006).
- 53 Bernstein, B.E. *et al.* Methylation of histone H3 Lys 4 in coding regions of active genes. *Proc Natl Acad Sci U S A* **99**, 8695-8700 (2002).
- 54 Gerber, M. & Shilatifard, A. Transcriptional Elongation by RNA Polymerase II and Histone Methylation. *J Biol Chem* **278**, 26303-26306 (2003).
- 55 Bannister, A.J. *et al.* Spatial distribution of di- and tri-methyl lysine 36 of histone H3 at active genes. *J Biol Chem* **280**, 17732-6 (2005).
- 56 Morris, S.A. *et al.* Histone H3 K36 methylation is associated with transcription elongation in *Schizosaccharomyces pombe*. *Eukaryot Cell* **4**, 1446-54 (2005).
- 57 Ng, H.H., Ciccone, D.N., Morshead, K.B., Oettinger, M.A. & Struhl, K. Lysine-79 of histone H3 is hypomethylated at silenced loci in yeast and mammalian cells: a potential mechanism for position-effect variegation. *Proc Natl Acad Sci U S A* **100**, 1820-5 (2003).
- 58 Roh, T.y., Ngau, W.C., Cui, K., Landsman, D. & Zhao, K. High-resolution genome-wide mapping of histone modifications. *Nat Biotech* **22**, 1013-1016 (2004).
- 59 Roh, T.Y., Cuddapah, S., Cui, K. & Zhao, K. The genomic landscape of histone modifications in human T cells. *Proc Natl Acad Sci U S A* **103**, 15782-7 (2006).
- 60 Santos-Rosa, H. *et al.* Active genes are tri-methylated at K4 of histone H3. **419**, 407-411 (2002).
- 61 Bernstein, B.E. *et al.* A bivalent chromatin structure marks key developmental genes in embryonic stem cells. *Cell* **125**, 315-26 (2006).
- 62 Kim, T.H. *et al.* A high-resolution map of active promoters in the human genome. **436**, 876-880 (2005).
- 63 Turner, B.M. Cellular Memory and the Histone Code. *Cell* **111**, 285-291 (2002).
- 64 Martinez-Balbas, M.A., Dey, A., Rabindran, S.K., Ozato, K. & Wu, C. Displacement of sequence-specific transcription factors from mitotic chromatin. *Cell* **83**, 29-38 (1995).
- 65 Zhou, G.L., Xin, L., Liu, D.P. & Liang, C.C. Remembering the cell fate during cellular differentiation. *J Cell Biochem* **96**, 962-70 (2005).
- 66 Schneider, R. *et al.* Histone H3 lysine 4 methylation patterns in higher eukaryotic genes. *Nat Cell Biol* **6**, 73-77 (2004).
- 67 Saha, A., Wittmeyer, J. & Cairns, B.R. Chromatin remodelling: the industrial revolution of DNA around histones. *Nat Rev Mol Cell Biol* **7**, 437-447 (2006).
- 68 Nightingale, K.P. *et al.* Cross-talk between histone modifications in response to histone deacetylase inhibitors: MLL4 links histone H3 acetylation and histone H3K4 methylation. *J Biol Chem* **282**, 4408-16 (2007).
- 69 Bannister, A.J. *et al.* Selective recognition of methylated lysine 9 on histone H3 by the HP1 chromo domain. *Nature* **410**, 120-4 (2001).
- 70 Lachner, M., O'Carroll, D., Rea, S., Mechtler, K. & Jenuwein, T. Methylation of histone H3 lysine 9 creates a binding site for HP1 proteins. *Nature* **410**, 116-20 (2001).
- 71 Sims, R.J., III *et al.* Human but Not Yeast CHD1 Binds Directly and Selectively to Histone H3 Methylated at Lysine 4 via Its Tandem Chromodomains. *J Biol Chem* **280**, 41789-41792 (2005).

- 72 Peña, P.V. *et al.* Molecular mechanism of histone H3K4me3 recognition by plant homeodomain of ING2. *Nature* **442**, 100-103 (2006).
- 73 Li, H. *et al.* Molecular basis for site-specific read-out of histone H3K4me3 by the BPTF PHD finger of NURF. *Nature* **442**, 91-95 (2006).
- 74 Bienz, M. The PHD finger, a nuclear protein-interaction domain. *Trends in Biochemical Sciences* **31**, 35-40 (2006).
- 75 Shi, X. *et al.* ING2 PHD domain links histone H3 lysine 4 methylation to active gene repression. *Nature* **442**, 96-99 (2006).
- 76 Wysocka, J. *et al.* A PHD finger of NURF couples histone H3 lysine 4 trimethylation with chromatin remodelling. *Nature* **442**, 86-90 (2006).
- 77 Lan, F. *et al.* Recognition of unmethylated histone H3 lysine 4 links BHC80 to LSD1-mediated gene repression. *Nature* **448**, 718-22 (2007).
- 78 Strahl, B.D. & Allis, C.D. The language of covalent histone modifications. *Nature* **403**, 41-5 (2000).
- 79 Liu, C.L. *et al.* Single-nucleosome mapping of histone modifications in *S. cerevisiae*. *PLoS Biol* **3**, e328 (2005).
- 80 Ballestar, E., Esteller, M. & Richardson, B.C. The epigenetic face of systemic lupus erythematosus. *J Immunol* **176**, 7143-7 (2006).
- 81 Rodenhiser, D. & Mann, M. Epigenetics and human disease: translating basic biology into clinical applications. *Cmaj* **174**, 341-8 (2006).
- 82 Villar-Garea, A. & Esteller, M. Histone deacetylase inhibitors: understanding a new wave of anticancer agents. *Int J Cancer* **112**, 171-8 (2004).
- 83 Liu, T., Kuljaca, S., Tee, A. & Marshall, G.M. Histone deacetylase inhibitors: multifunctional anticancer agents. *Cancer Treat Rev* **32**, 157-65 (2006).
- 84 Esteller, M. Epigenetics provides a new generation of oncogenes and tumour-suppressor genes. *Br J Cancer* **94**, 179-83 (2006).
- 85 Antonello Mai, S.M., Dante Rotili, Ilaria Cerbara, Sergio Valente, Riccardo Pezzi, Silvia Simeoni, Rino Ragno. Histone deacetylation in epigenetics: An attractive target for anticancer therapy. *Medicinal Research Reviews* **25**, 261-309 (2005).
- 86 McKinsey, T.A. & Olson, E.N. Cardiac histone acetylation - therapeutic opportunities abound. *Trends in Genetics* **20**, 206-213 (2004).
- 87 Illi, B. *et al.* Epigenetic Histone Modification and Cardiovascular Lineage Programming in Mouse Embryonic Stem Cells Exposed to Laminar Shear Stress. *Circ Res* **96**, 501-508 (2005).
- 88 Zhang, C.L. *et al.* Class II histone deacetylases act as signal-responsive repressors of cardiac hypertrophy. *Cell* **110**, 479-88 (2002).
- 89 Chang, S. *et al.* 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**, 8467-8476 (2004).
- 90 Montgomery, R.L. *et al.* Histone deacetylases 1 and 2 redundantly regulate cardiac morphogenesis, growth, and contractility. *Genes Dev* **21**, 1790-802 (2007).
- 91 Hoffman, J.I. Incidence of congenital heart disease: I. Postnatal incidence. *Pediatr Cardiol* **16**, 103-13 (1995).
- 92 Hoffman, J.I. Incidence of congenital heart disease: II. Prenatal incidence. *Pediatr Cardiol* **16**, 155-65 (1995).
- 93 Clark, K.L., Yutzey, K.E. & Benson, D.W. Transcription factors and congenital heart defects. *Annual Review of Physiology* **68**, 97-121 (2006).
- 94 Reecy, J.M. *et al.* Identification of upstream regulatory regions in the heart-expressed homeobox gene Nkx2-5. *Development* **126**, 839-849 (1999).
- 95 Searcy, R.D., Vincent, E.B., Liberatore, C.M. & Yutzey, K.E. A GATA-dependent nkx-2.5 regulatory element activates early cardiac gene expression in transgenic mice. *Development* **125**, 4461-4470 (1998).
- 96 Balza, R.O., Jr. & Misra, R.P. The role of serum response factor in regulating contractile apparatus gene expression and sarcomeric integrity in cardiomyocytes. *J Biol Chem* **281**, 6498-510 (2005).
- 97 Spencer, J.A. & Misra, R.P. Expression of the serum response factor gene is regulated by serum response factor binding sites. *J Biol Chem* **271**, 16535-43 (1996).
- 98 Marin-Husstege, M., Muggironi, M., Liu, A. & Casaccia-Bonnel, P. Histone deacetylase activity is necessary for oligodendrocyte lineage progression. *J Neurosci* **22**, 10333-45 (2002).
- 99 Karamboulas, C. *et al.* Disruption of MEF2 activity in cardiomyoblasts inhibits cardiomyogenesis. *J Cell Sci* **119**, 4315-4321 (2006).
- 100 Pikkarainen, S., Tokola, H., Kerkela, R. & Ruskoaho, H. GATA transcription factors in the developing and adult heart. *Cardiovascular Research* **63**, 196-207 (2004).
- 101 Laverriere, A.C. *et al.* GATA-4/5/6, a subfamily of three transcription factors transcribed in developing heart and gut. *J Biol Chem* **269**, 23177-84 (1994).
- 102 Evans, T. & Felsenfeld, G. The erythroid-specific transcription factor eryf1: A new finger protein. *Cell* **58**, 877-885 (1989).
- 103 Svensson, E.C., Tufts, R.L., Polk, C.E. & Leiden, J.M. Molecular cloning of FOG-2: a modulator of transcription factor GATA-4 in cardiomyocytes. *Proc Natl Acad Sci U S A* **96**, 956-61 (1999).
- 104 Katz, S.G. *et al.* Endothelial lineage-mediated loss of the GATA cofactor Friend of GATA 1 impairs cardiac development. *Proc Natl Acad Sci U S A* **100**, 14030-5 (2003).
- 105 Morin, S., Charron, F., Robitaille, L. & Nemer, M. GATA-dependent recruitment of MEF2 proteins to target promoters. *The EMBO Journal* **19**, 2046-2055 (2000).
- 106 Durocher, D., Charron, F., Warren, R., Schwartz, R.J. & Nemer, M. The cardiac transcription factors Nkx2-5 and GATA-4 are mutual cofactors. *Embo J* **16**, 5687-96 (1997).
- 107 Lee, Y. *et al.* The cardiac tissue-restricted homeobox protein Csx/Nkx2.5 physically associates with the zinc finger protein GATA4 and cooperatively activates atrial natriuretic factor gene expression. *Mol Cell Biol* **18**, 3120-9 (1998).

- 108 Shiojima, I. *et al.* Context-dependent transcriptional cooperation mediated by cardiac transcription factors Csx/Nkx-2.5 and GATA-4. *J Biol Chem* **274**, 8231-9 (1999).
- 109 Morin, S., Paradis, P., Aries, A. & Nemer, M. Serum response factor-GATA ternary complex required for nuclear signaling by a G-protein-coupled receptor. *Mol Cell Biol* **21**, 1036-44 (2001).
- 110 Belaguli, N.S. *et al.* Cardiac tissue enriched factors serum response factor and GATA-4 are mutual coregulators. *Mol Cell Biol* **20**, 7550-8 (2000).
- 111 Dai, Y.S., Cserjesi, P., Markham, B.E. & Molkenin, J.D. The transcription factors GATA4 and dHAND physically interact to synergistically activate cardiac gene expression through a p300-dependent mechanism. *J Biol Chem* **277**, 24390-8 (2002).
- 112 Charron, F., Paradis, P., Bronchain, O., Nemer, G. & Nemer, M. Cooperative interaction between GATA-4 and GATA-6 regulates myocardial gene expression. *Mol Cell Biol* **19**, 4355-65 (1999).
- 113 Molkenin, J.D. *et al.* A calcineurin-dependent transcriptional pathway for cardiac hypertrophy. *Cell* **93**, 215-28 (1998).
- 114 Dai, Y.S. & Markham, B.E. p300 Functions as a coactivator of transcription factor GATA-4. *J Biol Chem* **276**, 37178-85 (2001).
- 115 Clabby, M.L., Robison, T.A., Quigley, H.F., Wilson, D.B. & Kelly, D.P. Retinoid X receptor alpha represses GATA-4-mediated transcription via a retinoid-dependent interaction with the cardiac-enriched repressor FOG-2. *J Biol Chem* **278**, 5760-7 (2003).
- 116 Lavalley, G. *et al.* The Kruppel-like transcription factor KLF13 is a novel regulator of heart development. *Embo J* **25**, 5201-13 (2006).
- 117 Fluck, C.E. & Miller, W.L. GATA-4 and GATA-6 modulate tissue-specific transcription of the human gene for P450c17 by direct interaction with Sp1. *Mol Endocrinol* **18**, 1144-57 (2004).
- 118 Bhalla, S.S., Robitaille, L. & Nemer, M. Cooperative activation by GATA-4 and YY1 of the cardiac B-type natriuretic peptide promoter. *J Biol Chem* **276**, 11439-45 (2001).
- 119 Garg, V. *et al.* GATA4 mutations cause human congenital heart defects and reveal an interaction with TBX5. *Nature* **424**, 443-7 (2003).
- 120 Iwahori, A., Fraidenraich, D. & Basilico, C. A conserved enhancer element that drives FGF4 gene expression in the embryonic myotomes is synergistically activated by GATA and bHLH proteins. *Dev Biol* **270**, 525-37 (2004).
- 121 Liang, Q. *et al.* The transcription factor GATA4 is activated by extracellular signal-regulated kinase 1- and 2-mediated phosphorylation of serine 105 in cardiomyocytes. *Mol Cell Biol* **21**, 7460-9 (2001).
- 122 Arceci, R.J., King, A.A., Simon, M.C., Orkin, S.H. & Wilson, D.B. Mouse GATA-4: a retinoic acid-inducible GATA-binding transcription factor expressed in endodermally derived tissues and heart. *Mol Cell Biol* **13**, 2235-46 (1993).
- 123 Heikinheimo, M., Scandrett, J.M. & Wilson, D.B. Localization of transcription factor GATA-4 to regions of the mouse embryo involved in cardiac development. *Dev Biol* **164**, 361-73 (1994).
- 124 Brown, C.O., 3rd *et al.* The cardiac determination factor, Nkx2-5, is activated by mutual cofactors GATA-4 and Smad1/4 via a novel upstream enhancer. *J Biol Chem* **279**, 10659-69 (2004).
- 125 Morin, S., Charron, F., Robitaille, L. & Nemer, M. GATA-dependent recruitment of MEF2 proteins to target promoters. *Embo J* **19**, 2046-55 (2000).
- 126 Wang, J. *et al.* Convergence of protein kinase C and JAK-STAT signaling on transcription factor GATA-4. *Mol Cell Biol* **25**, 9829-44 (2005).
- 127 Grepin, C., Nemer, G. & Nemer, M. Enhanced cardiogenesis in embryonic stem cells overexpressing the GATA-4 transcription factor. *Development* **124**, 2387-95 (1997).
- 128 Grepin, C., Robitaille, L., Antakly, T. & Nemer, M. Inhibition of transcription factor GATA-4 expression blocks in vitro cardiac muscle differentiation. *Mol Cell Biol* **15**, 4095-102 (1995).
- 129 Narita, N., Bielinska, M. & Wilson, D.B. Cardiomyocyte differentiation by GATA-4-deficient embryonic stem cells. *Development* **124**, 3755-64 (1997).
- 130 Molkenin, J.D., Lin, Q., Duncan, S.A. & Olson, E.N. Requirement of the transcription factor GATA4 for heart tube formation and ventral morphogenesis. *Genes Dev* **11**, 1061-72 (1997).
- 131 Kuo, C.T. *et al.* GATA4 transcription factor is required for ventral morphogenesis and heart tube formation. *Genes Dev* **11**, 1048-60 (1997).
- 132 Hautala, N. *et al.* Pressure overload increases GATA4 binding activity via endothelin-1. *Circulation* **103**, 730-5 (2001).
- 133 Pehlivan, T. *et al.* GATA4 haploinsufficiency in patients with interstitial deletion of chromosome region 8p23.1 and congenital heart disease. *Am J Med Genet* **83**, 201-6 (1999).
- 134 Hirayama-Yamada, K. *et al.* Phenotypes with GATA4 or NKX2.5 mutations in familial atrial septal defect. *Am J Med Genet A* **135**, 47-52 (2005).
- 135 Sarkozy, A. *et al.* Spectrum of atrial septal defects associated with mutations of NKX2.5 and GATA4 transcription factors. *J Med Genet* **42**, e16 (2005).
- 136 Nemer, G. *et al.* A novel mutation in the GATA4 gene in patients with Tetralogy of Fallot. *Hum Mutat* **27**, 293-4 (2006).
- 137 Bodmer, R. The gene tinman is required for specification of the heart and visceral muscles in Drosophila. *Development* **118**, 719-29 (1993).
- 138 Komuro, I. & Izumo, S. Csx: a murine homeobox-containing gene specifically expressed in the developing heart. *Proc Natl Acad Sci U S A* **90**, 8145-9 (1993).
- 139 Akazawa, H. & Komuro, I. Cardiac transcription factor Csx/Nkx2-5: Its role in cardiac development and diseases. *Pharmacol Ther* **107**, 252-68 (2005).
- 140 Lints, T.J., Parsons, L.M., Hartley, L., Lyons, I. & Harvey, R.P. Nkx-2.5: a novel murine homeobox gene expressed in early heart progenitor cells and their myogenic descendants. *Development* **119**, 419-31 (1993).

References

- 141 Chen, C.Y. & Schwartz, R.J. Identification of novel DNA-binding targets and regulatory domains of a murine tinman homeodomain factor, nkx-2.5. *J Biol Chem* **270**, 15628-33 (1995).
- 142 Thomas, P.S. *et al.* Elevated expression of Nkx-2.5 in developing myocardial conduction cells. *Anat Rec* **263**, 307-13 (2001).
- 143 Jamali, M., Rogerson, P.J., Wilton, S. & Skerjanc, I.S. Nkx2-5 Activity Is Essential for Cardiomyogenesis. *J Biol Chem* **276**, 42252-42258 (2001).
- 144 Cleaver, O.B., Patterson, K.D. & Krieg, P.A. Overexpression of the tinman-related genes XNkx-2.5 and XNkx-2.3 in *Xenopus* embryos results in myocardial hyperplasia. *Development* **122**, 3549-56 (1996).
- 145 Chen, J.N. & Fishman, M.C. Zebrafish tinman homolog demarcates the heart field and initiates myocardial differentiation. *Development* **122**, 3809-16 (1996).
- 146 Prall, O.W. *et al.* An Nkx2-5/Bmp2/Smad1 negative feedback loop controls heart progenitor specification and proliferation. *Cell* **128**, 947-59 (2007).
- 147 Lyons, I. *et al.* Myogenic and morphogenetic defects in the heart tubes of murine embryos lacking the homeo box gene Nkx2-5. *Genes Dev* **9**, 1654-1666 (1995).
- 148 Schott, J.J. *et al.* Congenital heart disease caused by mutations in the transcription factor NKX2-5. *Science* **281**, 108-11 (1998).
- 149 Black, B.L. & Olson, E.N. Transcriptional control of muscle development by myocyte enhancer factor-2 (MEF2) proteins. *Annu Rev Cell Dev Biol* **14**, 167-96 (1998).
- 150 Molkentin, J.D. & Olson, E.N. Combinatorial control of muscle development by basic helix-loop-helix and MADS-box transcription factors. *Proc Natl Acad Sci U S A* **93**, 9366-73 (1996).
- 151 Edmondson, D.G., Lyons, G.E., Martin, J.F. & Olson, E.N. Mef2 gene expression marks the cardiac and skeletal muscle lineages during mouse embryogenesis. *Development* **120**, 1251-1263 (1994).
- 152 Iida, K. *et al.* Expression of MEF2 genes during human cardiac development. *Tohoku J Exp Med* **187**, 15-23 (1999).
- 153 Amacher, S.L., Buskin, J.N. & Hauschka, S.D. Multiple regulatory elements contribute differentially to muscle creatine kinase enhancer activity in skeletal and cardiac muscle. *Mol Cell Biol* **13**, 2753-2764 (1993).
- 154 Gajewski, K., Kim, Y., Lee, Y.M., Olson, E.N. & Schulz, R.A. D-mef2 is a target for Tinman activation during *Drosophila* heart development. *Embo J* **16**, 515-22 (1997).
- 155 Gajewski, K., Fossett, N., Molkentin, J.D. & Schulz, R.A. The zinc finger proteins Pannier and GATA4 function as cardiogenic factors in *Drosophila*. **126**, 5679-5688 (1999).
- 156 Tanaka, M., Chen, Z., Bartunkova, S., Yamasaki, N. & Izumo, S. The cardiac homeobox gene Csx/Nkx2.5 lies genetically upstream of multiple genes essential for heart development. **126**, 1269-1280 (1999).
- 157 Cripps, R.M., Zhao, B. & Olson, E.N. Transcription of the Myogenic Regulatory Gene Mef2 in Cardiac, Somatic, and Visceral Muscle Cell Lineages Is Regulated by a Tinman-Dependent Core Enhancer. *Developmental Biology* **215**, 420-430 (1999).
- 158 Lilly, B. *et al.* Requirement of MADS domain transcription factor D-MEF2 for muscle formation in *Drosophila*. *Science* **267**, 688-693 (1995).
- 159 Naya, F.J. *et al.* Mitochondrial deficiency and cardiac sudden death in mice lacking the MEF2A transcription factor. *Nat Med* **8**, 1303-1309 (2002).
- 160 Ornatsky, O.I., Andreucci, J.J. & McDermott, J.C. A dominant-negative form of transcription factor MEF2 inhibits myogenesis. *J Biol Chem* **272**, 33271-33278 (1997).
- 161 Wang, L., Fan, C., Topol, S.E., Topol, E.J. & Wang, Q. Mutation of MEF2A in an Inherited Disorder with Features of Coronary Artery Disease. *Science* **302**, 1578-1581 (2003).
- 162 Bhagavatula, M.R.K. *et al.* Transcription factor MEF2A mutations in patients with coronary artery disease. **13**, 3181-3188 (2004).
- 163 Li, J. *et al.* Study on novel mutations of MEF2A gene in Chinese patients with coronary artery disease. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi* **23**, 265-8 (2006).
- 164 Yuan, H. *et al.* MEF2A gene and susceptibility to coronary artery disease in the Chinese people. *Zhong Nan Da Xue Xue Bao Yi Xue Ban* **31**, 453-7 (2006).
- 165 Weng, L. *et al.* Lack of MEF2A mutations in coronary artery disease. *J Clin Invest* **115**, 1016-20 (2005).
- 166 Kajimoto, K. *et al.* Assessment of MEF2A mutations in myocardial infarction in Japanese patients. *Circ J* **69**, 1192-5 (2005).
- 167 Wang, Q., Rao, S. & Topol, E.J. Miscues on the "lack of MEF2A mutations" in coronary artery disease. *J Clin Invest* **115**, 1399-400; author reply 1400-1 (2005).
- 168 Altshuler, D. & Hirschhorn, J.N. MEF2A sequence variants and coronary artery disease: a change of heart? *J Clin Invest* **115**, 831-3 (2005).
- 169 Norman, C., Runswick, M., Pollock, R. & Treisman, R. Isolation and properties of cDNA clones encoding SRF, a transcription factor that binds to the c-fos serum response element. *Cell* **55**, 989-1003 (1988).
- 170 Sun, Q. *et al.* Defining the mammalian CArGome. *Genome Res* **16**, 197-207 (2006).
- 171 Belaguli, N.S., Schildmeyer, L.A. & Schwartz, R.J. Organization and myogenic restricted expression of the murine serum response factor gene. A role for autoregulation. *J Biol Chem* **272**, 18222-31 (1997).
- 172 Chen, C.Y. & Schwartz, R.J. Recruitment of the tinman homolog Nkx-2.5 by serum response factor activates cardiac alpha-actin gene transcription. *Mol Cell Biol* **16**, 6372-84 (1996).
- 173 Sepulveda, J.L., Vlahopoulos, S., Iyer, D., Belaguli, N. & Schwartz, R.J. Combinatorial Expression of GATA4, Nkx2-5, and Serum Response Factor Directs Early Cardiac Gene Activity. *J Biol Chem* **277**, 25775-25782 (2002).
- 174 Pipes, G.C.T., Creemers, E.E. & Olson, E.N. The myocardin family of transcriptional coactivators: versatile regulators of cell growth, migration, and myogenesis. **20**, 1545-1556 (2006).
- 175 Posern, G. & Treisman, R. Actin' together: serum response factor, its cofactors and the link to signal transduction. *Trends in Cell Biology* **16**, 588-596 (2006).

- 176 Wang, D.Z. & Olson, E.N. Control of smooth muscle development by the myocardin family of transcriptional
coactivators. *Current Opinion in Genetics & Development* **14**, 558-566 (2004).
- 177 Long, X., Creemers, E.E., Wang, D.Z., Olson, E.N. & Miano, J.M. Myocardin is a bifunctional switch for smooth
versus skeletal muscle differentiation. *Proc Natl Acad Sci U S A* **104**, 16570-5 (2007).
- 178 Kook, H. *et al.* Analysis of the Structure and Function of the Transcriptional Coregulator HOP(.). *Biochemistry* **45**,
10584-10590 (2006).
- 179 Chen, F. *et al.* Hop is an unusual homeobox gene that modulates cardiac development. *Cell* **110**, 713-23 (2002).
- 180 Shin, C.H. *et al.* Modulation of Cardiac Growth and Development by HOP, an Unusual Homeodomain Protein.
Cell **110**, 725-735 (2002).
- 181 Chen, F. *et al.* Hop Is an Unusual Homeobox Gene that Modulates Cardiac Development. *Cell* **110**, 713-723
(2002).
- 182 Kook, H. *et al.* Cardiac hypertrophy and histone deacetylase-dependent transcriptional repression mediated by the
atypical homeodomain protein Hop. *J Clin Invest* **112**, 863-871 (2003).
- 183 Davis, F.J., Gupta, M., Camoretti-Mercado, B., Schwartz, R.J. & Gupta, M.P. 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 (2003).
- 184 L'Honore, A. *et al.* Identification of a New Hybrid Serum Response Factor and Myocyte Enhancer Factor 2-binding
Element in MyoD Enhancer Required for MyoD Expression during Myogenesis. *Mol Biol Cell* **18**, 1992-2001
(2007).
- 185 Soulez, M., Tuil, D., Kahn, A. & Gilgenkrantz, H. The serum response factor (SRF) is needed for muscle-specific
activation of CArG boxes. *Biochem Biophys Res Commun* **219**, 418-22 (1996).
- 186 Wei, L. *et al.* RhoA signaling via serum response factor plays an obligatory role in myogenic differentiation. *J Biol
Chem* **273**, 30287-94 (1998).
- 187 Kaplan-Albuquerque, N., Van Putten, V., Weiser-Evans, M.C. & Nemenoff, R.A. Depletion of serum response
factor by RNA interference mimics the mitogenic effects of platelet derived growth factor-BB in vascular smooth
muscle cells. *Circ Res* **97**, 427-33 (2005).
- 188 Landerholm, T.E. *et al.* A role for serum response factor in coronary smooth muscle differentiation from
proepicardial cells. *Development* **126**, 2053-62 (1999).
- 189 Schrott, G. *et al.* Serum response factor is crucial for actin cytoskeletal organization and focal adhesion assembly in
embryonic stem cells. *J Cell Biol* **156**, 737-50 (2002).
- 190 Balza, R.O., Jr. & Misra, R.P. The role of serum response factor in regulating contractile apparatus gene expression
and sarcomeric integrity in cardiomyocytes. in *J Biol Chem* (2005).
- 191 Arsenian, S., Weinhold, B., Oelgeschlager, M., Ruther, U. & Nordheim, A. Serum response factor is essential for
mesoderm formation during mouse embryogenesis. *Embo J* **17**, 6289-99 (1998).
- 192 Li, S. *et al.* Requirement for serum response factor for skeletal muscle growth and maturation revealed by tissue-
specific gene deletion in mice. *Proc Natl Acad Sci U S A* **102**, 1082-7 (2005).
- 193 Miano, J.M. *et al.* Restricted inactivation of serum response factor to the cardiovascular system. *Proc Natl Acad Sci
U S A* **101**, 17132-7 (2004).
- 194 Lieb, J.D., Liu, X., Botstein, D. & Brown, P.O. Promotor-specific binding of Rap1 revealed by genome-wide maps
of protein-DNA association. *Nature Genetics* **28**, 327 -334 (2004).
- 195 Bernstein, B.E., Humphrey, E.L., Liu, C.L. & Schreiber, S.L. The use of chromatin immunoprecipitation assays in
genome-wide analyses of histone modifications. *Methods Enzymol* **376**, 349-60 (2004).
- 196 Chaya, D. & Zaret, K.S. Sequential chromatin immunoprecipitation from animal tissues. *Methods Enzymol* **376**,
361-72 (2004).
- 197 Kiermer, V. Embryos and biopsies on the ChIP-ing forecast. *Nat Methods* **3**, 583 (2006).
- 198 Kurdistani, S.K. & Grunstein, M. In vivo protein-protein and protein-DNA crosslinking for genomewide binding
microarray. *Methods* **31**, 90-5 (2003).
- 199 Viens, A., Mechold, U., Lehrmann, H., Harel-Bellan, A. & Ogryzko, V. Use of protein biotinylation in vivo for
chromatin immunoprecipitation. *Anal.Biochem.* **325**, 68-76 (2004).
- 200 Jiang, H., Daniels, P.J. & Andrews, G.K. Putative zinc-sensing zinc fingers of metal-response element-binding
transcription factor-1 stabilize a metal-dependent chromatin complex on the endogenous metallothionein-I
promoter. *J Biol Chem* **278**, 30394-402 (2003).
- 201 Puig, O. *et al.* The tandem affinity purification (TAP) method: a general procedure of protein complex purification.
Methods **24**, 218-29 (2001).
- 202 Bohlander, S.K., Espinosa, I., Rafael, Le Beau, M.M., Rowley, J.D. & Diaz, M.O. A method for the rapid
sequence-independent amplification of microdissected chromosomal material. *Genomics* **13**, 1322-1324 (1992).
- 203 Mueller, P.R. & Wold, B. In vivo footprinting of a muscle specific enhancer by ligation-mediated PCR. *Science*
246, 780-6 (1989).
- 204 Liu, C.L., Schreiber, S.L. & Bernstein, B.E. Development and validation of a T7 based linear amplification for
genomic DNA. *BMC Genomics* **4**, 19 (2003).
- 205 Fields, S. Site-Seeing by Sequencing. *Science* **316**, 1441-1442 (2007).
- 206 Summerton, J.E. Morpholino, siRNA, and S-DNA compared: impact of structure and mechanism of action on off-
target effects and sequence specificity. *Curr Top Med Chem* **7**, 651-60 (2007).
- 207 Summerton, J. & Weller, D. Morpholino antisense oligomers: design, preparation, and properties. *Antisense
Nucleic Acid Drug Dev* **7**, 187-95 (1997).
- 208 Capecchi, M.R. The new mouse genetics: altering the genome by gene targeting. *Trends Genet* **5**, 70-6 (1989).
- 209 Fire, A.Z. Gene silencing by double-stranded RNA (nobel lecture). *Angew Chem Int Ed Engl* **46**, 6966-84 (2007).
- 210 Mello, C.C. Return to the RNAi World: Rethinking Gene Expression and Evolution (Nobel Lecture). *Angew Chem
Int Ed Engl* **46**, 6985-6994 (2007).

- 211 Fire, A. *et al.* Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*. *Nature* **391**, 806-11 (1998).
- 212 Montgomery, M.K., Xu, S. & Fire, A. RNA as a target of double-stranded RNA-mediated genetic interference in *Caenorhabditis elegans*. *Proc Natl Acad Sci U S A* **95**, 15502-7 (1998).
- 213 Echeverri, C.J. *et al.* Minimizing the risk of reporting false positives in large-scale RNAi screens. *Nat Meth* **3**, 777-779 (2006).
- 214 Kawakami, S. & Hashida, M. Targeted delivery systems of small interfering RNA by systemic administration. *Drug Metab Pharmacokinet* **22**, 142-51 (2007).
- 215 Peters, L. & Meister, G. Argonaute proteins: mediators of RNA silencing. *Mol Cell* **26**, 611-23 (2007).
- 216 Mack, G.S. MicroRNA gets down to business. *Nat Biotechnol* **25**, 631-8 (2007).
- 217 Hannon, G.J., Rivas, F.V., Murchison, E.P. & Steitz, J.A. The expanding universe of noncoding RNAs. *Cold Spring Harb Symp Quant Biol* **71**, 551-64 (2006).
- 218 Behm-Ansmant, I., Rehwinkel, J. & Izaurralde, E. MicroRNAs silence gene expression by repressing protein expression and/or by promoting mRNA decay. *Cold Spring Harb Symp Quant Biol* **71**, 523-30 (2006).
- 219 Stefani, G. & Slack, F. MicroRNAs in search of a target. *Cold Spring Harb Symp Quant Biol* **71**, 129-34 (2006).
- 220 Patel, D.J. *et al.* Structural biology of RNA silencing and its functional implications. *Cold Spring Harb Symp Quant Biol* **71**, 81-93 (2006).
- 221 Svoboda, P. Off-targeting and other non-specific effects of RNAi experiments in mammalian cells. *Curr Opin Mol Ther* **9**, 248-57 (2007).
- 222 Parker, J.S., Roe, S.M. & Barford, D. Molecular mechanism of target RNA transcript recognition by Argonaute-guide complexes. *Cold Spring Harb Symp Quant Biol* **71**, 45-50 (2006).
- 223 Margueron, R., Trojer, P. & Reinberg, D. The key to development: interpreting the histone code? *Curr. Opin. Genet. Dev.* **15**, 163-76 (2005).
- 224 Cosgrove, M.S. & Wolberger, C. How does the histone code work? *Biochem. Cell Biol.* **83**, 468-76 (2005).
- 225 Loizou, J.I. *et al.* Epigenetic information in chromatin: the code of entry for DNA repair. *Cell Cycle* **5**, 696-701 (2006).
- 226 Liu, C.L. *et al.* Single-nucleosome mapping of histone modifications in *S. cerevisiae*. *PLoS Biol.* **3**, e328 (2005).
- 227 Bernstein, B.E. *et al.* Methylation of histone H3 Lys 4 in coding regions of active genes. *Proc. Natl. Acad. Sci. U S A* **99**, 8695-700 (2002).
- 228 Bernstein, B.E. *et al.* Genomic Maps and Comparative Analysis of Histone Modifications in Human and Mouse. *Cell* **120**, 169-181 (2005).
- 229 Schubeler, D. *et al.* The histone modification pattern of active genes revealed through genome-wide chromatin analysis of a higher eukaryote. *Genes Dev.* **18**, 1263-1271 (2004).
- 230 Liang, G. *et al.* Distinct localization of histone H3 acetylation and H3-K4 methylation to the transcription start sites in the human genome. *Proc. Natl. Acad. Sci. U S A* **101**, 7357-62 (2004).
- 231 Stockdale, F.E. Myogenic cell lineages. *Developmental Biology* **154**, 284-298 (1992).
- 232 Yaffe, D. & Saxel, O. Serial passaging and differentiation of myogenic cells isolated from dystrophic mouse muscle. *Nature* **270**, 725-727 (1977).
- 233 Shen, X. *et al.* Genome-wide examination of myoblast cell cycle withdrawal during differentiation. *Developmental Dynamics* **226**, 128-138 (2004).
- 234 Liu, S. *et al.* Interaction of MyoD family proteins with enhancers of acetylcholine receptor subunit genes in vivo. *J. Biol. Chem.* **275**, 41364-8 (2000).
- 235 Claycomb, W.C. *et al.* HL-1 cells: A cardiac muscle cell line that contracts and retains phenotypic characteristics of the adult cardiomyocyte. *Proc Natl Acad Sci U S A* **95**, 2979-2984 (1998).
- 236 White, S.M., Constantin, P.E. & Claycomb, W.C. Cardiac physiology at the cellular level: use of cultured HL-1 cardiomyocytes for studies of cardiac muscle cell structure and function. *AJP - Heart and Circulatory Physiology* **286**, H823-H829 (2004).
- 237 Claycomb, W.C. *et al.* HL-1 cells: a cardiac muscle cell line that contracts and retains phenotypic characteristics of the adult cardiomyocyte. *Proc. Natl. Acad. Sci. U S A* **95**, 2979-84 (1998).
- 238 Bradford, M.M. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. *Anal Biochem* **72**, 248-54 (1976).
- 239 Swillens, S., Goffard, J.C., Marechal, Y., de Kerchove, d.E.A. & El Housni, H. Instant evaluation of the absolute initial number of cDNA copies from a single real-time PCR curve. *Nucleic Acids Res.* **32**, e56 (2004).
- 240 Masotti, A. & Preckel, T. Analysis of small RNAs with the Agilent 2100 Bioanalyzer. *Nature Methods*, Published online: 21 July 2006 (2006).
- 241 Horak, C.E. *et al.* GATA-1 binding sites mapped in the beta-globin locus by using mammalian chIp-chip analysis. *Proc.Natl.Acad.Sci.U.S.A* **99**, 2924-2929 (2002).
- 242 Iyer, V.R. *et al.* Genomic binding sites of the yeast cell-cycle transcription factors SBF and MBF. *Nature* **409**, 533-8 (2001).
- 243 Kaynak, B. *et al.* Genome-wide array analysis of normal and malformed human hearts. *Circulation* **107**, 2467-2474 (2003).
- 244 Su, A.I. *et al.* A gene atlas of the mouse and human protein-encoding transcriptomes. *Proc. Natl. Acad. Sci. U S A* **101**, 6062-7 (2004).
- 245 Tabibiazar, R., Wagner, R.A., Liao, A. & Quertermous, T. Transcriptional profiling of the heart reveals chamber-specific gene expression patterns. *Circ. Res.* **93**, 1193-201 (2003).
- 246 Matys, V. *et al.* TRANSFAC and its module TRANSCmpel: transcriptional gene regulation in eukaryotes. *Nucleic Acids Res.* **34**, D108-10 (2006).
- 247 Siepel, A. *et al.* Evolutionarily conserved elements in vertebrate, insect, worm, and yeast genomes. *Genome Res* **15**, 1034-1050 (2005).

- 248 Kent, W.J. BLAT - the BLAST-like alignment tool. *Genome Res.* **12**, 656-64 (2002).
- 249 Huber, W., von Heydebreck, A., Sultmann, H., Poustka, A. & Vingron, M. Variance stabilization applied to microarray data calibration and to the quantification of differential expression. *Bioinformatics* **18 Suppl 1**, S96-104 (2002).
- 250 Irizarry, R.A. *et al.* Summaries of Affymetrix GeneChip probe level data. *Nucleic Acids Res.* **31**, e15 (2003).
- 251 Dudoit, S., Shaffer, J.P. & Boldrick, J.C. Multiple Hypothesis Testing in Microarray Experiments. *Statistical Science* **18**, 71-103 (2003).
- 252 Gentleman, R.C. *et al.* Bioconductor: open software development for computational biology and bioinformatics. *Genome Biol.* **5**, R80 (2004).
- 253 Smyth, G.K. Linear models and empirical bayes methods for assessing differential expression in microarray experiments. *Stat. Appl. Genet. Mol. Biol.* **3**, Article3 (2004).
- 254 Benjamini, Y. & Yekutieli, D. The control of the false discovery rate in multiple testing under dependency. *Annals of Statistics* **29**, 1165-1188 (2001).
- 255 Ashburner, M. *et al.* Gene ontology: tool for the unification of biology. The Gene Ontology Consortium. *Nat. Genet.* **25**, 25-9 (2000).
- 256 Alexa, A., Rahnenfuhrer, J. & Lengauer, T. Improved scoring of functional groups from gene expression data by decorrelating GO graph structure. *Bioinformatics* **22**, 1600-7 (2006).
- 257 Toedling, J., Sklyar, O. & Huber, W. Ringo - an R/Bioconductor package for analyzing ChIP-chip readouts. *BMC Bioinformatics* **8**, 221 (2007).
- 258 Bailey, T.L. & Gribskov, M. Combining evidence using p-values: application to sequence homology searches. *Bioinformatics* **14**, 48-54 (1998).
- 259 Hughes, J.D., Estep, P.W., Tavazoie, S. & Church, G.M. Computational identification of cis-regulatory elements associated with groups of functionally related genes in *Saccharomyces cerevisiae*. *J. Mol. Biol.* **296**, 1205-14 (2000).
- 260 Knuppel, R., Dietze, P., Lehnberg, W., Frech, K. & Wingender, E. TRANSFAC retrieval program: a network model database of eukaryotic transcription regulating sequences and proteins. *J Comput Biol* **1**, 191-8 (1994).
- 261 Kel, A.E. *et al.* MATCH: A tool for searching transcription factor binding sites in DNA sequences. *Nucleic Acids Res* **31**, 3576-9 (2003).
- 262 Liu, X.S., Brutlag, D.L. & Liu, J.S. An algorithm for finding protein-DNA-binding sites with applications to chromatin-immunoprecipitation microarray experiments. *Nat Biotech* **20**, 835-839 (2002).
- 263 Hughes, J.D., Estep, P.W., Tavazoie, S. & Church, G.M. Computational identification of Cis-regulatory elements associated with groups of functionally related genes in *Saccharomyces cerevisiae*. *Journal of Molecular Biology* **296**, 1205-1214 (2000).
- 264 Bailey, T.L. & Elkan, C. The value of prior knowledge in discovering motifs with MEME. *Proc Int Conf Intell Syst Mol Biol* **3**, 21-9 (1995).
- 265 Pavesi, G., Mereghetti, P., Mauri, G. & Pesole, G. Weeder Web: discovery of transcription factor binding sites in a set of sequences from co-regulated genes. in *Nucleic Acids Research* Vol. 32 W199-W203 (2004).
- 266 Kuhn, R.M. *et al.* The UCSC genome browser database: update 2007. **35**, D668-673 (2007).
- 267 Longabaugh, W.J., Davidson, E.H. & Bolouri, H. Computational representation of developmental genetic regulatory networks. *Dev Biol* **283**, 1-16 (2005).
- 268 Carey, V.J., Gentry, J., Whalen, E. & Gentleman, R. Network structures and algorithms in Bioconductor. *Bioinformatics* **21**, 135-6 (2005).
- 269 Hardison, R.C., Oeltjen, J. & Miller, W. Long Human-Mouse Sequence Alignments Reveal Novel Regulatory Elements: A Reason to Sequence the Mouse Genome. **7**, 959-966 (1997).
- 270 Hardison, R.C. Conserved noncoding sequences are reliable guides to regulatory elements. *Trends in Genetics* **16**, 369-372 (2000).
- 271 Wasserman, W.W., Palumbo, M., Thompson, W., Fickett, J.W. & Lawrence, C.E. Human-mouse genome comparisons to locate regulatory sites. *Nat Genet* **26**, 225-228 (2000).
- 272 Dieterich, C., Wang, H., Rateitschak, K., Luz, H. & Vingron, M. CORG: a database for COmparative Regulatory Genomics. *Nucleic Acids Res.* **31**, 55-57 (2003).
- 273 Allen, K.D. & Athanasiou, K.A. Effect of passage and topography on gene expression of temporomandibular joint disc cells. *Tissue Eng* **13**, 101-10 (2007).
- 274 Churchill, G.A. Fundamentals of experimental design for cDNA microarrays. *Nat Genet* **32 Suppl**, 490-5 (2002).
- 275 Tomczak, K.K. *et al.* Expression profiling and identification of novel genes involved in myogenic differentiation. *Faseb J* **18**, 403-5 (2004).
- 276 McKinsey, T.A., Zhang, C.L. & Olson, E.N. Control of muscle development by dueling HATs and HDACs. *Current Opinion in Genetics & Development* **11**, 497-504 (2001).
- 277 Tomczak, K.K. *et al.* Expression profiling and identification of novel genes involved in myogenic differentiation. *Faseb J.* **18**, 403-5 (2004).
- 278 Ruffle, R.A. *et al.* Distribution of constitutively expressed MEF-2A in adult rat and human nervous systems. *Synapse* **59**, 513-20 (2006).
- 279 Reguly, T. & Wrana, J.L. In or out? The dynamics of Smad nucleocytoplasmic shuttling. *Trends Cell Biol* **13**, 216-20 (2003).
- 280 Karamboulas, C. *et al.* Disruption of MEF2 activity in cardiomyoblasts inhibits cardiomyogenesis. *J Cell Sci* **119**, 4315-21 (2006).
- 281 Kobayashi, S. *et al.* Transcription factor *gata4* regulates cardiac *BCL2* gene expression in vitro and in vivo. *Faseb J* **20**, 800-2 (2006).
- 282 Bisping, E. *et al.* *Gata4* is required for maintenance of postnatal cardiac function and protection from pressure overload-induced heart failure. Vol. 103 14471-14476 (2006).

References

- 283 Kawamura, T. *et al.* Acetylation of GATA-4 is involved in the differentiation of embryonic stem cells into cardiac
myocytes. *J Biol Chem* **280**, 19682-8 (2005).
- 284 Brewer, A.C. *et al.* GATA factors lie upstream of Nkx 2.5 in the transcriptional regulatory cascade that effects
cardiogenesis. *Stem Cells Dev* **14**, 425-39 (2005).
- 285 Blais, A. *et al.* An initial blueprint for myogenic differentiation. *Genes Dev* **19**, 553-69 (2005).
- 286 Bergstrom, D.A. *et al.* Promoter-Specific Regulation of MyoD Binding and Signal Transduction Cooperate to
Pattern Gene Expression. *Molecular Cell* **9**, 587-600 (2002).
- 287 Toro, R., Saadi, I., Kuburas, A., Nemer, M. & Russo, A.F. Cell-specific activation of the atrial natriuretic factor
promoter by PITX2 and MEF2A. *J Biol Chem* **279**, 52087-94 (2004).
- 288 Zou, Y. *et al.* CARP, a cardiac ankyrin repeat protein, is downstream in the Nkx2-5 homeobox gene pathway.
Development **124**, 793-804 (1997).
- 289 Ueyama, T., Kasahara, H., Ishiwata, T., Nie, Q. & Izumo, S. Myocardin expression is regulated by Nkx2.5, and its
function is required for cardiomyogenesis. *Mol Cell Biol* **23**, 9222-32 (2003).
- 290 Prall, O.W.J. *et al.* An Nkx2-5/Bmp2/Smad1 Negative Feedback Loop Controls Heart Progenitor Specification and
Proliferation. *Cell* **128**, 947-959 (2007).
- 291 Palmer, S. *et al.* The small muscle-specific protein Csl modifies cell shape and promotes myocyte fusion in an
insulin-like growth factor 1-dependent manner. *J Cell Biol* **153**, 985-98 (2001).
- 292 Witt, C.C. *et al.* Induction and Myofibrillar Targeting of CARP, and Suppression of the Nkx2.5 Pathway in the
MDM Mouse with Impaired Titin-based Signaling. *Journal of Molecular Biology* **336**, 145-154 (2004).
- 293 Foster, D.N. *et al.* Positive and negative cis-acting regulatory elements mediate expression of the mouse vascular
smooth muscle alpha-actin gene. *J Biol Chem* **267**, 11995-2003 (1992).
- 294 Rangnekar, V.M., Aplin, A.C. & Sukhatme, V.P. The serum and TPA responsive promoter and intron-exon
structure of EGR2, a human early growth response gene encoding a zinc finger protein. *Nucleic Acids Res* **18**,
2749-57 (1990).
- 295 Minty, A. & Kedes, L. Upstream regions of the human cardiac actin gene that modulate its transcription in muscle
cells: presence of an evolutionarily conserved repeated motif. *Mol Cell Biol* **6**, 2125-36 (1986).
- 296 Townsend, K.J. *et al.* Regulation of MCL1 through a serum response factor/Elk-1-mediated mechanism links
expression of a viability-promoting member of the BCL2 family to the induction of hematopoietic cell
differentiation. *J Biol Chem* **274**, 1801-13 (1999).
- 297 Gilgenkrantz, H. *et al.* Positive and negative regulatory DNA elements including a CCArGG box are involved in
the cell type-specific expression of the human muscle dystrophin gene. *J Biol Chem* **267**, 10823-30 (1992).
- 298 Marshall, P., Chartrand, N. & Worton, R.G. The mouse dystrophin enhancer is regulated by MyoD, E-box-binding
factors, and by the serum response factor. in *J Biol Chem* Vol. 276 20719-26 (2001).
- 299 Kim, D.W., Cheriya, V., Roy, A.L. & Cochran, B.H. TFII-I enhances activation of the c-fos promoter through
interactions with upstream elements. *Mol Cell Biol* **18**, 3310-20 (1998).
- 300 Balza, R.O., Jr. & Misra, R.P. Role of the serum response factor in regulating contractile apparatus gene expression
and sarcomeric integrity in cardiomyocytes. in *J Biol Chem* Vol. 281 6498-510 (2006).
- 301 Perez-Albuena, E.D., Schattman, G., Sanders, L.K. & Nathans, D. Transcriptional regulatory elements
downstream of the JunB gene. in *Proc Natl Acad Sci U S A* Vol. 90 11960-4 (1993).
- 302 Selvaraj, A. & Prywes, R. Expression profiling of serum inducible genes identifies a subset of SRF target genes
that are MKL dependent. *BMC Mol Biol* **5**, 13 (2004).
- 303 Nakamura, M. *et al.* Transcriptional activation of beta-tropomyosin mediated by serum response factor and a novel
Barx homologue, Barx1b, in smooth muscle cells. *J Biol Chem* **276**, 18313-20 (2001).
- 304 Pavesi, G., Mauri, G. & Pesole, G. An algorithm for finding signals of unknown length in DNA sequences.
bioinformatics **17**, S207-214 (2001).
- 305 Lawrence, C.E. *et al.* Detecting subtle sequence signals: a Gibbs sampling strategy for multiple alignment. *Science*
262, 208-14 (1993).
- 306 Tuerk, C. & Gold, L. Systematic evolution of ligands by exponential enrichment: RNA ligands to bacteriophage T4
DNA polymerase. *Science* **249**, 505-10 (1990).
- 307 Andres, V., Cervera, M. & Mahdavi, V. Determination of the consensus binding site for MEF2 expressed in muscle
and brain reveals tissue-specific sequence constraints. *J Biol Chem* **270**, 23246-9 (1995).
- 308 Vlieghe, D. *et al.* A new generation of JASPAR, the open-access repository for transcription factor binding site
profiles. *Nucleic Acids Res* **34**, D95-7 (2006).
- 309 Kuhn, R.M. *et al.* The UCSC genome browser database: update 2007. *Nucleic Acids Res* **35**, D668-73 (2007).
- 310 Bruneau, B.G. *et al.* A murine model of Holt-Oram syndrome defines roles of the T-box transcription factor Tbx5
in cardiogenesis and disease. *Cell* **106**, 709-21 (2001).
- 311 Pu, W.T., Ishiwata, T., Juraszek, A.L., Ma, Q. & Izumo, S. GATA4 is a dosage-sensitive regulator of cardiac
morphogenesis. *Developmental Biology* **275**, 235-244 (2004).
- 312 Kirk, E.P. *et al.* Mutations in cardiac T-box factor gene TBX20 are associated with diverse cardiac pathologies,
including defects of septation and valvulogenesis and cardiomyopathy. *Am J Hum Genet* **81**, 280-91 (2007).
- 313 Szeto, D.P., Griffin, K.J. & Kimelman, D. HrT is required for cardiovascular development in zebrafish.
Development **129**, 5093-101 (2002).
- 314 Takeuchi, J.K. *et al.* Tbx20 dose-dependently regulates transcription factor networks required for mouse heart and
motoneuron development. *Development* **132**, 2463-74 (2005).
- 315 Stennard, F.A. *et al.* Murine T-box transcription factor Tbx20 acts as a repressor during heart development, and is
essential for adult heart integrity, function and adaptation. *Development* **132**, 2451-62 (2005).
- 316 Tanaka, T.S. *et al.* Genome-wide expression profiling of mid-gestation placenta and embryo using a 15,000 mouse
developmental cDNA microarray. *Proc Natl Acad Sci U S A* **97**, 9127-32 (2000).
- 317 Zheng, M., Barrera, L.O., Ren, B. & Wu, Y.N. ChIP-chip: data, model, and analysis. *Biometrics* **63**, 787-96 (2007).

- 318 Johnson, W.E. *et al.* Model-based analysis of tiling-arrays for ChIP-chip. *Proc Natl Acad Sci U S A* **103**, 12457-62 (2006).
- 319 Ji, H. & Wong, W.H. TileMap: create chromosomal map of tiling array hybridizations. *Bioinformatics* **21**, 3629-36 (2005).
- 320 Scacheri, P.C., Crawford, G.E. & Davis, S. Statistics for ChIP-chip and DNase hypersensitivity experiments on NimbleGen arrays. *Methods Enzymol* **411**, 270-82 (2006).
- 321 Keles, S. Mixture modeling for genome-wide localization of transcription factors. *Biometrics* **63**, 10-21 (2007).
- 322 Buck, M.J., Nobel, A.B. & Lieb, J.D. ChIPOTle: a user-friendly tool for the analysis of ChIP-chip data. *Genome Biol* **6**, R97 (2005).
- 323 Smith, C.M. Quantification of acetylation at proximal lysine residues using isotopic labeling and tandem mass spectrometry. *Methods* **36**, 395-403 (2005).
- 324 Clark, D.J. & Shen, C.H. Mapping histone modifications by nucleosome immunoprecipitation. *Methods Enzymol* **410**, 416-30 (2006).
- 325 Ioshikhes, I.P., Albert, I., Zanton, S.J. & Pugh, B.F. Nucleosome positions predicted through comparative genomics. *Nat. Genet.* **38**, 1210-1215 (2006).
- 326 Yuan, G.-C. *et al.* Genome-scale identification of nucleosome positions in *S. cerevisiae*. *Science* **309**, 626-630 (2005).
- 327 Oszolak, F., Song, J.S., Liu, X.S. & Fisher, D.E. High-throughput mapping of the chromatin structure of human promoters. *Nat Biotech* **25**, 244-248 (2007).
- 328 Schneider, R. *et al.* Histone H3 lysine 4 methylation patterns in higher eukaryotic genes. *Nat. Cell Biol.* **6**, 73-77 (2004).
- 329 Miao, F. & Natarajan, R. Mapping Global Histone Methylation Patterns in the Coding Regions of Human Genes. *Mol. Cell. Biol.* **25**, 4650-4661 (2005).
- 330 Rougeulle, C., Navarro, P. & Avner, P. Promoter-restricted H3 Lys 4 di-methylation is an epigenetic mark for monoallelic expression. *Hum Mol Genet* **12**, 3343-8 (2003).
- 331 Okitsu, C.Y. & Hsieh, C.L. DNA methylation dictates histone H3K4 methylation. *Mol Cell Biol* **27**, 2746-57 (2007).
- 332 Kim, T.H. *et al.* A high-resolution map of active promoters in the human genome. *Nature* **436**, 876-880 (2005).
- 333 Brinkman, A.B. *et al.* Histone modification patterns associated with the human X chromosome. *EMBO Rep* **7**, 628-34 (2006).
- 334 Clayton, A.L., Hazzalin, C.A. & Mahadevan, L.C. Enhanced histone acetylation and transcription: a dynamic perspective. *Mol Cell* **23**, 289-96 (2006).
- 335 Verdone, L., Caserta, M. & Di Mauro, E. Role of histone acetylation in the control of gene expression. *Biochem. Cell Biol.* **83**, 344-53 (2005).
- 336 Shi, X. *et al.* ING2 PHD domain links histone H3 lysine 4 methylation to active gene repression. *Nature* **442**, 96-9 (2006).
- 337 McKinsey, T.A., Zhang, C.L. & Olson, E.N. Control of muscle development by dueling HATs and HDACs. *Curr. Opin. Genet. Dev.* **11**, 497-504 (2001).
- 338 Paris, J., Virtanen, C., Lu, Z. & Takahashi, M. Identification of MEF2-regulated genes during muscle differentiation. *Physiol Genomics* **20**, 143-51 (2004).
- 339 Sandmann, T. *et al.* A Temporal Map of Transcription Factor Activity: Mef2 Directly Regulates Target Genes at All Stages of Muscle Development. *Developmental Cell* **10**, 797-807 (2006).
- 340 Cooper, S.J., Trinklein, N.D., Nguyen, L. & Myers, R.M. Serum response factor binding sites differ in three human cell types. *Genome Res* **17**, 136-44 (2007).
- 341 ENCODE, T.P.C. Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project. *Nature* **447**, 799-816 (2007).
- 342 Caramori, G. *et al.* Expression of GATA family of transcription factors in T-cells, monocytes and bronchial biopsies. *Eur Respir J* **18**, 466-73 (2001).
- 343 Lyons, I. *et al.* Myogenic and morphogenetic defects in the heart tubes of murine embryos lacking the homeo box gene Nkx2-5. Vol. 9 1654-1666 (1995).
- 344 Jay, P.Y. *et al.* Nkx2-5 mutation causes anatomic hypoplasia of the cardiac conduction system. *J Clin Invest* **113**, 1130-7 (2004).
- 345 Niu, Z. *et al.* Conditional mutagenesis of the murine serum response factor gene blocks cardiogenesis and the transcription of downstream gene targets. *J Biol Chem* **280**, 32531-8 (2005).
- 346 Sepulveda, J.L. *et al.* GATA-4 and Nkx-2.5 Coactivate Nkx-2 DNA-Binding Targets: Role for Regulating Early Cardiac Gene Expression. *Mol Cell Biol* **18**, 3405-3415 (1998).
- 347 Creemers, E.E., Sutherland, L.B., Oh, J., Barbosa, A.C. & Olson, E.N. Coactivation of MEF2 by the SAP Domain Proteins Myocardin and MASTR. *Molecular Cell* **23**, 83-96 (2006).
- 348 Matys, V. *et al.* TRANSFAC and its module TRANSCompel: transcriptional gene regulation in eukaryotes. *Nucleic Acids Res* **34**, D108-10 (2006).
- 349 Chang, P.S., Li, L., McAnally, J. & Olson, E.N. Muscle specificity encoded by specific serum response factor-binding sites. *J Biol Chem* **276**, 17206-12 (2001).
- 350 Cao, D. *et al.* Modulation of smooth muscle gene expression by association of histone acetyltransferases and deacetylases with myocardin. *Mol Cell Biol* **25**, 364-76 (2005).
- 351 McKinsey, T.A., Zhang, C.L. & Olson, E.N. MEF2: a calcium-dependent regulator of cell division, differentiation and death. *Trends in Biochemical Sciences* **27**, 40-47 (2002).
- 352 Chen, S.L., Loffler, K.A., Chen, D., Stallcup, M.R. & Muscat, G.E. The coactivator-associated arginine methyltransferase is necessary for muscle differentiation: CARM1 coactivates myocyte enhancer factor-2. *J Biol Chem* **277**, 4324-33 (2002).

References

- 353 Ma, K., Chan, J.K., Zhu, G. & Wu, Z. Myocyte enhancer factor 2 acetylation by p300 enhances its DNA-binding activity, transcriptional activity, and myogenic differentiation. *Mol Cell Biol* **25**, 3575-82 (2005).
- 354 Chen, S.L., Loffler, K.A., Chen, D., Stallcup, M.R. & Muscat, G.E.O. The Coactivator-associated Arginine Methyltransferase Is Necessary for Muscle Differentiation. CARM1 COACTIVATES MYOCYTE ENHANCER FACTOR-2. Vol. 277 4324-4333 (2002).
- 355 Kim, T.G., Jung, J., Mysliwiec, M.R., Kang, S. & Lee, Y. Jumonji represses alpha-cardiac myosin heavy chain expression via inhibiting MEF2 activity. *Biochem Biophys Res Commun* **329**, 544-53 (2005).
- 356 Kim, T.G., Chen, J., Sadoshima, J. & Lee, Y. Jumonji represses atrial natriuretic factor gene expression by inhibiting transcriptional activities of cardiac transcription factors. *Mol Cell Biol* **24**, 10151-60 (2004).
- 357 Klose, R.J. *et al.* The transcriptional repressor JHDM3A demethylates trimethyl histone H3 lysine 9 and lysine 36. *Nature* **442**, 312-6 (2006).
- 358 Lee, Y. *et al.* Jumonji, a nuclear protein that is necessary for normal heart development. *Circ Res* **86**, 932-8 (2000).
- 359 Loh, Y.H. *et al.* The Oct4 and Nanog transcription network regulates pluripotency in mouse embryonic stem cells. *Nat Genet* **38**, 431-40 (2006).
- 360 Page, T.J. *et al.* Genome-wide analysis of human HSF1 signaling reveals a transcriptional program linked to cellular adaptation and survival. *Mol Biosyst* **2**, 627-39 (2006).
- 361 Palomero, T. *et al.* Transcriptional regulatory networks downstream of TAL1/SCL in T-cell acute lymphoblastic leukemia. *Blood* **108**, 986-92 (2006).
- 362 Peterkin, T., Gibson, A., Loose, M. & Patient, R. The roles of GATA-4, -5 and -6 in vertebrate heart development. *Semin.Cell Dev.Biol* **16**, 83-94 (2005).
- 363 Olson, E.N., Backs, J. & McKinsey, T.A. Control of cardiac hypertrophy and heart failure by histone acetylation/deacetylation. *Novartis Found Symp* **274**, 3-12; discussion 13-9, 152-5, 272-6 (2006).
- 364 Olson, E.N. & Schneider, M.D. Sizing up the heart: development redux in disease. *Genes Dev* **17**, 1937-56 (2003).
- 365 Olson, E.N. Gene regulatory networks in the evolution and development of the heart. *Science* **313**, 1922-7 (2006).

