[Frontiers in Bioscience 6, d1024-1047, September 1, 2001]

THE LINK BETWEEN CHROMATIN STRUCTURE, PROTEIN ACETYLATION AND CELLULAR DIFFERENTIATION

Vittorio Sartorelli[1] and Pier Lorenzo Puri[2]

[1]Laboratory of Muscle Biology, Muscle Gene Expression Group, NIAMS-IRP, National Institutes of Health, Bethesda, Maryland 20892,[2]The Salk Institute for Biological Studies, Peptide Biology Laboratory, La Jolla, California 92093 and Fondazione "A. Cesalpino", University of Rome La Sapienza, 00161, Rome, Italy

TABLE OF CONTENTS

1. ABSTRACT

Chromatin remodeling and protein acetylation control gene expression and consequently regulate cellular growth and differentiation. Here we review the role of individual chromatin remodeling factors, acetyltransferases and deacetylases in the establishment and maintenance of different cell lineages and in the genesis of some human diseases.

2. INTRODUCTION

The clarification of the mechanisms leading to the establishment of highly specialized cell lineages starting from a fertilized egg remains elusive and it continues to be a fascinating area of investigation.

Asymmetric partitioning of maternal material to daughter cells and extracellular signals mediated by either soluble or membrane-anchored molecules contribute to instruct a group of given cells to adopt a defined fate. Recent findings indicate that while the fate may be defined is not definitive. Some cells reserve the option of changing their mind and, under circumstances that remain to be investigated, can and will modify their phenotype (65,89,110,212,127,71).

Mechanistically, generating most- if not all- cell types relies on a common feature. That is, no matter what the nature of the signals and the pathways chosen to transduce them may be, the resulting information needs to reach the nucleus of the cell to influence gene expression. Of the many genes comprising the genome of a multicellular organism, only a defined combination is turned on in a given subset of cells. Therefore, cell differentiation is largely a matter of transcriptional regulation.

The DNA regions regulating gene expression are not readily accessible to transcription factors because of a

physical barrier represented by the chromatin (104,75,83, 283). An increased DNA accessibility to a variety of enzymes and chemical probes denotes a redistribution of the nucleosomal array (279) - a phenomenon known as chromatin remodeling - that precedes transcriptional activation. This process is brought about by ATP-dependent molecular machines comprised of several protein subunits (130,68,70). Chromatin remodeling facilitates the binding of transcription factors to nucleosome particles, at least in an *in vitro* system (51).

Whilst DNA binding of transcription factors and chromatin remodeling enzymes is a prerequisite for gene activation, it is not sufficient to initiate transcription. As elegantly illustrated in yeast, a chronologically ordered series of events is required to activate transcription (50). The yeast transcriptional activator Swi5 recruits the chromatin remodeling SWI/SNF complex on the promoter of the HO gene. The engagement of SWI/SNF is not sufficient to stimulate HO transcription, which is allowed to proceed only after the acetyltransferase Gcn5 joins the Swi5-SWI/SNF complex and promotes acetylation of the histones surrounding the HO gene. Surprisingly, once SWI/SNF and Gcn5 have been recruited to the HO promoter, the presence of the activator Swi5 becomes dispensable. Recent experiments indicate that retention of the SWI/SNF complex on promoter regions is accomplished by histone acetylation and that once acetylation has been achieved, the transcriptional activator is no longer needed (96). Therefore, acetylation of histones- and possibly of other proteins- seems to temporally follow chromatin remodeling. At the same time, histone acetylation is necessary to productively retain remodeling machines on chromatin in a complex series of events culminating in transcription (96). An increasing number of proteins previously known to be transcriptional regulators including p300/CBP (199) (12), P/CAF (287), GCN5 (33), ACTR (43), Src-1 (249) and TAFII250 (167) have been shown to have intrinsic histone acetyltransferase (HAT) activity (for recent reviews on HAT enzymes see (32,18,30,128,48). A link between histone acetylation, methylation and eukaryotic gene expression has been suggested since 1964 (1). Further studies have indicated that active euchromatin is associated with hyperacetylated histones (25,63) whereas the histones of inactive heterochromatin are hypoacetylated (29, 114). An additional evidence supporting the role of histone acetylation and deacetylation in regulating transcription has emerged from the isolation and characterization of several mammalian histone deacetylases with the founding member HD1 (260) being related to the yeast transcriptional repressor Rpd3 (181,266). How histone acetylation promotes transcription is not well understood. It is generally believed that acetylation at the ε-amino groups neutralizes the positive charge of specific lysines located at the N-terminus of histones H3 and H4 therefore weakening the electrostatic interaction of histones with DNA. The resulting loosening of the nucleosome structure would favor binding of transcription factors to their DNA targets (32). On the contrary, removal of acetyl groups from the ε–amino groups of lysines could reinforce the electrostatic interaction between histones and DNA precluding transcriptional activation. While this scenario may be partially correct, the recent solution of the crystal structure of the nucleosome core particles indicates that the histone N-terminus (the tail) does not seem to contact directly the DNA but rather seems to interact with adjacent nucleosomes (145). It is therefore likely that acetylation modifies several proteins engaged in controlling transcription including histones, enhancer-binding factors and members of the basal transcriptional machinery (105) and that stimulation of transcription derives from the sum of these modifications (48).

Here we will review recent advancements in the field of transcriptional regulation of different cell-types with a particular focus on the role of acetylation/deacetylation.

3. SKELETAL MYOGENESIS

The understanding of how skeletal muscle cells are specified, maintained and undergo differentiation has received a tremendous impetus since the isolation of MyoD (53). MyoD- related factors have been isolated that belong to the same family of transcriptional activators, the myogenic bHLH proteins (277,202). The myogenic bHLH interact with a specific DNA motif, the E-box, and they are assisted in promoting transcription by two general activators, the E proteins and the MADS-box –containing factors MEF2 (134,170). Overexpression of any of the myogenic bHLH proteins redirects the fate of both established cell lines and primary cells to take up the skeletal muscle phenotype (280). Genetic ablation of the individual genes in animal models has revealed a specific role for each of the myogenic bHLH. MyoD and Myf-5 are responsible for the specification (28, 231, 232) whereas myogenin controls differentiation of skeletal muscle cells (97,177). MyoD is also involved in muscle regeneration (159). The role of MRF4 is less clear at the moment (201).

3.1. Chromatin remodeling

Over the years, it has been appreciated that chromatin remodeling is a hallmark of the initial steps that may result in gene activation and that chromatin remodeling enzymes are involved in regulating both chromatin modification and gene expression (267). MyoD expression causes chromatin remodeling of muscle-specific genes including those for myogenin, muscle creatine kinase and MyoD itself (73). Importantly, changes in chromatin structure could be directly ascribed to the activity of MyoD since they were observed in the presence of the protein synthesis inhibitor cycloheximide (73). The effects exerted by MyoD on chromatin are highly specific and are limited to regulatory regions controlling expression of muscle – restricted genes. In fact, the structure of the chromatin surrounding the locus control region of the beta globin cluster and the immunoglobulin enhancer - active in red blood cells and lymphocytes, respectively- is not affected by MyoD expression (73). Two regions of MyoD, the cysteine-histidine rich domain (73) and the carboxyl-terminus (73,19), mediate chromatin remodeling activity. Reflecting the different roles of the individual myogenic bHLH proteins observed in the animal, Myf-5 but not myogenin also causes chromatin modification at muscle-

specific loci (73). The SWI/SNF complex or related chromatin remodeling complexes (70) may mediate the activity of MyoD. Upon inducible expression of a dominant-negative version of either BRG1 or BRM, the ATPase subunits of SWI/SNF, MyoD-dependent conversion of NIH3T3 fibroblasts is prevented and, most importantly, this correlates with lack of chromatin remodeling on the promoter of an endogenous muscle-specific gene (55). Recent experiments suggest that SWI/SNF associates with MyoD (C. Palmer and M.A. Rudnicki, personal communication).

3.2. Co-activation and acetylation

3.2.1. MyoD

Numerous proteins counteract the ability of skeletal muscle cells to differentiate in tissue culture. Among these are the viral oncoproteins E1A and SV 40 T antigen (222). The transcriptional coactivator p300 has been purified exploiting its ability to interact with E1A (94, 60). The SV40 T antigen also interacts with p300 (7, 61). While E1A interacts with several cellular proteins including pRb, p130 and p107 (94), deletion of 30 amino acids at its N-terminus prevents p300 binding and greatly diminishes the ability of E1A to prevent muscle differentiation (38) – despite the integrity of the other E1A modules necessary to interact with the aforementioned cellular proteins-. These findings prompted several groups to ask the question of whether p300 may be a coactivator of muscle transcription. Indeed, p300 was found to interact and augment transcription mediated by both MyoD (289, 62, 221, 233) and MEF2 (233) and microinjection of p300-specific antisera blocked differentiation of cultured muscle cells (223, 62).

While Eckner *et al*. (62) found the bHLH region of MyoD could mediate interaction with MyoD, Sartorelli *et al*. (233) reported that the N-terminal region of MyoD – containing an acidic activator domain- was to mediate both interaction and sense coactivation of MyoD. The N-terminal region of MyoD is required for cooperative binding of MyoD to two adjacent DNA binding sites (E-boxes) and transcriptional activation of MCK enhancer (276). Deletion of 53 amino acids located at the N-terminal region of MyoD renders it inactive when tested in transient transfection assays (278) whilst it does not seem to affect the ability of stably transfected MyoD to activate transcription of endogenous muscle genes (259). It may be possible that, in the cellular context, MyoD may simultaneously interact with p300 through both the N-terminal and the bHLH regions. On p300, two regions encompassing amino acids 1-596 and including the cysteine/histidine-rich region 1 (C/H1) (60) and amino acids 1572-1900 spanning the C/H3 region (60) independently mediate interaction with MyoD and possibly other myogenic bHLH proteins (289, 62, 233, 228). In addition, p300 seems to be also involved in controlling cell cycle exit of myoblasts induced to differentiate. Indeed, microinjection of anti-p300 antibodies prevents up-regulation of the cell cycle inhibitor p21 and abrogates MyoD-dependent cell cycle arrest (62, 221). Thus, p300 provides a pivotal function in at least two critical steps of the myogenic program, that is cell cycle arrest and expression of muscle-specific genes. It is likely that E1A and SV40 T Ag may cause cell cycle progression and block expression of muscle-restricted proteins by competing with MyoD for p300 binding. The p300/CBP-associated factor P/CAF competes with the oncoprotein E1A for binding to p300/CBP (287). Both P/CAF and MyoD interact with an overlapping but distinct region of p300 (223). Furthermore, P/CAF directly interacts with MyoD albeit with a much lower affinity than that exhibited for p300 (223).

Microinjection experiments conducted with a P/CAF antiserum resulted in a blockade of muscle differentiation indicating the need of P/CAF for this process (223). It is worth noting that the P/CAF antisera utilized in those experiments cross-react with GCN5 (R. L. Schiltz, personal communication) raising the possibility that both P/CAF and GCN5 were neutralized. Based on co-immunoprecipitation experiments and relative protein affinities, a model has been proposed where the primary function of p300 would be to recruit P/CAF on MyoD to activate transcription. Both p300/CBP and P/CAF have intrinsic acetyltransferase activities (199, 12, 287) raising the question of why MyoD engages two different proteins with the same enzymatic activity to promote transcription. Using deletion mutants of both p300 and P/CAF with no detectable histone acetyltransferase activity, MyoD-dependent transcription was found to require the HAT activity of P/CAF but not of p300 (224). This difference is unlikely to reside in the distinct patter of histone acetylation observed for p300 and P/CAF. In fact, while p300/CBP acetylates the majority of the H3 lysines and all the H4 lysines acetylated *in vivo*, P/CAF acetylates only a subset of them (237).

A possible level of discrimination between the HAT activity of p300 and P/CAF may reside in the observation that whilst MyoD itself is acetylated by both p300 (234, 217) and PCAF (234, 150), only acetylation mediated by the latter causes an increase in DNA binding and modify MyoD conformation (235). The functional relevance of MyoD acetylation is suggested by the observation that mutagenesis of the acetylated lysines reduces MyoD activity (234, 217). Additional mechanisms - possibly involving the ability of MyoD to interact with or repulse a specific subset of cellular proteins in an acetylated-dependent manner- are likely to mediate the transcriptional effect of MyoD acetylation. A further support for a positive role MyoD acetylation derives from experiments in which recombinant MyoD was first *in vitro* acetylated using either p300 or P/CAF and then microinjected in mouse fibroblasts. Acetylated MyoD was more efficient in activating a muscle-specific reporter when compared to non-acetylated MyoD (217). Considering that only a small fraction of recombinant MyoD can be acetylated in an *in vitro* acetylation reaction (V. Sartorelli and P.L. Puri, unpublished results), it is likely that the role of MyoD acetylation on transcription may have been underestimated. Both p300 and P/CAF acetylate overlapping lysines of MyoD and the artificial acetylation induced by either acetyltransferases *in vitro* (217) precludes to conclusively ascribe to either one or the other a role in acetylating MyoD in the cell. Additional experiments have

suggested that the HAT of p300 may regulate MyoD-dependent transcription. Frog oocytes microinjected with MyoD and p300 RNAs were subsequently re-microinjected with the p300 HAT-specific inhibitor Lys-CoA. After one hour the oocytes were microinjected with the frog MyoD promoter fused to 100 bp of its coding region and transcription evaluated using primer extension using a radiolabeled MyoD primer. The MyoD coactivation exerted by p300 was counteracted in a dose-dependent manner by Lys-CoA (135). While it is not clear which MyoD promoter regions has been employed by Lau *et al*., previous reports indicate that a region of the *Xenopus* MyoD promoter retaining tissue-specific activation does not contain any MyoD-binding sites (137). It is therefore formally possible that the Lys-CoA blockade may target the activity of molecule/s induced by MyoD and not MyoD itself. Further circumstantial evidence supporting a role for MyoD acetylation derives from studies conducted with the oncoprotein E1A and the bHLH Twist which both inhibit muscle-specific transcription and differentiation (273, 98, 250, 92). By directly interacting with p300 and P/CAF, both E1A and Twist inhibit their acetyltransferase activity (91,39) and indeed MyoD acetylation is blocked by either E1A or Twist (P.L.Puri, Y. Hamamori, and V. Sartorelli, unpublished results). Consistently, two studies have reported the identification of an endogenous E1A-like inhibitor of differentiation (the EID-1 protein), whose ability to prevent muscle-specific transcription correlates with the inhibition of p300 HAT activity (165, 148). Whether EID-1 also blocks the acetyltransferase activity of P/CAF has not been investigated yet.

Additional studies will be required to clarify the very detailed mechanisms through which acetylation influence muscle differentiation. Nevertheless, it seems now clear that MyoD requires both SWI/SNF (55) and acetyltransferase activity (234, 217) to promote muscle –specific transcription and cell differentiation. Thus, it is possible that the ordered sequence of molecular events described in yeast for the HO gene (50) may well be taking place also for MyoD-dependent transcription in mammalian cells.

3.2.2. MEF2

The myocyte enhancer factors 2 MEF2 synergize with the myogenic bHLH factors in activating muscle transcription and differentiation (169). Recently, such synergism has been shown to be mediated by the cell-cycle regulator and tumor suppressor pRb (187). MEF2-dependent transcription is augmented by p300 (233,216) and this may rely on the fact that p300 interacts with MADS-box (233) of MEF2 (62). The myogenic bHLH also interact with the MADS-box of MEF2 (118,168) making it attractive to speculate that p300, myogenic bHLH and MEF2 may form a transcriptional complex. The apparently elevated concentration of p300 present in rabbit reticulocyte lysate (62) may in fact be responsible for the interaction between myogenin and MEF2 observed when reticulocyte lysate is employed to transcribe and translate these two proteins (168). MEF2 is also *in vitro* acetylated by p300 (C.Poizat and L.Kedes, personal communication) but whether this modification is functionally relevant has not been investigated yet.

Using an analogy with the nuclear receptor-mediated transcription -where recruitment of p300-P/CAF has been suggested to involve the presence of the steroid receptor coactivator SRC-GRIP-1- (203), Chen *et al*. (45) have postulated that GRIP-1 may participate in regulating muscle differentiation. Indeed, these authors have found that GRIP-1 interacts with and coactivates MEF2C. Muscle cells expressing GRIP-1 antisense RNA do not activate muscle-specific transcription and fail to undergo differentiation. GRIP-1 also interacts directly with the myogenic bHLH myogenin but this interaction is not accompanied by functional transcriptional coactivation. Transcriptional coactivation exerted by GRIP-1 on MEF2C does not require DNA binding of the latter protein suggesting that, in muscle cells, the GRIP-1-MEF2C complex may be tethered on the DNA by another protein, possibly a myogenic bHLH. In view of the reported physical and genetic interaction of MEF2 with p300 and P/CAF (233, 160), it will be of interest to biochemically purify complexes containing GRIP-1 to establish their protein composition in muscle cells.

The MEF2 factors control expression of the insulin-sensitive glucose transporter (GLUT4), the principal insulin-sensitive transporter in skeletal muscle, which has been implicated in the genesis of type 2 diabetes (295). Recent studies suggest that GLUT4 expression in skeletal muscle is controlled by the concerted action of MEF2C and the cold-inducible coactivator PGC-1 (160). Cultured muscle cells lack GLUT4 expression, which is promptly restored once the cultured cells are infected with an adenovirus expressing PGC-1. PGC-1 expression is accompanied by both GLUT4 expression and stimulation of both basal and insulin-stimulated glucose transport. Since the GLUT4 promoter is activated by MEF2 (261), the effects of PGC-1 on GLUT4 expression are likely due to its ability to directly interact with an activation domain of MEF2C and coactivates MEF2-dependent transcription. Removal of the PGC-1 region shown to interact with MEF2C should abrogate its ability to stimulate GLUT4 expression and insulin-stimulated glucose transport in cultured myotubes. At variance with other transcriptional coactivators, PGC-1 has no detectable intrinsic acetyltransferase activity (220) but recruits both p300 and SRC-1 acetylases (220). Whether the enzymatic activities of p300/SRC-1 contribute to the effects of PGC-1 on GLUT4 gene expression remains to be determined.

3.3. Deacetylation

As predicted by the experiments conducted with acetyltransferases, their deacetylase counterparts impinge on muscle transcription and differentiation. Class II deacetylases have a N-terminal domain absent from class I deacetylases (81). It is this N-terminal region of HDAC 4 and 5 that serves as interface for interaction with MEF2 (163,268). HDAC 4 and 5 overexpression prevents skeletal myogenesis in culture and *in vitro* experiments indicate that the HDAC4/5-MEF2 complex may be present on MEF2-DNA binding sites, but this evidence is not supported by *in vivo* approaches (143). Importantly, the repressive activity of HDAC 4 and 5 on muscle transcription was mapped to their deacetylase domain, even though residual repression

was observed with deacetylase mutants. HDAC 4 and 5 do not interact with the myogenic bHLH but forced expression of MyoD restored activation of the MCK enhancer in the presence of exogenously transfected HDAC 5 (143). Recently, the corepressor SMRT has been shown to be involved in maintaining both HDAC4 and 5 in the nucleus. Furthermore, in transient transfection experiments, SMRT synergizes with HDAC4-5 to mediate MEF2-dependent transcriptional inhibition (Wu *et al*., in press). MEF2 is a positive regulator of myogenesis. How is HDAC-mediated repression of MEF2 relieved? Upon differentiation of C2C12 muscle cells, HDAC 4 and 5 relocate from the nucleus to the cytoplasm (164,157), a phenomenon that is stimulated by the calcium/calmodulin-dependent protein kinase CaMK (157). CaMK also impinges of HDAC-MEF2 interaction by phosphorylating HDAC 5 and dissociating it from MEF2 (142). Therefore CaMK seems to favor muscle differentiation by two independent but functionally converging mechanisms: dissociation of HDACs from MEF2 (142) and cytoplasmic export of HDACs (157).

Once shuttled to the cytoplasm, phosphorylated HDAC 4 and 5 are there retained via interaction with members of the 14-3-3 protein family (82, 269, 158). MEF2 is also negatively regulated by the co-repressor MITR (248). Isolated in a two-hybrid screening, MITR binds to both Xenopus XMEF2A and XMEF2D and represses MEF2-dependent transcription in injected oocytes. As suggested by protein-protein interaction studies, MITR is likely to mediate MEF2 repression by recruiting class I deacetylase HDAC1. In frog embryos, MITR is initially expressed within the mature somite and is later restricted to the myotomal muscle. Since both XMEF2A and D are expressed in differentiated skeletal muscle and in cardiac precursors, respectively, their interaction with MITR is likely to be developmentally regulated. Surprisingly, ectopic expression of MITR in the whole frog embryo shows no effect on myogenesis. Nevertheless, when two phosphorylated serine residues(Ser-218 and Ser-448) that regulate MITR interaction with 14-3- proteins are substituted with alanines, MITR becomes a repressor of myogenesis. These data suggest that stimuli favoring muscle differentiation may promote phosphorylation and subsequent cytoplasmic retention of MITR. Therefore, class II deacetylases and MITR undergo a similar cellular redistribution mediated by 14-3-3 proteins (290)

Class I deactylase HDAC1 and 2 regulate muscle differentiation using a different mechanism from that described for HDAC 4 and 5. MyoD is transcriptionally inactive in undifferentiated myoblats and becomes competent once muscle cells initiate to differentiate. The inability of MyoD to promote transcription has been ascribed to the presence of Id1, an HLH protein devoid of the basic domain, that competes for binding to E-proteins – ubiquitous bHLH proteins necessary for MyoD binding to DNA (17). This model has been substantiated by the *in vivo* findings that an E-box of the MCK enhancer is unoccupied in myoblasts and becomes “footprinted” in differentiated myotubes (173). Nevertheless, several observations suggest an alternative scenario.

Overexpression of Id1 only retards differentiation without blocking it (113). Furthermore, the levels of several Id proteins (1-4) in myoblasts are much lower than those of E-proteins (274), rendering a direct titration effect unlikely. Additionally, genetic ablation of both Id 1 and 3 have revealed a role for these genes in neurogenesis and angiogenesis, but was without consequences on myogenesis (146). Since Id 4 is not expressed in muscle (112), its hypothetical compensatory role can be excluded. Therefore, while Id can clearly counteract the activity of MyoD (17), additional mechanisms may operate to keep MyoD function in check (274). Accordingly, MyoD has been found associated with class I HDAC1 in undifferentiated myoblasts (150) (Puri *et al*. submitted). HDAC1 immunoprecipitated from undifferentiated cells can deacetylate both an acetylated MyoD peptide (Puri *et al*., submitted) and recombinant acetylated MyoD (150) more efficiently than HDAC1 obtained from differentiated myotubes. This is partly due to reduced transcription of the HDAC1 gene (Puri *et al*., submitted) and consequent lowered levels of HDAC1 protein present in differentiated cells (150) (Puri *et al*., submitted). Nevertheless, post-translational modifications of either HDAC1 and /or MyoD itself may account for the reduced deacetylase activity of HDAC1 obtained from differentiated muscle cells. In agreement with a positive role of MyoD acetylation (234, 217), overexpression of HDAC1 reduces the transactivation abilities of MyoD (150) (Puri *et al*, submitted) and P/CAF-dependent MyoD coactivation (150). Importantly, the transcriptional synergism exerted by MyoD and MEF2 (168) is interrupted by forced expression of either class I HDAC1 or class II HDAC4 (Puri *et al*., submitted). Association of MyoD with HDAC1 and P/CAF may be mutually exclusive as indicated by the absence of PCAF in complexes containing MyoD derived from undifferentiated myoblasts (150). Upon cellular differentiation, HDAC1 is released from MyoD and this may allow the engagement of P/CAF (150). Beside the reduced levels of HDAC1 (150) (Puri *et al*., submitted), pRb hypophosphorylation may be a regulatory switch that allows the disengagement of HDAC1 from MyoD during muscle differentiation (Puri *et al*., submitted). As a result of p21 induction (90), pRb is progressively hypophosphorylated in differentiating myocytes (84) and such hypophosphorylation increases the affinity of HDAC1 for pRb (93) (Puri *et al*., submitted). Biochemical experiments indicate that while HDAC1 is associated with MyoD in undifferentiated myoblasts, a pRb-HDAC1 complex –absent in myoblasts- is detected in differentiated myotubes (Puri *et al*., submitted). Interaction between hypophosphorylated pRb and HDAC1 is functionally relevant since a single amino acid substitution introduced in pRb that abolish its binding to HDAC1 (46) also diminishes pRb-dependent coactivation of MyoD activity and activation of endogenous muscle gene expression (Puri *et al*., submitted). The HDAC1-pRb interaction is also important for the establishment of the irreversible cell cycle arrest in terminally differentiated myotubes (46). Finally, the deacetylase inhibitor trichostatin A (TSA) anticipates muscle gene expression and favors differentiation when applied to undifferentiated myoblasts (Sartorelli *et al*., submitted). Notably, embryos exposed during their fetal life to non-toxic doses of TSA

display an increased number of somites expressing the myogenic bHLH Myf-5 (183).

4. NEUROGENESIS AND ENDOCRINE PANCREATIC DIFFERENTIATION

Tissue-specific bHLH proteins have been implicated in promoting neuronal and oligodendrocyte differentiation during development of the central nervous system (CNS). Genetic evidence has revealed the critical role of the bHLH proteins neurogenin (Ngn1 and Ngn2), Math1, Mash1 and NeuroD1/Beta2 during neuronal differentiation (85, 147, 16, 69, 166) whereas two other bHLH factors – oligo 1 and oligo 2 -are involved in oligodendrocyte differentiation (144, 293). NeuroD1/Beta2 plays also an important role in development and differentiation of intestinal endocrine cells and endocrine pancreas (182). The similarity in structure, function and regulation between these proteins and the muscle-specific bHLH regulatory factors suggests that acetyltransferases could also be involved in the regulation of both pancreatic cells and neuronal differentiation.

Indeed, several groups have reported both physical and functional interactions between p300/CBP and NeuroD1/Beta2. Mutoh *et al*. first showed that p300 could associate with NeuroD1/Beta2 to promote transcription of the secretin gene and to induce cell cycle arrest by enhancing p21 transcription in enteroendocrine cells (176). This dual function of p300 in intestinal cells – induction of both tissue-specific gene expression and cell cycle arrest - is reminiscent of the role of p300 during skeletal myogenesis and suggests that this coactivator may have a specific role in the induction of terminal differentiation. Further experiments have established the importance of p300 in mediating the activation of the insulin gene transcription in pancreatic β cells. These studies have shown that p300 can potentiate NeuroD1/Beta2 dependent insulin transcription via an E-box site (225). Notably, insulin expression is controlled by two critical cis-elements in the insulin promoter - the E-box binding site for NeuroD1/Beta2 and a PDX-1-binding element. Another study has suggested the importance of p300/CBP also in mediating PDX-1 dependent activation of insulin transcription (6). Thus, both NeuroD/Beta2 and PDX-1 can recruit p300/CBP to the regulatory region of the insulin gene. However, whether p300/CBP is preferentially recruited only by one or both these DNA binding proteins remains to be established. Since NeuroD1/Beta2 and PDX-1 are required for normal pancreas development (115, 197,182), p300 function is likely to be important during pancreatic differentiation. Interestingly, a p300 mutant in which amino acids 1680 to 1811 - a region next to the acetyltransferase domain - were deleted continued to coactivate NeuroD1/Beta2-dependent activation of insulin transcription (225). However, whether the acetyltransferase activity of p300, or other p300-binding HAT proteins, is required for NeuroD1/Beta2-dependent transcription has not clearly addressed. The regions of NeuroD1/Beta2 that mediate the interaction with p300 were mapped within two evolutionary conserved sequences spanning the bHLH region and the C-terminal activation domain (241). The same regions are necessary for activation of insulin transcription and ectopic neurogenesis upon injection of NeuroD1/Beta2 in Xenopus (241). Remarkably, a mutation in the C-terminal domain of NeuroD1/Beta2, giving rise to a truncated peptide unable to associate with p300/CBP, has been identified in patients with type 2 diabetes (151), further underscoring the importance of p300-dependent co-activation in controlling insulin transcription. A defective function of p300 has also been reported in a rare autosomal dominant form of diabetes, which is characterized by an abnormal insulin secretion in response to glucose – the maturity-onset diabetes of the young (MODY). In this study, Soutoglou *et al*. show that two dominant-negative mutants of hepatocyte nuclear factor 1α (HNF-1α) detected in MODY3 patients can interact with CBP and P/CAF with a stronger affinity, as compared to the HNF-1 wild type. However, the CBP and P/CAF recruited by these HNF-1α mutants have deficient HAT activity (247). Previous studies reported the ability of HNF-1 to recruit both CBP and P/CAF in one complex, with interactions of CBP to the N-terminal of HFN-1 increasing the association of P/CAF to the C terminal of HFN-1 (246). Furthermore, HNF4, which is also mutated in MODY1, requires both p300 and SRC-1/GRIP1 to activate target genes (271).

Taken together, these observations establish a causative link between malfunctioning transcription and certain forms of diabetes. Specifically, they establish that in both type 2 diabetes and MODY1 disregulated transcription is consequent to defective acetyltransferase-dependent transcriptional coactivation.

A more complicated picture involving p300/CBP in the regulation of CNS development emerges from recent observations reporting on two distinct mechanisms controlling gene expression during cell fate specification of cortical progenitors (255). Progenitor cells lining the ventricular cavities of the brain give rise to three cell types: neurons, astrocytes, and oligodendrocytes. In a series of elegant experiments, Sun *et al*. have provided evidence that Ngn1 associates with CBP to promote the expression of genes required for neurogenesis and, at the same time, to sequester the CBP-Smad1 complex away from STAT1 and STAT3, two critical inducers of astrocyte differentiation (255). Thus, Ngn1/CBP complex formation mediates both induction of neurogenesis and inhibition of glial differentiation. Within cell-fate specification in the cerebral cortex , neurogenesis precedes gliogenesis. Therefore, the regulated recruitment of CBP into discrete protein complexes not only controls transcription of different set of genes but also dictates the temporal sequence of events leading to an ordered development of the CNS. The ability of proneural bHLH factors to inhibit gliogenesis is established also by genetic studies conducted in the mouse embryo (264, 186, 172) and confirmed in Xenopus embryo. Xenopus neurogenin-1 (XNGN-1) promotes the expression of genes required for neuronal differentiation by recruiting p300/CBP and P/CAF. Moreover, it was observed that the same complex (XNGN-1-p300/CBP-P/CAF) also activates the expression of genes that antagonize neuronal differentiation in neighbour cells – a process named lateral inhibition. While the HAT of p300/CBP and P/CAF seems

to be important only during the activation of neuronal differentiation , it is dispensable for the regulation of genes involved in the lateral inhibitory pathways (129). In agreement with these studies, Kato *et al*. have reported that inhibition of p300/CBP function leads to neural induction and primary neurogenesis in the entire embryo (117).

p300/CBP and P/CAF are likely to be only part of a larger number of acetyltransferases involved in cerebral cortex development. In fact, Querkopf, a member of the MYST family of zinc finger histone acetyltransferases – which include MOZ, Ybf2/Sas3, Sas2, HBO-1 and Tip 60, reviewed in (252)– has also been implicated in the development of the cerebral cortex (262) . In this study, the authors show that Querkopf is strongly expressed in cells within the ventricular zone of the cortex and that mice homozygous for Querkopf mutations display defective cerebral cortex development (262). Consistent with an essential role of MYST acetyltransferases in brain development, another MYST protein (the enoki mushroom, "enok") is required for the formation of the mushroom bodies – the centers for olfactory learning and memory in Drosophila brain. Interestingly, either genetic ablation of Enok or a point mutation within the zinc finger domain ,impairing its HAT activity, produces a block in neuroblast proliferation (240). Given the recent observation of biochemical and genetic interactions between MYST family members and the replication factors mcm-2 and orc-1 (34) and the role of TIP 60 in DNA repair and apoptosis (102), it is tempting to speculate that MYST HAT activity may be important in the process of DNA replication , proliferation and apoptosis of neural precursors during brain development. It is intriguing to note that also p300 null embryos show defect in neuralization and reduced DNA synthesis, suggesting that defective proliferation may be responsible for the neural phenotype in p300 nullizygous mice (288). Finally, the involvement of HAT proteins in neuronal differentiation is underscored by the positive effects of deacetylase inhibitors on differentiation of established cultures of cells with neurogenic potentyial *in vitro* (106, 162).

4.1. Coactivators, corepressors and neurodegenerative disorders

Huntington's disease (HD) and dentatorubral and pallidoluysian atrophy (DRPLA) are neurodegenerative disorders caused by an expansion of a polyglutamine tract in the huntingtin (htt) and atrophin-1 proteins, respectively (87, 86, 15). HD is clinically characterized by choreoathetotic movements and progressive dementia and is transmitted as an autosomal dominant disease (88, 211). Pathological features of HD include a distinctive atrophy of the caudate nucleus, the putamen and the globus pallidus (285). Histologically, neuronal intranuclear and cytoplasmic inclusions are observed in both transgenic mice expressing an amino-terminal fragment of htt (52) and HD patients (14). There is not presently form of treatment for HD. The neuronal inclusions contain a truncated form of htt and ubiquitin (57). The acetyltransferase CBP has been shown to be present in nuclear inclusions of both transgenic mice and human HD and DRPLA postmortem brains (119, 251, 188). Furthermore, co-localization and biochemical studies indicate that htt with expanded polyglutamine repeat sequesters CBP via interaction with a polyglutamine-rich region present on CBP (188). The CBP- related p300 protein – which does not have a polyglutamine repeat- fails to interact with htt and it is not found in nuclear inclusions (188). Furthermore, CBP mutants devoid of the polyglutamine repeat do not associate with htt. CBP is located in the nucleus. Upon interaction with htt, CBP is redistributed in the cytoplasm where it is found in htt aggregates (188). Overexpression of htt with an expanded polyglutamine repeat, inhibits CBP-dependent transcriptional coactivation suggesting that CBP-mediated transcription may be defective in HD. Notably, CBP overexpresion can rescue htt- and atrophin-1-induced cellular toxicity (188). Htt also interacts with the tumor suppressor p53 protein and the corepressor mSin3a (251). CBP was found in postmortem brain of patients affected by the spinal bulbar muscular atrophy/Kennedy's disease- also caused by an expanded polyglutamine repeat (251). The results of these studies are consistent with the possibility that expanded polyglutamine repeats of htt and atrophin-1 may disturb transcriptional regulation through interaction with coactivators, corepressors and transcription factors and that such disregulation may result in neuronal alterations and cell death. On this note, expression of the neuronal survival protein BDNF – which is coregulated by CBP via interaction with CREB- has been reported to be reduced in HD patients (66). Furthermore, htt has been recently shown to up-regulate transcription of BDNF and to loose this property in HD patients (296).

5. CARDIAC GENE EXPRESSION AND MORPHOGENESIS.

A role for p300 in controlling cardiac gene expression and heart development emerges from three independent lines of evidence. As discussed in the previous paragraph, MEF2 activity is influenced by both acetyltransferases and deacetylases. MEF2C is expressed in heart precursor and mice homozygous for a MEF2C null mutation die before birth. No viable embryos are observed after E10.5 and the heart defects affect both atria and ventricles (140). These defects include poor ventricular trabeculation and pericardial effusion, both signs of heart failure. The timing of interrupted development and phenotype of MEF2C null animals remarkably resemble those of p300 null animals (288). At E10.5, 50% of p300 nullizygous are dead and show reduced heart trabeculation and severe pericardial effusion. A comparison of the transcriptional profiles of the MEF2 and p300 nullizygous animals cannot be drawn since the markers used in the two studies differ. In MEF2 nullizygous animals, transcripts for atrial natriuretic factor, cardiac α-actin and α-myosin heavy chain are severely downregulated whereas those for myosin light chain MLC2V and MLC2A are normal (140). p300 null embryos have reduced levels of myosin heavy chain and α-actinin transcripts (288). Given that p300 also regulates neurogenesis (see below), it is not surprising that p300 mutant embryos have also neural tube defects (288).

Further circumstantial evidence for a role of p300 in cardiac transcription derives from studies that employed the adenoviral E1A oncoprotein. Regions of E1A interacting with p300 (122) (95) and p107 (122) are necessary to mediate the inhibition exerted by E1A on

cardiac gene expression. On the other hand, Bishopric *et al*. have reported that E1A-mediated inhibition of cardiac transcription is independent from its ability to interact with p300 (21). Nevertheless, in the same study p300 overexpresion could bypass the transcriptional repression exerted by E1A (21). The same authors have recently reported that MEF2D utilizes p300 to activate cardiac-specific transcription in primary isolated rat cardiomyocytes (244).

Finally, a recent study implicates p300 in mediating the transcriptional effects of the cardiotoxic antineoplastic drug doxorubicin. Poizat *et al*. (216) have indicated that overexpression of p300 in primary neonatal cardiomyocytes augments MEF2-dependent transcription. This effect is due not solely to the ability that p300 has to coactivate MEF2 protein but possibly also to a p300-mediated increased transcription of the MEF2 gene itself. In this study, p300 is also shown to coactivate Nkx 2.5-mediated transcription. Doxorubicin represses skeletal and cardiac–specific transcription (133, 109). Exposure of primary cardiomyocytes to doxorubicin causes repression of MEF2-dependent transcription and p300 overepression counteracts this effect (216). Transcripts for the cardiac transcription factors MEF2C, dHAND, eHAND and NKX2.5- but not those of p300- are rapidly depleted upon doxorubicin treatments of primary cardiomyocytes. Interestingly, doxorubicin exposure induces proteasome-mediated degradation of the p300 protein that may or may not be dependent on ubiquitination of p300 (216). Degradation of p300 protein is observed also in C2C12 skeletal muscle cells and may be responsible- along with an increased transcription of the Id gene (133)- for the observed transcriptional repression exerted doxorubicin.
Whether or not the effects that p300 seems to have on cardiac transcription and morphogenesis depends on its acetyltransferases activity remains to be determined in future studies.

6. HEMATOPOIESIS

In 1973, Axel, Cedar and Felsenfeld observed that the RNA polymerase derived from *E.coli* promoted transcription of globin genes derived from reticulocyte chromatin but not from either liver or brain chromatin (9). This observation was followed by a seminal paper by Weintraub and Groudine who reported that " globin genes are digested by deoxyribonuclease I in red blood cell nuclei but not in fibroblast nuclei" (279) and suggested that histones of the chromatin surrounding the globin genes in red blood cells are in a conformation that differs from that of the same genes in fibroblasts where globins are not produced. These studies established the technical and conceptual framework to investigate chromatin remodeling.

6.1. Chromatin remodeling

During erythroid maturation, expression of genes residing in the β-globin locus and encoding for embryonic, fetal and adult globins is temporally regulated to allow production of globin isoforms with different physical-chemical properties that better suit the distinct developmental stages of the organism. In particular, the transition from fetal to adult life is characterized by activation of adult β-globin genes δ and β and repression of the fetal γ-globin Gγ, Aγ and ψβ genes (205) ?

The transcription factor Ikaros binds to a pyrimidine-rich sequence between the human fetal γ-globin and adult β-globin-like genes (194). Deletion of this DNA region causes a delayed switch from fetal to adult globin expression in transgenic animals indicating that this region is involved in globin switch (193). Ikaros is found associated with components of the SWI/SNF and NuRD remodeling complexes in extracts derived from mature erythroid cells (194). While the SWI/SNF complex has an ATP-dependent remodeling acitivity – provided by either BRM or BRG1 subunits- (121) the NuRD complex contains both nucleosome remodeling and histone deacetylase activities provided by class I deacetylase HDAC1 and 2 and RbAp46/48. It is not clear whether Ikaros exists in two distinct complexes- one with nucleosome remodeling activity and the other with remodeling as well as deacetylase activity- (121). Furthermore, the functional relevance of the Ikaros-SWI/SNF-NuRD complex on globin isoform switching remains to be addressed.

The role of the transcription factor EKLF in fetal and adult hematopoiesis is more clearly defined. EKLF is a zinc-finger transcriptional activator required for fetal hematopoiesis (189) and ELKF nullizygous animals die because of β-thalassemia (209). Interestingly, ELKF-/- animals display a delayed switch from fetal to adult globin expression (209) such as that observed in animals lacking the pyrimidine-rich sequence containing an Ikaros-binding site (193). EKLF associates with the E-RC1 complex containing subunits of the SWI/SNF complex. In this case, chromatin remodeling and transcription driven from a chromatinized β-globin promoter requires both ELKF – more specifically its activation domain- and E-RC1 indicating a functional link between chromatin remodeling, transcription and complex formation (3). Recently, p300-mediated acetylation of EKLF has been reported to increase its affinity for the SWI/SNF complex (292) once again indicating an intimate relationship between chromatin remodeling and acetylation

6.2. Co-activation and acetylation

Numerous transcriptionl regulators participate in regulating erythroid differentiation and several of these proteins have been shown to interact and sense coactivation of p300/CBP. A comprehensive revision of the literature on the role of CBP/p300 in hematopoiesis is reported in (22). GATA-1 is a zinc finger-containing transcriptional activator required for erythroid (215, 214) and megakaryocytic proliferation and differentiation (242). A point mutation abolishing binding of GATA-1 to the promoter region of the Duffy antigen/chemokine receptor gene (DARC), a blood group antigen, abolishes DARC expression in erythrocytes and it is responsible for its absence in Duffy-negative individuals (265). GATA-1-dependent transcription is inhibited by the oncoprotein E1A (23) and is augmented by overexpressing p300/CBP (27) (23). While there is general agreement on the findings that

p300/CBP promotes GATA-1 acetylation (23, 27), the molecular consequences on hematopoietic transcription have not been unequivocally determined and whilst a study indicates that acetylation enhances GATA-1 DNA binding (27) another has failed to detect such enhancement (23).

Besides recruiting the chromatin remodeling E-RC1 complex (3), EKLF interacts also with p300/CBP and P/CAF (291). Interestingly, both p300/CBP and P/CAF interact with EKLF but only p300/CBP, and not P/CAF, coactivates EKLF-dependent transcription. These findings correlate with the ability of p300/CBP and inability of P/CAF to acetylate EKLF both *in vitro* and *vivo* (291). Acetylated ELKF has an increased affinity towards the chromatin remodeling enzymes SWI/SNF and is a more effective transactivator when tested on chromatinized DNA templates (292)

6.3. Deacetylation

Sodium butyrate and trichostatin A, two deacetylase inhibitors, reactivate fetal γ-globin expression in adult erythroid cells (35, 210, 58, 108, 229). These observations suggest that deacetylation is a mechanism utilized during erythroid differentiation to silence gene expression. Isobutyramide, a derivative of butyric acid, can stimulate fetal hemoglobin production in patients with thalassemia intermedia (37). *In vivo* footprinting analysis conducted on erythroblasts isolated from patients with beta-globin disorders before and after butyrate therapy indicates the appearance of new “footprints’ on the gamma-globin gene promoter of responsive patients. The footprinted region (BRE-G, for butyrate-response elements gamma) confers butyrate-inducibility in reporter gene assays (103). Using as a model the human erythroleukemia K562 cells, McCaffrey *et al*. (156) showed that a CCAAT box and flanking sequences located in the gamma-globin promoter are critical for gene activation promoted by the histone deacetylase inhibitors butyrate, trapoxin, and trichostatin. Taken together, these studies suggest that the gene silencing that occurs on the fetal globin genes during adult hematopoiesis is an active process that can be reverted by the use of histone deacetylase inhibitors. Whereas the detailed molecular mechanisms leading to reactivation of fetal globin genes remain to be worked out, nonetheless, the treatment of hemoglobinopathies with histone deacetylase inhibitors offers an example of successful “chromatin” therapy.

7. LYMPHOCYTE DIFFERENTIATION

B and T lymphocytes and natural killer (NK) cells are likely to derive from a common lymphoid progenitor (126). Cues deriving from the extracellular milieu instruct uncommitted progenitors to choose between alternative fates (64). Ikaros (see Hematopoiesis section) forms homo- and heterodimers with Aiolos (101,171) and is required for the development of a common lymphoid progenitor. In fact, animals with germline mutations in the DNA-binding domain of Ikaros lack B, T and NK cells whilst the erythroid and myeloid cells develop normally (24, 72, 49, 184, 185). Furthermore, a dominant mutation in the Ikaros gene is associated with the development of T and B leukemias and lymphomas in the mouse (282), T-cell acute lymphoblastic leukemia in children (253) and B-cell acute lymphoblastic leukemia in adults (179).

Once the identity of the uncommitted lymphoid progenitor has been established, cells face the decision to take up either the B or T phenotype.

7.1. B cells

B-lymphocytes commitment is initiated by the two basic HLH EBF (139) and E2A gene products (294, 10, 11, 196). B lymphocytes derived from mice with inactivated EBF or E2A genes are arrested at the earliest stage before rearrangement of the IgH gene (36). EBF and E2A genetically cooperate since compound heterozygous EBF+/- E2A+/- animals have a more severe B cell defect (195). Furthermore, forced expression of E2A and EBF in hematopoietic precursors can synergistically activate transcription of several B-lymphoid-specific genes (243) (120). The E2A and EBF gene products activate expression of the downstream target Pax5 (195), which is required for B cell commitment and development beyond the early pro-B cell stage. The normal expression of E2A in Pax5-/- pro-B cells indicate that the bHLH proteins are hierarchically upstream of Pax5 (191).

As elegantly shown by Nutt *et al*. (192), the initial activation of Pax-5 expression is stochastic, reversible, monoallelic and independent of the parental origin. Pro-B cells derived from Pax5-/- animals exhibit fascinating properties. When cultured *in vitro*, they have the ability to redirect their fate according to extracellular stimuli. In the presence of macrophage-colony-stimulating factor (M-CSF), they differentiate into macrophages, when exposed to granulocyte-CSF they become granulocytes, they differentiate into NK when treated with IL-2, into dendritic cells when treated with granulocyte-macrophage CSF and osteoclasts when challenged with TRANCE (190). Some of the properties of Pax5-/- cells are observed also in the animal. For instance, when injected into RAG2-deficient mice, Pax5-/- pro-B cells acquire the T cell phenotype (230) and become osteoclasts when introduced in osteoclasts-deficient *c-fos*-/- mice (80).

The behavior of Pax5-/- cells indicates that while Pax-positive pro-B cells are destined to the B-lymphoid lineage, their Pax5-/- counterparts are far from being committed and retain multilineage capabilities. It also suggests that Pax5 is required to repress genes necessary for later stages of B-cell development. Examples of genes repressed by Pax5 are those encoding for the M-CSF receptor, myeloperoxidase, perforin, and GATA-1 (190).

7.2. T cells

The molecular understanding of T cell commitment and differentiation is less advanced if compared to what it is known for B cells (207). Beside its role in establishing lineage commitment (see above), Ikaros is also involved in controlling critical stages of thymocyte differentiation (281, 8). An additional regulator of thymocyte differentiation is the zinc-finger-containing transcription factor GATA-3. GATA-3 is required for

development of T- cells *in vitro* (132). Since GATA-3 -/- nullizygous animals are embryonic lethal (208), embryonic stem (ES) cells derived from GATA-3 -/- animals were employed to populate mice with a RAG2-/- genotype. The GATA-3-/- embryonic stem cells were unable to contribute to CD4-/CD8- double-negative cell indicating that T cell development is blocked at the earliest stage (263). The transmembrane protein Notch1 has been implicated in establishing the specification of the T cell fate (206). Analogously to GATA-3 nullizygous animals (208), Notch1-/- embryos die early (256). Using a conditional gene inactivation protocol, Radtke *et al*. have shown that T cells development in Notch-/- animals is arrested at the most immature stage whereas differentiation along the B cell and other hematopoietic lineages is preserved (226). Interestingly, immature B cells were observed in the thymus (226). A complementary approach has utilized the intracellular domain (constitutively active form) of Notch1 delivered by infecting the bone marrow of mice with a Notch-expressing retrovirus (219). In this case, T cell development ectopically occurred in the bone marrow and was thymus-independent. Furthermore, B cell development was impaired (219). The results of these experiments suggest that there is a cross-talk between B and T cell development whose molecular basis may reside in the ability of Notch to interfere with the transcriptional activity of the bHLH protein E47 (219, 204). According to this scenario, Notch signaling would prevent maturation of B lymphocytes from the uncommitted progenitor via E2A blockade and would-by default- promote T lymphocytes development through a secondary fate instructive commitment in the thymus. Finally, recent evidence indicates that Notch may protect developing T cells from programmed cell death (56, 111).

7.3. Co-activation and acetylation

GATA-3- dependent transcription is augment by p300 and p300 can acetylate *in vitro* GATA-3. Importantly, GATA-3 is acetylated in T cells (286). Substituting the acetylated lysines with arginines decreases GATA-3 acetylation and impairs its ability to transactivate. To address the role of GATA-3 acetylation in T cell function, Yamagata *et al*. (286) have expressed a non-acetylatable (KRR-GATA3) form in the T-cells of transgenic mice using the T-cell – specific Lck distal promoter. The spleen derived from KRRGATA3 mice was enlarged with an increased T/B cell ratio. An increased T cell population was also evident in the peripheral blood whereas the peripheral lymphnodes and the Peyer's patches displayed a decreased presence of T cells. The cellular basis of the abnormal ratio of T/B cells in different organs seems to reside in both a defective homing and increased survival of the T cells. To date, this is the study (286) that more directly assesses the role of acetylation in controlling the function of transcription factors in the animal. Mutations of two lysines to arginines (KKK>KRR) as those present in KRR-GATA3 are not expected to induce significant conformational changes in GATA3. Nevertheless, this possibility should be taken into account when interpreting the data obtained with the KRR-GATA3 mice.

The E2A gene products E12 and E47 interact with and are coactivated by p300 (62, 204). As with MyoD, the E12 interaction sites may be multiple since both the HLH (62) and the activation domains AD1 and AD2 of E12 have been reported to interact with p300 (225). The AD1 and AD2 activation domains are conserved in the other members of the bHLH family, E2-2 and HEB (153). Within the AD1, the LDFS motif is conserved in the yeast bHLH transcription factor Rtg3p. A series of genetic and biochemical experiments indicate that the LDFS motif of both the E2A and Rtg3p mediate transcriptional activation and is required to recruit purified yeast SAGA complex, containing an acetyltransferase activity (152). The ability of the mammalian equivalent of the yeast SAGA complex, P/CAF and hGCN5 to interact with E2A was not investigated in this study. Nevertheless, the biochemically indistinguishible properties of the SAGA (77) and P/CAF-hGCN5 (198) complexes suggest that the transactivation domain AD1 may interact with P/CAF/hGCN5. The requirement for the HAT activity of SAGA to sustain E2A transcriptional activation has not been addressed yet.

7.4. Gene silencing and deacetylases

Depending on the experimental conditions, Ikaros can either promote or inhibit transcription. In proliferating lymphocytes, a significant fraction of Ikaros is found at centromeric DNA in close association with heterochromatin-containing foci (31), suggesting that Ikaros may be involved in gene silencing. Ikaros, and Aiolos co-localize with the DNA-dependent ATPase Mi-2 and the deacetylase HDAC-1 at discrete DNA foci located at heterochromatin regions (121, 125). The Ikaros-associated proteins have the ability to remodel chromatin *in vitro* and deacetylate histones (121). Ikaros also interacts with the co-repressor C-terminal binding protein (CtBP) and mutations in Ikaros preventing CtBP binding reduce its ability to repress transcription (124). CtBP represses transcription in a histone deacetylase-independent manner indicating that Ikaros utilizes both dependent- and independent-deacetylase strategies to silence transcription. In agreement with its transcriptional stimulatory properties, Ikaros was also found associated with the chromatin remodeling machine SWI/SNF (194). Therefore, Ikaros is present in two separable protein complexes, one containing Mi-2 and HDAC-1 (121) and the other SWI/SNF (194). Interestingly, the composition and location of the Ikaros-complexes is dynamic and subject to modification according to the different phases of the cell cycle. These biochemical findings support the notion that Ikaros (and Aiolos) may behave as either transcriptional activators or repressors, depending on the cellular circumstances.

Recently, the transcriptional repression properties of Pax5 have been associated with its ability to recruit corepressors of the Groucho/TLE protein family (59).

Upon interaction with its cellular receptors Jagged and Delta, the transmembrane receptor Notch (4) (5) is processed and its intracellular (IC Notch) domain is translocated to the nucleus (239) where it associated with the DNA-binding protein CBF1/RBP-Jk. In the absence of IC Notch, CBF1/RBP-Jk is a transcriptional repressor. The direct interaction of CBF1/RBP-Jk with the corepressor SMRT and the deacetylase HDAC-1 confers transcriptional

repression (116). Notch activation (154, 254, 155) and nuclear translocation (239) disrupts formation of the repressor complex allowing the molecular switch that turns CBF1/RBP-Jk into an activator (116). The newly formed IC-Notch-CBF1/RBP-Jk protein complex positively regulates transcription of the *Hairy/Enhancer of Split (HES*) gene (116). In turn, the HES proteins repress transcription of several bHLH transcription factors including the neurogenic regulators Mash1 (44, 54, 107) and neurogenin (2, 257). The HES proteins bring about repression by engaging the *Groucho*/TLE repressor via their tetrapeptide motif WRPW (67, 78). There are evidences indicating the *Groucho*/TLE can recruit the deacetylases HDAC1 and Rpd3 (42, 41). Recently, Notch has been shown to regulate expression of additional genes, the Hey (149), HRT (178), *gridlock* (275) and HERPs family which interact with the HES proteins and mediate transcritptional repression by interacting with the transcriptional repressor NcoR and the deacetylase HDAC1 (Iso, T., V. Sartorelli, C. Poizat, S. Iezzi, H-Y Wu, L. Kedes, and Y Hamamori, in press). At variance with the HES proteins, interaction of HDAC1 is mediated through the bHLH domain and not the WRPW motif of HERPs (Iso, T, V. Sartorelli, G, Chung, T. Shichinohe, L. Kedes, and Y. Hamamori, in press). The sequential engagement/disengagement of corepressors and deacetylases by CBF-1/RBP-Jk and its target protein HES/HERPs offers an example of how regulated protein interactions can modulate gene expression within a defined molecular pathway.

The genes regulated by Notch in T cells have not been identified yet. Nonetheless, a clue on the potential targets has come from the observation that expression of IC Notch protects both T cell lines and thymocytes from apoptosis induced by glucocorticoids (56). During negative selection, thymocytes undergo apoptosis mediated-at least in part- by the nuclear hormone receptor Nur77 (141, 284). Recent experiments indicate that Notch1 causes repression of Nur77 activity suggesting a molecular explanation of the protective role of Notch in T cell death (111).

7.5. Acetyltransferases and Disregulated Hematopoiesis

Patients affected by the Rubinstein Taybi syndrome (RTS) bear mutations in one CBP allele (see below) and have an increased incidence of cancers (161). Furthermore, biallelic mutations of the p300 gene have been described in some patients with gastrointestinal cancers (174). Therefore, CBP/p300 (74) and the associate factor P/CAF (238) have been proposed to behave as tumor suppressor genes. This hypothesis seems to be substantiated – at least for CBP- by a genetic analysis conducted in animals with a monoallelic inactivation of the CBP gene (131). These animals recapitulate some features of the RTS including growth retardation and craniofacial abnormalities. Unexpectedly, CBP heterozygous animals display also multiple abnormalities of the hematopietic system including splenomegaly, reduced bone marrow cellularity and deficiencies in pre-B cell and myeloid colony-forming progenitor cells (131). On the other hand, p300 heterozygous animals do not reveal any hematopoietic abnormality. As the CBP heterozygous animals age, histiocytic sarcomas, myelogenous and lymphocytic leukamias develop. These malignancies can be transmitted to sublethally irradiated recipients transplanted with either bone marrow or spleen cells derived from tumor-affected donors (131). Consistent with a tumor-suppressor activity of CBP, tumors derived from CBP hemyzygous animals reveal loss of the second CBP allele (131). Several questions can now be addressed including the specific role of CBP in hematopoiesis and the target genes of CBP coactivation . To address the role of the acetyltrasnferase activity of CBP in the genesis of these malignancies , it will be of interest to reconstitute the CBP hemyzygous animals with a HAT-deficient allele of CBP.

The MYST acetyltransferase MOZ and the mixed-lineage leukemia (MLL) are often translocated in acute leukemias or myelodysplasia secondary to therapy with drugs that target DNA topo isomerase II, respectively, to either the p300 or CBP locus giving rise to fusion proteins composed of either MOZ-CBP (26), MOZ-p300 (123) or MLL-CBP (245). Fusion of MLL occurs with the bromodomain and the HAT region of CBP. Bone marrow trasnplantation of cells trasnduced with the MLL-CBP protein induces myeloid leukemia in recipient animals (136). The bromodomain and the HAT region of CBP fused to the amino region of MLL are sufficient to induce leukemia (136) suggesting an active role of the acetyltransferase activity of CBP in leukemogenesis. The MOZ region translocated to CBP retains the HAT domain (138) but whether this has any role in neoplastic transformation has not been addressed.

8. MELANOCYTES AND SKELETAL DEVELOPMENT

As indicated by genetic inactivation studies, the bHLHZip transcription factor Microphtalmia (Mi) regulates melanocyte differentiation and survival (100). While Mi expression is up-regulated in response to exposure to melanocyte stimulating hormone, Mi activity is induced upon stimulation of the c-Kit signaling pathway. Concomitantly, the c-Kit pathway activates the MAPK system, which in turn phosphorylates Mi (20, 99). Phosphorylated Mi recruits p300/CBP, which enhances the transcriptional activity of Mi (218). The p300/CBP binding region of region of Mi was mapped at the N-terminal activation domain and the synergistic activation of transcription could be inhibited by E1A (236). Genetic studies have also implicated CBP function in the development of the skeletal system. Abnormal skeletal patterning was observed by Tanaka *et al*. in embryos lacking one CBP allele (258). This phenotype is reminiscent of the Rubinstein Taybi syndrome (RTS), an autosomal dominant disease associated with mutation of CBP gene (213). Another study has subsequently showed that heterozygous CBP-deficient mice with a truncated CBP protein (residues 1-1084) exhibit a typical RTS phenotype, indicating that CBP mutations may produce a dominant negative molecule (200). Finally, Murata *et al*. have identified in human RTS patients mutations which may impair the HAT activity of CBP, implicating that acetylation may play an important role in skeletal development and related diseases (175).

The involvement of p300/CBP and other acetyltransferases in differentiation of additional cell lineages as well as in the development of other animal models (e.g. Drosophila and Xenopus) are illustrated in other excellent reviews (76).

9. CONCLUDING REMARKS

The molecular foundations of chromatin remodeling and acetylation have begun to be clarified. Perhaps one of the most intriguing observations relates to the differential roles of even closely related acetyltransferases and deacetylases in controlling distinct cellular processes (223, 291). Specific inhibitors that interfere with the acetyltransferase activity of either p300/CBP or PCAF/GCN5 are already available (135) and may be used to selectively interfere with cellular processes such as apoptosis and differentiation. Clearly, these compounds have the potential to be employed as therapeutical tools. Deacetylase inhibitors are already used in clinical trials (see Hematopoiesis) (272, 79)

Acetylation seems to act in concert with other post-translational modifications including histone phosphorylation (for a review see (47) and methylation (1, 40, 180, 13, 270) for a review see (227) suggesting that combinatorial histone (and perhaps transcription factors) modifications may serve as a"code" to either attract or repulse transcriptional complexes. Elucidation of the temporal and spatial modifications will allow to interfere with specific cellular functions.

Only five years have passed since the initial isolation and characterizations of nuclear acetyltransferases (33) and deacetylases (260) and the progresses in the understanding of their biological roles have been impressive. The involvement of both acetyltransferases and deacetylases in the genesis of several human pathological conditions should provide a continuous incentive for the clarification of their functioning.

10. REFERENCES

1. Alfrey, V. G., R. Faulkner, and A. E. Mirsky:: Acetylation and methylation of histones and their possible role in the regulation of RNA synthesis. *PNAS* 51, 787-794 (1964)

2. Apelqvist, A., H. Li, L. Sommer, P. Beatus, D. J. Anderson, T. Honjo, M. Hrabe de Angelis, U. Lendahl, and H. Edlund: Notch signalling controls pancreatic cell differentiation. *Nature* 400, 877-81 (1999)

3. Armstrong, J. A., J. J. Bieker, and B. M. Emerson: A SWI/SNF-related chromatin remodeling complex, E-RC1, is required for tissue-specific transcriptional regulation by EKLF *in vitro*. *Cell* 95, 93-104 (1998)

4. Artavanis-Tsakonas, S., K. Matsuno, and M. E. Fortini: Notch signaling. *Science* 268, 225-32 (1995)

5. Artavanis-Tsakonas, S., M. D. Rand, and R. J. Lake: Notch signaling: cell fate control and signal integration in development. *Science.*284, 770-6 (1999)

6. Asahara, H., S. Dutta, H. Y. Kao, R. M. Evans, and M. Montminy: Pbx-Hox heterodimers recruit coactivator-corepressor complexes in an isoform-specific manner *Mol Cell Biol* 19, 8219-25 (1999)

7. Avantaggiati, M. L., M. Carbone, A. Graessmann, Y. Nakatani, B. Howard, and A. S. Levine: The SV40 large T antigen and adenovirus E1a oncoproteins interact with distinct isoforms of the transcriptional co-activator, p300 *Embo J* 15, 2236-48 (1996)

8. Avitahl, N., S. Winandy, C. Friedrich, B. Jones, Y. Ge, and K. Georgopoulos: Ikaros sets thresholds for T cell activation and regulates chromosome propagation. *Immunity* 10, 333-43 (1999)

9. Axel, R., H. Cedar, and G. Felsenfeld: Synthesis of globin ribonucleic acid from duck-reticulocyte chromatin *in vitro*. *Proc Natl Acad Sci U S A* 70,2029-32 (1973)

10. Bain, G., E. C. Maandag, D. J. Izon, D. Amsen, A. M. Kruisbeek, B. C. Weintraub, I. Krop, M. S. Schlissel, A. J. Feeney, M. van Roon: E2A proteins are required for proper B cell development and initiation of immunoglobulin gene rearrangements. *Cell* 79, 885-92 (1994).

11. Bain, G., E. C. Robanus Maandag, H. P. te Riele, A. J. Feeney, A. Sheehy, M. Schlissel, S. A. Shinton, R. R. Hardy, and C. Murre: Both E12 and E47 allow commitment to the B cell lineage. *Immunity* 6,145-54 (1997)

12. Bannister, A. J., and T. Kouzarides: The CBP co-activator is a histone acetyltransferase. *Nature* 384,641-3 (1996)

13. Bannister, A. J., P. Zegerman, J. F. Partridge, E. A. Miska, J. O. Thomas, R. C. Allshire, and T. Kouzarides: Selective recognition of methylated lysine 9 on histone H3 by the HP1 chromo domain. *Nature* 410,120-4 (2001)

14. Becher, M. W., J. A. Kotzuk, A. H. Sharp, S. W. Davies, G. P. Bates, D. L. Price, and C. A. Ross: Intranuclear neuronal inclusions in Huntington's disease and dentatorubral and pallidoluysian atrophy: correlation between the density of inclusions and IT15 CAG triplet repeat length. *Neurobol Dis* 4,387-97 (1998)

15. Becher, M. W., D. C. Rubinsztein, J. Leggo, M. V. Wagster, O. C. Stine, N. G. Ranen, M. L. Franz, M. H. Abbott, M. Sherr, J. C. MacMillan, L. Barron, M. Porteous, P. S. Harper, and C. A. Ross:.Dentatorubral and pallidoluysian atrophy (DRPLA). Clinical and neuropathological findings in genetically confirmed North American and European pedigrees. *Mov Disord* 12,519-30 (1997)

16. Ben-Arie, N., H. J. Bellen, D. L. Armstrong, A. E. McCall, P. R. Gordadze, Q. Guo, M. M. Matzuk, and H. Y. Zoghbi: Math1 is essential for genesis of cerebellar granule neurons. *Nature* 390,169-72 (1997)

17. Benezra, R., R. L. Davis, D. Lockshon, D. L. Turner, and H. Weintraub: The protein Id: a negative regulator of helix-loop-helix DNA binding proteins. *Cell* 61,49-59 (1990)

18. Berger, S. L.: Gene activation by histone and factor acetyltransferases. *Curr Opin Cell Biol* 11,336-41 (1999)

19. Bergstrom, D. A., and S. J. Tapscott: Molecular distinction between specification and differentiation in the myogenic basic helix-loop-helix transcription factor family. *Mol Cell Biol* 21,2404-12 (2001)

20. Bertolotto, C., P. Abbe, T. J. Hemesath, K. Bille, D. E. Fisher, J. P. Ortonne, and R. Ballotti: Microphthalmia gene product as a signal transducer in cAMP-induced differentiation of melanocytes. *J Cell Biol* 142,827-35 (1998)

21. Bishopric, N. H., G. Q. Zeng, B. Sato, and K. A. Webster: Adenovirus E1A inhibits cardiac myocyte-specific gene expression through its amino terminus. *J Biol Chem* 27,:20584-94 (1997)

22. Blobel, G.A.: CREB-binding protein and p300: molecular integrators of hematopoietic transcription.*Blood*.95,745-55 (2000)

23. Blobel, G. A., T. Nakajima, R. Eckner, M. Montminy, and S. H. Orkin: CREB-binding protein cooperates with transcription factor GATA-1 and is required for erythroid differentiation .*Proc Natl Acad Sci U S A* 95,2061-6 (1998)

24. Boggs, S. S., M. Trevisan, K. Patrene, and K. Geogopoulos: Lack of natural killer cell precursors in fetal liver of ikaros knockout mutant mice. *Nat Immun* 16:137-45 (1999)

25. Bone, J. R., J. Lavender, R. Richman, M. J. Palmer, B. M. Turner, and M. I. Kuroda: Acetylated histone H4 on the male X chromosome is associated with dosage compensation in Drosophila. *Genes Dev* 8,96-104 (1994)

26. Borrow, J., V. P. Stanton, Jr., J. M. Andresen, R. Becher, F. G. Behm, R. S. Chaganti, C. I. Civin, C. Disteche, I. Dube, A. M. Frischauf, D. Horsman, F. Mitelman, S. Volinia, A. E. Watmore, and D. E. Housman: The translocation t(8;16)(p11;p13) of acute myeloid leukaemia fuses a putative acetyltransferase to the CREB-binding protein. *Nat Genet* 14,33-41 (1996)

27. Boyes, J., P. Byfield, Y. Nakatani, and V. Ogryzko: Regulation of activity of the transcription factor GATA-1 by acetylation. *Nature* 396,594-8 (1998)

28. Braun, T., M. A. Rudnicki, H. H. Arnold, and R. Jaenisch: Targeted inactivation of the muscle regulatory gene Myf-5 results in abnormal rib development and perinatal death. *Cell* 7,369-82 (1992)

29. Braunstein, M., A. B. Rose, S. G. Holmes, C. D. Allis, and J. R. Broach: Transcriptional silencing in yeast is associated with reduced nucleosome acetylation. *Genes Dev 7*, 592-604 (1993)

30. Brown, C. E., T. Lechner, L. Howe, and J. L. Workman: The many HATs of transcription coactivators. *Trends Biochem Sci.* 25,15-9 (2000)

31. Brown, K. E., S. S. Guest, S. T. Smale, K. Hahm, M. Merkenschlager, and A. G. Fisher: Association of transcriptionally silent genes with Ikaros complexes at centromeric heterochromatin. *Cell* 91,845-54 (1997)

32. Brownell, J. E., and C. D. Allis: Special HATs for special occasions: linking histone acetylation to chromatin assembly and gene activation. *Curr Opin Genet Dev* 6,176-84 (1996)

33. Brownell, J. E., J. Zhou, T. Ranalli, R. Kobayashi, D. G. Edmondson, S. Y. Roth, and C. D. Allis: Tetrahymena histone acetyltransferase A: a homolog to yeast Gcn5p linking histone acetylation to gene activation. *Cell* 84,843-51 (1996)

34. Burke, T. W., J. G. Cook, M. Asano, and J. R. Nevins: Replication factors mcm2 and orc1 interact with the histone acetyltransferase hbo1 . *J Biol Chem* 276,15397-408 (2001)

35. Burns, L. J., J. G. Glauber, and G. D. Ginder: Butyrate induces selective transcriptional activation of a hypomethylated embryonic globin gene in adult erythroid cells. *Blood* 72,1536-42 (1988)

36. Busslinger, M., S. L. Nutt, and A. G. Rolink: Lineage commitment in lymphopoiesis. *Curr Opin Immunol* 12,151-8 (2000)

37. Cappellini, M., G. Graziadei, L. Ciceri, A. Comino, P. Bianchi, A. Porcella, and G. Fiorelli: Oral isobutyramide therapy in patients with thalassemia intermedia: results of a phase II open study. *Blood Cells Mol Dis* 26,105-11 (2000)

38. Caruso, M., F. Martelli, A. Giordano, and A. Felsani: Regulation of MyoD gene transcription and protein function by the transforming domains of the adenovirus E1A oncoprotein. *Oncogene* 8,267-78 (1993)

39. Chakravarti, D., V. Ogryzko, H. Y. Kao, A. Nash, H. Chen, Y. Nakatani, and R. M. Evans: A viral mechanism for inhibition of p300 and PCAF acetyltransferase activity. *Cell* 96,393-403 (1999)

40. Chen, D., H. Ma, H. Hong, S. S. Koh, S. M. Huang, B. T. Schurter, D. W. Aswad, and M. R. Stallcup: Regulation of transcription by a protein methyltransferase. *Science* 284,2174-7 (1999)

41. Chen, G., and A. J. Courey: Groucho/TLE family proteins and transcriptional repression. *Gene* 249,1-16 (2000)

42. Chen, G., J. Fernandez, S. Mische, and A. J. Courey: A functional interaction between the histone deacetylase Rpd3 and the corepressor groucho in Drosophila development. *Genes Dev* 13,2218-30 (1999)

43. Chen, H., R. J. Lin, R. L. Schiltz, D. Chakravarti, A. Nash, L. Nagy, M. L. Privalsky, Y. Nakatani, and R. M. Evans:(Nuclear receptor coactivator ACTR is a novel histone acetyltransferase and forms a multimeric activation complex with P/CAF and CBP/p300. *Cell* 90,569-80 (1997)

44. Chen, H., A. Thiagalingam, H. Chopra, M. W. Borges, J. N. Feder, B. D. Nelkin, S. B. Baylin, and D. W. Ball 1997. Conservation of the Drosophila lateral inhibition pathway in human lung cancer: a hairy-related protein (HES-1) directly represses achaete- scute homolog-1 expression Proc Natl Acad Sci U S A. 94:5355-60

45. Chen, S. L., D. H. Dowhan, B. M. Hosking, and G. E. Muscat 2000. The steroid receptor coactivator, GRIP-1, is necessary for MEF-2C- dependent gene expression and skeletal muscle differentiation Genes Dev. 14:1209-28

46. Chen, T. T., and J. Y. Wang 2000. Establishment of irreversible growth arrest in myogenic differentiation requires the RB LXCXE-binding function Mol Cell Biol. 20:5571-80

47. Cheung, P., C. D. Allis, and P. Sassone-Corsi 2000. Signaling to chromatin through histone modifications Cell. 103:263-71

48. Cheung, W. L., S. D. Briggs, and C. D. Allis 2000. Acetylation and chromosomal functions Curr Opin Cell Biol. 12:326-33

49. Cortes, M., E. Wong, J. Koipally, and K. Georgopoulos 1999. Control of lymphocyte development by the Ikaros gene family Curr Opin Immunol. 11:167-71

50. Cosma, M. P., T. Tanaka, and K. Nasmyth 1999. Ordered recruitment of transcription and chromatin remodeling factors to a cell cycle- and developmentally regulated promoter Cell. 97:299-311

51. Cote, J., C. L. Peterson, and J. L. Workman 1998. Perturbation of nucleosome core structure by the SWI/SNF complex persists after its detachment, enhancing subsequent transcription factor binding Proc Natl Acad Sci U S A. 95:4947-52.

52. Davies, S. W., M. Turmaine, B. A. Cozens, M. DiFiglia, A. H. Sharp, C. A. Ross, E. Scherzinger, E. E. Wanker, L. Mangiarini, and G. P. Bates 1997. Formation of neuronal intranuclear inclusions underlies the neurological dysfunction in mice transgenic for the HD mutation Cell. 90:537-48
.
53. Davis, R. L., H. Weintraub, and A. B. Lassar 1987. Expression of a single transfected cDNA converts fibroblasts to myoblasts Cell. 51:987-1000

54. de la Pompa, J. L., A. Wakeham, K. M. Correia, E. Samper, S. Brown, R. J. Aguilera, T. Nakano, T. Honjo, T. W. Mak, J. Rossant, and R. A. Conlon 1997. Conservation of the Notch signalling pathway in mammalian neurogenesis Development. 124:1139-48

55. de la Serna, I. L., K. A. Carlson, and A. N. Imbalzano 2001. Mammalian SWI/SNF complexes promote MyoD-mediated muscle differentiation Nat Genet. 27:187-90

56. Deftos, M. L., Y. W. He, E. W. Ojala, and M. J. Bevan 1998. Correlating notch signaling with thymocyte maturation Immunity. 9:777-86

57. DiFiglia, M., E. Sapp, K. O. Chase, S. W. Davies, G. P. Bates, J. P. Vonsattel, and N. Aronin 1997. Aggregation of huntingtin in neuronal intranuclear inclusions and dystrophic neurites in brain Science. 277:1990-3

58. Dover, G. J., S. Brusilow, and S. Charache 1994. Induction of fetal hemoglobin production in subjects with sickle cell anemia by oral sodium phenylbutyrate Blood. 84:339-43

59. Eberhard, D., G. Jimenez, B. Heavey, and M. Busslinger 2000. Transcriptional repression by Pax5 (BSAP) through interaction with corepressors of the Groucho family Embo J. 19:2292-303

60. Eckner, R., M. E. Ewen, D. Newsome, M. Gerdes, J. A. DeCaprio, J. B. Lawrence, and D. M. Livingston 1994. Molecular cloning and functional analysis of the adenovirus E1A-associated 300-kD protein (p300) reveals a protein with properties of a transcriptional adaptor Genes & Development. 8:869-84

61. Eckner, R., J. W. Ludlow, N. L. Lill, E. Oldread, Z. Arany, N. Modjtahedi, J. A. DeCaprio, D. M. Livingston, and J. A. Morgan 1996. Association of p300 and CBP with simian virus 40 large T antigen Mol Cell Biol. 16:3454-64

62. Eckner, R., T. P. Yao, E. Oldread, and D. M. Livingston 1996. Interaction and functional collaboration of p300/CBP and bHLH proteins in muscle and B-cell differentiation Genes & Development. 10:2478-90

63. Edmondson, D. G., M. M. Smith, and S. Y. Roth 1996. Repression domain of the yeast global repressor Tup1 interacts directly with histones H3 and H4 Genes Dev. 10:1247-59

64. Enver, T., and M. Greaves 1998. Loops, lineage, and leukemia Cell. 94:9-12

65. Ferrari, G., G. Cusella-De Angelis, M. Coletta, E. Paolucci, A. Stornaiuolo, G. Cossu, and F. Mavilio 1998. Muscle regeneration by bone marrow-derived myogenic progenitors Science. 279:1528-30

66. Ferrer, I., E. Goutan, C. Marin, M. J. Rey, and T. Ribalta 2000. Brain-derived neurotrophic factor in Huntington disease Brain Res. 866:257-61

67. Fisher, A. L., S. Ohsako, and M. Caudy 1996. The WRPW motif of the hairy-related basic helix-loop-helix repressor proteins acts as a 4-amino-acid transcription repression and protein- protein interaction domain Mol Cell Biol. 16:2670-7

68. Flaus, A., and T. Owen-Hughes 2001. Mechanisms for ATP-dependent chromatin remodelling Curr Opin Genet Dev. 11:148-54

69. Fode, C., Q. Ma, S. Casarosa, S. L. Ang, D. J. Anderson, and F. Guillemot 2000. A role for neural determination genes in specifying the dorsoventral identity of telencephalic neurons Genes Dev. 14:67-80

70. Fry, C. J., and C. L. Peterson 2001. Chromatin remodeling enzymes: who's on first? Curr Biol. 11:R185-97

71. Galli, R., U. Borello, A. Gritti, M. G. Minasi, C. Bjornson, M. Coletta, M. Mora, M. G. De Angelis, R. Fiocco, G. Cossu, and A. L. Vescovi 2000. Skeletal myogenic potential of human and mouse neural stem cells Nat Neurosci. 3:986-91

72. Georgopoulos, K., S. Winandy, and N. Avitahl 1997. The role of the Ikaros gene in lymphocyte development and homeostasis Annu Rev Immunol. 15:155-76

73. Gerber, A. N., T. R. Klesert, D. A. Bergstrom, and S. J. Tapscott 1997. Two domains of MyoD mediate transcriptional activation of genes in repressive chromatin: a mechanism for lineage determination in myogenesis Genes & Development. 11:436-50

74. Giles, R. H., D. J. Peters, and M. H. Breuning 1998. Conjunction dysfunction: CBP/p300 in human disease Trends Genet. 14:178-83

75. Godde, J. S., Y. Nakatani, and A. P. Wolffe 1995. The amino-terminal tails of the core histones and the translational position of the TATA box determine TBP/TFIIA association with nucleosomal DNA Nucleic Acids Res. 23:4557-64

76. Goodman, R. H., and S. Smolik 2000. CBP/p300 in cell growth, transformation, and development Genes Dev. 14:1553-77

77. Grant, P. A., D. Schieltz, M. G. Pray-Grant, D. J. Steger, J. C. Reese, J. R. Yates, 3rd, and J. L. Workman 1998. A subset of TAF(II)s are integral components of the SAGA complex required for nucleosome acetylation and transcriptional stimulation Cell. 94:45-53

78. Grbavec, D., and S. Stifani 1996. Molecular interaction between TLE1 and the carboxyl-terminal domain of HES-1 containing the WRPW motif Biochem Biophys Res Commun. 223:701-5

79. Grignani, F., M. Fagioli, M. Alcalay, L. Longo, P. P. Pandolfi, E. Donti, A. Biondi, F. Lo Coco, and P. G. Pelicci 1994. Acute promyelocytic leukemia: from genetics to treatment Blood. 83:10-25

80. Grigoriadis, A. E., Z. Q. Wang, M. G. Cecchini, W. Hofstetter, R. Felix, H. A. Fleisch, and E. F. Wagner 1994. c-Fos: a key regulator of osteoclast-macrophage lineage determination and bone remodeling Science. 266:443-8

81. Grozinger, C. M., C. A. Hassig, and S. L. Schreiber 1999. Three proteins define a class of human histone deacetylases related to yeast Hda1p Proc Natl Acad Sci U S A. 96:4868-73

82. Grozinger, C. M., and S. L. Schreiber 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

83. Grunstein, M. 1997. Histone acetylation in chromatin structure and transcription Nature. 389:349-52

84. Gu, W., J. W. Schneider, G. Condorelli, S. Kaushal, V. Mahdavi, and B. Nadal-Ginard 1993. Interaction of myogenic factors and the retinoblastoma protein mediates muscle cell commitment and differentiation Cell. 72:309-24

85. Guillemot, F., L. C. Lo, J. E. Johnson, A. Auerbach, D. J. Anderson, and A. L. Joyner 1993. Mammalian achaete-scute homolog 1 is required for the early development of olfactory and autonomic neurons Cell. 75:463-76

86. Gusella, J. F., and M. E. MacDonald 2000. Molecular genetics: unmasking polyglutamine triggers in neurodegenerative disease Nat Rev Neurosci. 1:109-15

87. Gusella, J. F., and M. E. MacDonald 1996. Trinucleotide instability: a repeating theme in human inherited disorders Annu Rev Med. 47:201-9

88. Gusella, J. F., S. McNeil, F. Persichetti, J. Srinidhi, A. Novelletto, E. Bird, P. Faber, J. P. Vonsattel, R. H. Myers, and M. E. MacDonald 1996. Huntington's disease Cold Spring Harb Symp Quant Biol. 61:615-26

89. Gussoni, E., Y. Soneoka, C. D. Strickland, E. A. Buzney, M. K. Khan, A. F. Flint, L. M. Kunkel, and R. C. Mulligan 1999. Dystrophin expression in the mdx mouse restored by stem cell transplantation Nature. 401:390-4

90. Halevy, O., B. G. Novitch, D. B. Spicer, S. X. Skapek, J. Rhee, G. J. Hannon, D. Beach, and A. B. Lassar 1995. Correlation of terminal cell cycle arrest of skeletal muscle with induction of p21 by MyoD [see comments] Science. 267:1018-21

91. Hamamori, Y., V. Sartorelli, V. Ogryzko, P. L. Puri, H. Y. Wu, J. Y. Wang, Y. Nakatani, and L. Kedes 1999. Regulation of histone acetyltransferases p300 and PCAF by the bHLH protein twist and adenoviral oncoprotein E1A Cell. 96:405-13

92. Hamamori, Y., H. Y. Wu, V. Sartorelli, and L. Kedes 1997. The basic domain of myogenic basic helix-loop-helix (bHLH) proteins is the novel target for direct inhibition by another bHLH protein, Twist Molecular & Cellular Biology. 17:6563-73

93. Harbour, J. W., R. X. Luo, A. Dei Santi, A. A. Postigo, and D. C. Dean 1999. Cdk phosphorylation triggers sequential intramolecular interactions that progressively block Rb functions as cells move through G1 Cell. 98:859-69

94. Harlow, E., P. Whyte, B. R. Franza, Jr., and C. Schley 1986. Association of adenovirus early-region 1A proteins with cellular polypeptides Mol Cell Biol. 6:1579-89

95. Hasegawa, K., M. B. Meyers, and R. N. Kitsis 1997. Transcriptional coactivator p300 stimulates cell type-specific gene expression in cardiac myocytes J Biol Chem. 272:20049-54

96. Hassan, A. H., K. E. Neely, and J. L. Workman 2001. Histone acetyltransferase complexes stabilize swi/snf binding to promoter nucleosomes Cell. 104:817-27

97. Hasty, P., A. Bradley, J. H. Morris, D. G. Edmondson, J. M. Venuti, E. N. Olson, and W. H. Klein 1993. Muscle deficiency and neonatal death in mice with a targeted mutation in the myogenin gene Nature. 364:501-6

98. Hebrok, M., K. Wertz, and E. M. Fuchtbauer 1994. M-twist is an inhibitor of muscle differentiation Developmental Biology (Orlando). 165:537-44

99. Hemesath, T. J., E. R. Price, C. Takemoto, T. Badalian, and D. E. Fisher 1998. MAP kinase links the transcription factor Microphthalmia to c-Kit signalling in melanocytes Nature. 391:298-301

100. Hodgkinson, C. A., K. J. Moore, A. Nakayama, E. Steingrimsson, N. G. Copeland, N. A. Jenkins, and H. Arnheiter 1993. Mutations at the mouse microphthalmia locus are associated with defects in a gene encoding a novel basic-helix-loop-helix-zipper protein Cell. 74:395-404

101. Hosokawa, Y., Y. Maeda, E. Takahashi, M. Suzuki, and M. Seto 1999. Human aiolos, an ikaros-related zinc finger DNA binding protein: cDNA cloning, tissue expression pattern, and chromosomal mapping Genomics. 61:326-9

102. Ikura, T., V. V. Ogryzko, M. Grigoriev, R. Groisman, J. Wang, M. Horikoshi, R. Scully, J. Qin, and Y. Nakatani 2000. Involvement of the TIP60 histone acetylase complex in DNA repair and apoptosis Cell. 102:463-73

103. Ikuta, T., Y. W. Kan, P. S. Swerdlow, D. V. Faller, and S. P. Perrine 1998. Alterations in protein-DNA interactions in the gamma-globin gene promoter in response to butyrate therapy Blood. 92:2924-33

104. Imbalzano, A. N., H. Kwon, M. R. Green, and R. E. Kingston 1994. Facilitated binding of TATA-binding protein to nucleosomal DNA Nature. 370:481-5

105. Imhof, A., X. J. Yang, V. V. Ogryzko, Y. Nakatani, A. P. Wolffe, and H. Ge 1997. Acetylation of general transcription factors by histone acetyltransferases Curr Biol. 7:689-92

106. Inokoshi, J., M. Katagiri, S. Arima, H. Tanaka, M. Hayashi, Y. B. Kim, R. Furumai, M. Yoshida, S. Horinouchi, and S. Omura 1999. Neuronal differentiation of neuro 2a cells by inhibitors of cell cycle progression, trichostatin A and butyrolactone I Biochem Biophys Res Commun. 256:372-6

107. Ishibashi, M., S. L. Ang, K. Shiota, S. Nakanishi, R. Kageyama, and F. Guillemot 1995. Targeted disruption of mammalian hairy and Enhancer of split homolog-1 (HES-1) leads to up-regulation of neural helix-loop-helix factors, premature neurogenesis, and severe neural tube defects Genes Dev. 9:3136-48

108. Ishiguro, K., and A. C. Sartorelli 1998. Coinduction of embryonic and adult-type globin mRNAs by sodium butyrate and trichostatin A in two murine interleukin-3-dependent bone marrow- derived cell lines Blood. 92:4383-93

109. Ito, H., S. C. Miller, M. E. Billingham, H. Akimoto, S. V. Torti, R. Wade, R. Gahlmann, G. Lyons, L. Kedes, and F. M. Torti 1990. Doxorubicin selectively inhibits muscle gene expression in cardiac muscle cells *in vivo* and *in vitro* Proc Natl Acad Sci U S A. 87:4275-9

110. Jackson, K. A., T. Mi, and M. A. Goodell 1999. Hematopoietic potential of stem cells isolated from murine skeletal muscle Proc Natl Acad Sci U S A. 96:14482-6

111. Jehn, B. M., W. Bielke, W. S. Pear, and B. A. Osborne 1999. Cutting edge: protective effects of notch-1 on TCR-induced apoptosis J Immunol. 162:635-8

112. Jen, Y., K. Manova, and R. Benezra 1996. Expression patterns of Id1, Id2, and Id3 are highly related but distinct from that of Id4 during mouse embryogenesis Dev Dyn. 207:235-52

113. Jen, Y., H. Weintraub, and R. Benezra 1992. Overexpression of Id protein inhibits the muscle differentiation program: *in vivo* association of Id with E2A proteins Genes & Development. 6:1466-79

114. Jeppesen, P., and B. M. Turner 1993. The inactive X chromosome in female mammals is distinguished by a lack of histone H4 acetylation, a cytogenetic marker for gene expression Cell. 74:281-9

115. Jonsson, J., L. Carlsson, T. Edlund, and H. Edlund 1994. Insulin-promoter-factor 1 is required for pancreas development in mice Nature. 371:606-9

116. Kao, H. Y., P. Ordentlich, N. Koyano-Nakagawa, Z. Tang, M. Downes, C. R. Kintner, R. M. Evans, and T. Kadesch 1998. A histone deacetylase corepressor complex regulates the Notch signal transduction pathway Genes Dev. 12:2269-77

117. Kato, Y., Y. Shi, and X. He 1999. Neuralization of the Xenopus embryo by inhibition of p300/ CREB-binding protein function J Neurosci. 19:9364-73

118. Kaushal, S., J. W. Schneider, B. Nadal-Ginard, and V. Mahdavi 1994. Activation of the myogenic lineage by MEF2A, a factor that induces and cooperates with MyoD Science. 266:1236-40

119. Kazantsev, A., E. Preisinger, A. Dranovsky, D. Goldgaber, and D. Housman 1999. Insoluble detergent-resistant aggregates form between pathological and nonpathological lengths of polyglutamine in mammalian cells Proc Natl Acad Sci U S A. 96:11404-9

120. Kee, B. L., and C. Murre 1998. Induction of early B cell factor (EBF) and multiple B lineage genes by the basic helix-loop-helix transcription factor E12 J Exp Med. 188:699-713

121. Kim, J., S. Sif, B. Jones, A. Jackson, J. Koipally, E. Heller, S. Winandy, A. Viel, A. Sawyer, T. Ikeda, R. Kingston, and K. Georgopoulos 1999. Ikaros DNA-binding proteins direct formation of chromatin remodeling complexes in lymphocytes Immunity. 10:345-55

122. Kirshenbaum, L. A., and M. D. Schneider 1995. Adenovirus E1A represses cardiac gene transcription and reactivates DNA synthesis in ventricular myocytes, via alternative pocket protein- and p300-binding domains J Biol Chem. 270:7791-4

123. Kitabayashi, I., Y. Aikawa, A. Yokoyama, F. Hosoda, M. Nagai, N. Kakazu, T. Abe, and M. Ohki 2001. Fusion of MOZ and p300 histone acetyltransferases in acute monocytic leukemia with a t(8;22)(p11;q13) chromosome translocation Leukemia. 15:89-94

124. Koipally, J., and K. Georgopoulos 2000. Ikaros interactions with CtBP reveal a repression mechanism that is independent of histone deacetylase activity J Biol Chem. 275:19594-602

125. Koipally, J., A. Renold, J. Kim, and K. Georgopoulos 1999. Repression by Ikaros and Aiolos is mediated through histone deacetylase complexes Embo J. 18:3090-100

126. Kondo, M., I. L. Weissman, and K. Akashi 1997. Identification of clonogenic common lymphoid progenitors in mouse bone marrow Cell. 91:661-72

127. Kopen, G. C., D. J. Prockop, and D. G. Phinney 1999. Marrow stromal cells migrate throughout forebrain and cerebellum, and they differentiate into astrocytes after injection into neonatal mouse brains Proc Natl Acad Sci U S A. 96:10711-6

128. Kouzarides, T. 2000. Acetylation: a regulatory modification to rival phosphorylation? Embo J. 19:1176-9

129. Koyano-Nakagawa, N., D. Wettstein, and C. Kintner 1999. Activation of Xenopus genes required for lateral inhibition and neuronal differentiation during primary neurogenesis Mol Cell Neurosci. 14:327-39

130. Krebs, J. E., C. J. Fry, M. L. Samuels, and C. L. Peterson 2000. Global role for chromatin remodeling enzymes in mitotic gene expression Cell. 102:587-98

131. Kung, A. L., V. I. Rebel, R. T. Bronson, L. E. Ch'ng, C. A. Sieff, D. M. Livingston, and T. P. Yao 2000. Gene dose-dependent control of hematopoiesis and hematologic tumor suppression by CBP Genes Dev. 14:272-7

132. Kuo, C. T., and J. M. Leiden 1999. Transcriptional regulation of T lymphocyte development and function Annu Rev Immunol. 17:149-87

133. Kurabayashi, M., R. Jeyaseelan, and L. Kedes 1993. Antineoplastic agent doxorubicin inhibits myogenic differentiation of C2 myoblasts J Biol Chem. 268:5524-9

134. Lassar, A., and A. Münsterberg 1994. Wiring diagrams: regulatory circuits and the control of skeletal myogenesis. Current Opinion in Cell Biology. 6:432-42

135. Lau, O. D., T. K. Kundu, R. E. Soccio, S. Ait-Si-Ali, E. M. Khalil, A. Vassilev, A. P. Wolffe, Y. Nakatani, R. G. Roeder, and P. A. Cole 2000. HATs off: selective synthetic inhibitors of the histone acetyltransferases p300 and PCAF Mol Cell. 5:589-95

136. Lavau, C., C. Du, M. Thirman, and N. Zeleznik-Le 2000. Chromatin-related properties of CBP fused to MLL generate a myelodysplastic-like syndrome that evolves into myeloid leukemia Embo J. 19:4655-64

137. Leibham, D., M. W. Wong, T. C. Cheng, S. Schroeder, P. A. Weil, E. N. Olson, and M. Perry 1994. Binding of TFIID and MEF2 to the TATA element activates transcription of the Xenopus MyoDa promoter Mol Cell Biol. 14:686-99

138. Liang, J., L. Prouty, B. J. Williams, M. A. Dayton, and K. L. Blanchard 1998. Acute mixed lineage leukemia with an inv(8)(p11q13) resulting in fusion of the genes for MOZ and TIF2 Blood. 92:2118-22

139. Lin, H., and R. Grosschedl 1995. Failure of B-cell differentiation in mice lacking the transcription factor EBF Nature. 376:263-7

140. Lin, Q., J. Schwarz, C. Bucana, and E. N. Olson 1997. Control of mouse cardiac morphogenesis and myogenesis by transcription factor MEF2C Science. 276:1404-7

141. Liu, Z. G., S. W. Smith, K. A. McLaughlin, L. M. Schwartz, and B. A. Osborne 1994. Apoptotic signals delivered through the T-cell receptor of a T-cell hybrid require the immediate-early gene nur77 Nature. 367:281-4

142. Lu, J., T. A. McKinsey, R. L. Nicol, and E. N. Olson 2000. Signal-dependent activation of the MEF2 transcription factor by dissociation from histone deacetylases Proc Natl Acad Sci U S A. 97:4070-5

143. Lu, J., T. A. McKinsey, C. L. Zhang, and E. N. Olson 2000. Regulation of skeletal myogenesis by association of the MEF2 transcription factor with class II histone deacetylases Mol Cell. 6:233-44

144. Lu, Q. R., D. Yuk, J. A. Alberta, Z. Zhu, I. Pawlitzky, J. Chan, A. P. McMahon, C. D. Stiles, and D. H. Rowitch 2000. Sonic hedgehog--regulated oligodendrocyte lineage genes encoding bHLH proteins in the mammalian central nervous system Neuron. 25:317-29

145. Luger, K., A. W. Mader, R. K. Richmond, D. F. Sargent, and T. J. Richmond 1997. Crystal structure of the nucleosome core particle at 2.8 A resolution Nature. 389:251-60

146. Lyden, D., A. Z. Young, D. Zagzag, W. Yan, W. Gerald, R. O'Reilly, B. L. Bader, R. O. Hynes, Y. Zhuang,

K. Manova, and R. Benezra 1999. Id1 and Id3 are required for neurogenesis, angiogenesis and vascularization of tumour xenografts Nature. 401:670-7

147. Ma, Q., C. Fode, F. Guillemot, and D. J. Anderson 1999. Neurogenin1 and neurogenin2 control two distinct waves of neurogenesis in developing dorsal root ganglia Genes Dev. 13:1717-28

148. MacLellan, W. R., G. Xiao, M. Abdellatif, and M. D. Schneider 2000. A novel Rb- and p300-binding protein inhibits transactivation by MyoD Mol Cell Biol. 20:8903-15

149. Maier, M. M., and M. Gessler 2000. Comparative analysis of the human and mouse Hey1 promoter: Hey genes are new Notch target genes Biochem Biophys Res Commun. 275:652-60

150. Mal, A., M. Sturniolo, R. L. Schiltz, M. K. Ghosh, and M. L. Harter 2001. A role for histone deacetylase HDAC1 in modulating the transcriptional activity of MyoD: inhibition of the myogenic program Embo J. 20:1739-1753

151. Malecki, M. T., U. S. Jhala, A. Antonellis, L. Fields, A. Doria, T. Orban, M. Saad, J. H. Warram, M. Montminy, and A. S. Krolewski 1999. Mutations in NEUROD1 are associated with the development of type 2 diabetes mellitus Nat Genet. 23:323-8

152. Massari, M. E., P. A. Grant, M. G. Pray-Grant, S. L. Berger, J. L. Workman, and C. Murre 1999. A conserved motif present in a class of helix-loop-helix proteins activates transcription by direct recruitment of the SAGA complex Mol Cell. 4:63-73

153. Massari, M. E., P. A. Jennings, and C. Murre 1996. The AD1 transactivation domain of E2A contains a highly conserved helix which is required for its activity in both Saccharomyces cerevisiae and mammalian cells Mol Cell Biol. 16:121-9

154. Matsuno, K., R. J. Diederich, M. J. Go, C. M. Blaumueller, and S. Artavanis-Tsakonas 1995. Deltex acts as a positive regulator of Notch signaling through interactions with the Notch ankyrin repeats Development. 121:2633-44

155. Matsuno, K., D. Eastman, T. Mitsiades, A. M. Quinn, M. L. Carcanciu, P. Ordentlich, T. Kadesch, and S. Artavanis-Tsakonas 1998. Human deltex is a conserved regulator of Notch signalling Nat Genet. 19:74-8

156. McCaffrey, P. G., D. A. Newsome, E. Fibach, M. Yoshida, and M. S. Su 1997. Induction of gamma-globin by histone deacetylase inhibitors Blood. 90:2075-83

157. McKinsey, T. A., C. L. Zhang, J. Lu, and E. N. Olson 2000. Signal-dependent nuclear export of a histone deacetylase regulates muscle differentiation Nature. 408:106-11

158. McKinsey, T. A., C. L. Zhang, and E. N. Olson 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

159. Megeney, L. A., B. Kablar, K. Garrett, J. E. Anderson, and M. A. Rudnicki 1996. MyoD is required for myogenic stem cell function in adult skeletal muscle Genes Dev. 10:1173-83

160. Michael, L. F., Z. Wu, R. B. Cheatham, P. Puigserver, G. Adelmant, J. J. Lehman, D. P. Kelly, and B. M. Spiegelman 2001. Restoration of insulin-sensitive glucose transporter (GLUT4) gene expression in muscle cells by the transcriptional coactivator PGC-1 Proc Natl Acad Sci U S A. 98:3820-5

161. Miller, R. W., and J. H. Rubinstein 1995. Tumors in Rubinstein-Taybi syndrome Am J Med Genet. 56:112-5

162. Minucci, S., V. Horn, N. Bhattacharyya, V. Russanova, V. V. Ogryzko, L. Gabriele, B. H. Howard, and K. Ozato 1997. A histone deacetylase inhibitor potentiates retinoid receptor action in embryonal carcinoma cells Proc Natl Acad Sci U S A. 94:11295-300

163. Miska, E. A., C. Karlsson, E. Langley, S. J. Nielsen, J. Pines, and T. Kouzarides 1999. HDAC4 deacetylase associates with and represses the MEF2 transcription factor Embo J. 18:5099-107

164. Miska, E. A., C. Karlsson, E. Langley, S. J. Nielsen, J. Pines, and T. Kouzarides 1999. HDAC4 deacetylase associates with and represses the MEF2 transcription factor EMBO Journal. 18:5099-107

165. Miyake, S., W. R. Sellers, M. Safran, X. Li, W. Zhao, S. R. Grossman, J. Gan, J. A. DeCaprio, P. D. Adams, and W. G. Kaelin, Jr. 2000. Cells degrade a novel inhibitor of differentiation with E1A-like properties upon exiting the cell cycle Mol Cell Biol. 20:8889-902

166. Miyata, T., T. Maeda, and J. E. Lee 1999. NeuroD is required for differentiation of the granule cells in the cerebellum and hippocampus Genes Dev. 13:1647-52

167. Mizzen, C. A., X. J. Yang, T. Kokubo, J. E. Brownell, A. J. Bannister, T. Owen-Hughes, J. Workman, L. Wang, S. L. Berger, T. Kouzarides, Y. Nakatani, and C. D. Allis 1996. The TAF(II)250 subunit of TFIID has histone acetyltransferase activity Cell. 87:1261-70

168. Molkentin, J. D., B. L. Black, J. F. Martin, and E. N. Olson 1995. Cooperative activation of muscle gene expression by MEF2 and myogenic bHLH proteins Cell. 83:1125-36

169. Molkentin, J. D., and E. N. Olson 1996. Combinatorial control of muscle development by basic helix-loop-helix and MADS-box transcription factors Proceedings of the National Academy of Sciences of the United States of America. 93:9366-73

170. Molkentin, J. D., and E. N. Olson 1996. Defining the regulatory networks for muscle development Current Opinion in Genetics & Development. 6:445-53

171. Morgan, B., L. Sun, N. Avitahl, K. Andrikopoulos, T. Ikeda, E. Gonzales, P. Wu, S. Neben, and K. Georgopoulos 1997. Aiolos, a lymphoid restricted transcription factor that interacts with Ikaros to regulate lymphocyte differentiation Embo J. 16:2004-13

172. Morrison, S. J. 2001. Neuronal differentiation: Proneural genes inhibit gliogenesis Curr Biol. 11:R349-51

173. Mueller, P. R., and B. Wold 1989. *In vivo* footprinting of a muscle specific enhancer by ligation mediated PCR [published erratum appears in Science 1990 May 18;248(4957):802] Science. 246:780-6

174. Muraoka, M., M. Konishi, R. Kikuchi-Yanoshita, K. Tanaka, N. Shitara, J. M. Chong, T. Iwama, and M. Miyaki 1996. p300 gene alterations in colorectal and gastric carcinomas Oncogene. 12:1565-9

175. Murata, T., R. Kurokawa, A. Krones, K. Tatsumi, M. Ishii, T. Taki, M. Masuno, H. Ohashi, M. Yanagisawa, M. G. Rosenfeld, C. K. Glass, and Y. Hayashi 2001. Defect of histone acetyltransferase activity of the nuclear transcriptional coactivator CBP in Rubinstein-Taybi syndrome Hum Mol Genet. 10:1071-6

176. Mutoh, H., F. J. Naya, M. J. Tsai, and A. B. Leiter 1998. The basic helix-loop-helix protein BETA2 interacts with p300 to coordinate differentiation of secretin-expressing enteroendocrine cells Genes Dev. 12:820-30

177. Nabeshima, Y., K. Hanaoka, M. Hayasaka, E. Esumi, S. Li, and I. Nonaka 1993. Myogenin gene disruption results in perinatal lethality because of severe muscle defect Nature. 364:532-5

178. Nakagawa, O., D. G. McFadden, M. Nakagawa, H. Yanagisawa, T. Hu, D. Srivastava, and E. N. Olson 2000. Members of the HRT family of basic helix-loop-helix proteins act as transcriptional repressors downstream of Notch signaling Proc Natl Acad Sci U S A. 97:13655-60

179. Nakase, K., F. Ishimaru, N. Avitahl, H. Dansako, K. Matsuo, K. Fujii, N. Sezaki, H. Nakayama, T. Yano, S. Fukuda, K. Imajoh, M. Takeuchi, A. Miyata, M. Hara, M. Yasukawa, I. Takahashi, H. Taguchi, K. Matsue, S. Nakao, Y. Niho, K. Takenaka, K. Shinagawa, K. Ikeda, K. Niiya, and M. Harada 2000. Dominant negative isoform of the Ikaros gene in patients with adult B- cell acute lymphoblastic leukemia Cancer Res. 60:4062-5

180. Nakayama, J., J. C. Rice, B. D. Strahl, C. D. Allis, and S. I. Grewal 2001. Role of histone H3 lysine 9 methylation in epigenetic control of heterochromatin assembly Science. 292:110-3

181. Nasmyth, K., D. Stillman, and D. Kipling 1987. Both positive and negative regulators of HO transcription are required for mother-cell-specific mating-type switching in yeast Cell. 48:579-87

182. Naya, F. J., H. P. Huang, Y. Qiu, H. Mutoh, F. J. DeMayo, A. B. Leiter, and M. J. Tsai 1997. Diabetes, defective pancreatic morphogenesis, and abnormal enteroendocrine differentiation in BETA2/neuroD-deficient mice Genes Dev. 11:2323-34

183. Nervi, C., U. Borello, F. Fazi, V. Buffa, P. G. Pelicci, and G. Cossu 2001. Inhibition of histone deacetylase activity by trichostatin A modulates gene expression during mouse embryogenesis without apparent toxicity Cancer Res. 61:1247-9

184. Nichogiannopoulou, A., M. Trevisan, C. Friedrich, and K. Georgopoulos 1998. Ikaros in hemopoietic lineage determination and homeostasis Semin Immunol. 10:119-25

185. Nichogiannopoulou, A., M. Trevisan, S. Neben, C. Friedrich, and K. Georgopoulos 1999. Defects in hemopoietic stem cell activity in Ikaros mutant mice J Exp Med. 190:1201-14

186. Nieto, M., C. Schuurmans, O. Britz, and F. Guillemot 2001. Neural bHLH genes control the neuronal versus glial fate decision in cortical progenitors Neuron. 29:401-13

187. Novitch, B. G., D. B. Spicer, P. S. Kim, W. L. Cheung, and A. B. Lassar 1999. pRb is required for MEF2-dependent gene expression as well as cell-cycle arrest during skeletal muscle differentiation Current Biology. 9:449-59

188. Nucifora, F. C., Jr., M. Sasaki, M. F. Peters, H. Huang, J. K. Cooper, M. Yamada, H. Takahashi, S. Tsuji, J. Troncoso, V. L. Dawson, T. M. Dawson, and C. A. Ross 2001. Interference by huntingtin and atrophin-1 with cbp-mediated transcription leading to cellular toxicity Science. 291:2423-8

189. Nuez, B., D. Michalovich, A. Bygrave, R. Ploemacher, and F. Grosveld 1995. Defective haematopoiesis in fetal liver resulting from inactivation of the EKLF gene Nature. 375:316-8

190. Nutt, S. L., B. Heavey, A. G. Rolink, and M. Busslinger 1999. Commitment to the B-lymphoid lineage depends on the transcription factor Pax5 Nature. 401:556-62

191. Nutt, S. L., P. Urbanek, A. Rolink, and M. Busslinger 1997. Essential functions of Pax5 (BSAP) in pro-B cell development: difference between fetal and adult B lymphopoiesis and reduced V-to-DJ recombination at the IgH locus Genes Dev. 11:476-91

192. Nutt, S. L., S. Vambrie, P. Steinlein, Z. Kozmik, A. Rolink, A. Weith, and M. Busslinger 1999. Independent regulation of the two Pax5 alleles during B-cell development Nat Genet. 21:390-5

193. O'Neill, D., J. Yang, H. Erdjument-Bromage, K. Bornschlegel, P. Tempst, and A. Bank 1999. Tissue-specific and developmental stage-specific DNA binding by a mammalian SWI/SNF complex associated with human fetal-to-adult globin gene switching Proc Natl Acad Sci U S A. 96:349-54

194. O'Neill, D. W., S. S. Schoetz, R. A. Lopez, M. Castle, L. Rabinowitz, E. Shor, D. Krawchuk, M. G. Goll, M. Renz, H. P. Seelig, S. Han, R. H. Seong, S. D. Park, T. Agalioti, N. Munshi, D. Thanos, H. Erdjument-Bromage, P. Tempst, and A. Bank 2000. An ikaros-containing chromatin-remodeling complex in adult-type erythroid cells Mol Cell Biol. 20:7572-82

195. O'Riordan, M., and R. Grosschedl 1999. Coordinate regulation of B cell differentiation by the transcription factors EBF and E2A Immunity. 11:21-31

196. O'Riordan, M., and R. Grosschedl 2000. Transcriptional regulation of early B-lymphocyte differentiation Immunol Rev. 175:94-103

197. Offield, M. F., T. L. Jetton, P. A. Labosky, M. Ray, R. W. Stein, M. A. Magnuson, B. L. Hogan, and C. V. Wright 1996. PDX-1 is required for pancreatic outgrowth and differentiation of the rostral duodenum Development. 122:983-95

198. Ogryzko, V. V., T. Kotani, X. Zhang, R. L. Schlitz, T. Howard, X. J. Yang, B. H. Howard, J. Qin, and Y. Nakatani 1998. Histone-like TAFs within the PCAF histone acetylase complex Cell. 94:35-44

199. Ogryzko, V. V., R. L. Schiltz, V. Russanova, B. H. Howard, and Y. Nakatani 1996. The transcriptional coactivators p300 and CBP are histone acetyltransferases Cell. 87:953-9

200. Oike, Y., A. Hata, T. Mamiya, T. Kaname, Y. Noda, M. Suzuki, H. Yasue, T. Nabeshima, K. Araki, and K. Yamamura 1999. Truncated CBP protein leads to classical Rubinstein-Taybi syndrome phenotypes in mice: implications for a dominant-negative mechanism Hum Mol Genet. 8:387-96

201. Olson, E. N., H. H. Arnold, P. W. Rigby, and B. J. Wold 1996. Know your neighbors: three phenotypes in null mutants of the myogenic bHLH gene MRF4 Cell. 85:1-4

202. Olson, E. N., and W. H. Klein 1994. bHLH factors in muscle development: dead lines and commitments, what to leave in and what to leave out Genes Dev. 8:1-8

203. Onate, S. A., S. Y. Tsai, M. J. Tsai, and B. W. O'Malley 1995. Sequence and characterization of a coactivator for the steroid hormone receptor superfamily Science. 270:1354-7

204. Ordentlich, P., A. Lin, C. P. Shen, C. Blaumueller, K. Matsuno, S. Artavanis-Tsakonas, and T. Kadesch 1998. Notch inhibition of E47 supports the existence of a novel signaling pathway Mol Cell Biol. 18:2230-9

205. Orkin, S. H. 1995. Regulation of globin gene expression in erythroid cells Eur J Biochem. 231:271-81.

206. Osborne, B., and L. Miele 1999. Notch and the immune system Immunity. 11:653-63

207. Osborne, B. A. 2000. Transcriptional control of T cell development Curr Opin Immunol. 12:301-6

208. Pandolfi, P. P., M. E. Roth, A. Karis, M. W. Leonard, E. Dzierzak, F. G. Grosveld, J. D. Engel, and M. H. Lindenbaum 1995. Targeted disruption of the GATA3 gene causes severe abnormalities in the nervous system and in fetal liver haematopoiesis Nat Genet. 11:40-4

209. Perkins, A. C., A. H. Sharpe, and S. H. Orkin 1995. Lethal beta-thalassaemia in mice lacking the erythroid CACCC- transcription factor EKLF Nature. 375:318-22

210. Perrine, S. P., B. A. Miller, D. V. Faller, R. A. Cohen, E. P. Vichinsky, D. Hurst, B. H. Lubin, and T. Papayannopoulou 1989. Sodium butyrate enhances fetal globin gene expression in erythroid progenitors of patients with Hb SS and beta thalassemia Blood. 74:454-9

211. Petersen, A., K. Mani, and P. Brundin 1999. Recent advances on the pathogenesis of Huntington's disease Exp Neurol. 157:1-18

212. Petersen, B. E., W. C. Bowen, K. D. Patrene, W. M. Mars, A. K. Sullivan, N. Murase, S. S. Boggs, J. S. Greenberger, and J. P. Goff 1999. Bone marrow as a potential source of hepatic oval cells Science. 284:1168-70

213. Petrij, F., R. H. Giles, H. G. Dauwerse, J. J. Saris, R. C. Hennekam, M. Masuno, N. Tommerup, G. J. van Ommen, R. H. Goodman, D. J. Peters, and *et al*. 1995. Rubinstein-Taybi syndrome caused by mutations in the transcriptional co- activator CBP Nature. 376:348-51

214. Pevny, L., C. S. Lin, V. D'Agati, M. C. Simon, S. H. Orkin, and F. Costantini 1995. Development of hematopoietic cells lacking transcription factor GATA-1 Development. 121:163-72

215. Pevny, L., M. C. Simon, E. Robertson, W. H. Klein, S. F. Tsai, V. D'Agati, S. H. Orkin, and F. Costantini 1991. Erythroid differentiation in chimaeric mice blocked by a targeted mutation in the gene for transcription factor GATA-1 Nature. 349:257-60

216. Poizat, C., V. Sartorelli, G. Chung, R. A. Kloner, and L. Kedes 2000. Proteasome-mediated degradation of the coactivator p300 impairs cardiac transcription Mol Cell Biol. 20:8643-54

217. Polesskaya, A., A. Duquet, I. Naguibneva, C. Weise, A. Vervisch, E. Bengal, F. Hucho, P. Robin, and A. Harel-Bellan 2000. CREB-binding Protein/p300 activates MyoD by acetylation J Biol Chem. 275:34359-64.

218. Price, E. R., H. F. Ding, T. Badalian, S. Bhattacharya, C. Takemoto, T. P. Yao, T. J. Hemesath, and D. E. Fisher 1998. Lineage-specific signaling in melanocytes. C-kit stimulation recruits p300/CBP to microphthalmia J Biol Chem. 273:17983-6

219. Pui, J. C., D. Allman, L. Xu, S. DeRocco, F. G. Karnell, S. Bakkour, J. Y. Lee, T. Kadesch, R. R. Hardy, J. C. Aster, and W. S. Pear 1999. Notch1 expression in early lymphopoiesis influences B versus T lineage determination Immunity. 11:299-308

220. Puigserver, P., Z. Wu, C. W. Park, R. Graves, M. Wright, and B. M. Spiegelman 1998. A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis Cell. 92:829-39

221. Puri, P. L., M. L. Avantaggiati, C. Balsano, N. Sang, A. Graessmann, A. Giordano, and M. Levrero 1997. p300 is required for MyoD-dependent cell cycle arrest and muscle-specific gene transcription EMBO Journal. 16:369-83

222. Puri, P. L., and V. Sartorelli 2000. Regulation of muscle regulatory factors by DNA-binding, interacting proteins, and post-transcriptional modifications J Cell Physiol. 185:155-73

223. Puri, P. L., V. Sartorelli, X. J. Yang, Y. Hamamori, V. V. Ogryzko, B. H. Howard, L. Kedes, J. Y. Wang, A. Graessmann, Y. Nakatani, and M. Levrero 1997. Differential roles of p300 and PCAF acetyltransferases in muscle differentiation Molecular Cell. 1:35-45

224. Puri, P. L., V. Sartorelli, X. J. Yang, Y. Hamamori, V. V. Ogryzko, B. H. Howard, L. Kedes, J. Y. Wang, A. Graessmann, Y. Nakatani, and M. Levrero 1997. Differential roles of p300 and PCAF acetyltransferases in muscle differentiation Mol Cell. 1:35-45

225. Qiu, Y., A. Sharma, and R. Stein 1998. p300 mediates transcriptional stimulation by the basic helix-loop-helix activators of the insulin gene Mol Cell Biol. 18:2957-64

226. Radtke, F., A. Wilson, G. Stark, M. Bauer, J. van Meerwijk, H. R. MacDonald, and M. Aguet 1999. Deficient T cell fate specification in mice with an induced inactivation of Notch1 Immunity. 10:547-58

227. Rice, J. C., and C. D. Allis 2001. Histone methylation versus histone acetylation: new insights into epigenetic regulation Curr Opin Cell Biol. 13:263-73

228. Riou, P., F. Bex, and L. Gazzolo 2000. The human T cell leukemia/lymphotropic virus type 1 Tax protein represses MyoD-dependent transcription by inhibiting MyoD-binding to the KIX domain of p300. A potential mechanism for Tax-mediated repression of the transcriptional activity of basic helix-loop-helix factors J Biol Chem. 275:10551-60

229. Rodgers, G. P., and Y. Saunthararajah 2001. Advances in experimental treatment of beta-thalassaemia Expert Opin Investig Drugs. 10:925-34

230. Rolink, A. G., S. L. Nutt, F. Melchers, and M. Busslinger 1999. Long-term *in vivo* reconstitution of T-cell development by Pax5- deficient B-cell progenitors Nature. 401:603-6

231. Rudnicki, M. A., T. Braun, S. Hinuma, and R. Jaenisch 1992. Inactivation of MyoD in mice leads to up-regulation of the myogenic HLH gene Myf-5 and results in apparently normal muscle development Cell. 71:383-90

232. Rudnicki, M. A., P. N. Schnegelsberg, R. H. Stead, T. Braun, H. H. Arnold, and R. Jaenisch 1993. MyoD or Myf-5 is required for the formation of skeletal muscle Cell. 75:1351-9

233. Sartorelli, V., J. Huang, Y. Hamamori, and L. Kedes 1997. Molecular mechanisms of myogenic coactivation by p300: direct interaction with the activation domain of MyoD and with the MADS box of MEF2C Molecular & Cellular Biology. 17:1010-26

234. Sartorelli, V., P. L. Puri, Y. Hamamori, V. Ogryzko, G. Chung, Y. Nakatani, J. Y. Wang, and L. Kedes 1999. Acetylation of MyoD directed by PCAF is necessary for the execution of the muscle program Molecular Cell. 4:725-34

235. Sartorelli, V., P. L. Puri, Y. Hamamori, V. Ogryzko, G. Chung, Y. Nakatani, J. Y. Wang, and L. Kedes 1999. Acetylation of MyoD directed by PCAF is necessary for the execution of the muscle program Mol Cell. 4:725-34

236. Sato, S., K. Roberts, G. Gambino, A. Cook, T. Kouzarides, and C. R. Goding 1997. CBP/p300 as a co-factor for the Microphthalmia transcription factor Oncogene. 14:3083-92

237. Schiltz, R. L., C. A. Mizzen, A. Vassilev, R. G. Cook, C. D. Allis, and Y. Nakatani 1999. Overlapping but distinct patterns of histone acetylation by the human coactivators p300 and PCAF within nucleosomal substrates J Biol Chem. 274:1189-92

238. Schiltz, R. L., and Y. Nakatani 2000. The PCAF acetylase complex as a potential tumor suppressor Biochim Biophys Acta. 1470:M37-53

239. Schroeter, E. H., J. A. Kisslinger, and R. Kopan 1998. Notch-1 signalling requires ligand-induced proteolytic release of intracellular domain Nature. 393:382-6

240. Scott, E. K., T. Lee, and L. Luo 2001. enok encodes a Drosophila putative histone acetyltransferase required for mushroom body neuroblast proliferation Curr Biol. 11:99-104

241. Sharma, A., M. Moore, E. Marcora, J. E. Lee, Y. Qiu, S. Samaras, and R. Stein 1999. The NeuroD1/BETA2 sequences essential for insulin gene transcription colocalize with those necessary for neurogenesis and p300/CREB binding protein binding Mol Cell Biol. 19:704-13

242. Shivdasani, R. A., Y. Fujiwara, M. A. McDevitt, and S. H. Orkin 1997. A lineage-selective knockout establishes the critical role of transcription factor GATA-1 in megakaryocyte growth and platelet development Embo J. 16:3965-73

243. Sigvardsson, M., M. O'Riordan, and R. Grosschedl 1997. EBF and E47 collaborate to induce expression of the endogenous immunoglobulin surrogate light chain genes Immunity. 7:25-36

244. Slepak, T. I., K. A. Webster, J. Zang, H. Prentice, A. O'Dowd, M. N. Hicks, and N. H. Bishopric 2001. Control

of Cardiac-specific Transcription by p300 through Myocyte Enhancer Factor-2D J Biol Chem. 276:7575-85

245. Sobulo, O. M., J. Borrow, R. Tomek, S. Reshmi, A. Harden, B. Schlegelberger, D. Housman, N. A. Doggett, J. D. Rowley, and N. J. Zeleznik-Le 1997. MLL is fused to CBP, a histone acetyltransferase, in therapy-related acute myeloid leukemia with a t(11;16)(q23;p13.3) Proc Natl Acad Sci U S A. 94:8732-7

246. Soutoglou, E., G. Papafotiou, N. Katrakili, and I. Talianidis 2000. Transcriptional activation by hepatocyte nuclear factor-1 requires synergism between multiple coactivator proteins J Biol Chem. 275:12515-20

247. Soutoglou, E., B. Viollet, M. Vaxillaire, M. Yaniv, M. Pontoglio, and I. Talianidis 2001. Transcription factor-dependent regulation of CBP and P/CAF histone acetyltransferase activity Embo J. 20:1984-92

248. Sparrow, D. B., E. A. Miska, E. Langley, S. Reynaud-Deonauth, S. Kotecha, N. Towers, G. Spohr, T. Kouzarides, and T. J. Mohun 1999. MEF-2 function is modified by a novel co-repressor, MITR EMBO Journal. 18:5085-98

249. Spencer, T. E., G. Jenster, M. M. Burcin, C. D. Allis, J. Zhou, C. A. Mizzen, N. J. McKenna, S. A. Onate, S. Y. Tsai, M. J. Tsai, and B. W. O'Malley 1997. Steroid receptor coactivator-1 is a histone acetyltransferase Nature. 389:194-8

250. Spicer, D. B., J. Rhee, W. L. Cheung, and A. B. Lassar 1996. Inhibition of myogenic bHLH and MEF2 transcription factors by the bHLH protein Twist [see comments] Science. 272:1476-80

251. Steffan, J. S., A. Kazantsev, O. Spasic-Boskovic, M. Greenwald, Y. Z. Zhu, H. Gohler, E. E. Wanker, G. P. Bates, D. E. Housman, and L. M. Thompson 2000. The Huntington's disease protein interacts with p53 and CREB-binding protein and represses transcription Proc Natl Acad Sci U S A. 97:6763-8

252. Sterner, D. E., and S. L. Berger 2000. Acetylation of histones and transcription-related factors Microbiol Mol Biol Rev. 64:435-59

253. Sun, L., M. L. Crotty, M. Sensel, H. Sather, C. Navara, J. Nachman, P. G. Steinherz, P. S. Gaynon, N. Seibel, C. Mao, A. Vassilev, G. H. Reaman, and F. M. Uckun 1999. Expression of dominant-negative Ikaros isoforms in T-cell acute lymphoblastic leukemia Clin Cancer Res. 5:2112-20

254. Sun, X., and S. Artavanis-Tsakonas 1996. The intracellular deletions of Delta and Serrate define dominant negative forms of the Drosophila Notch ligands Development. 122:2465-74

255. Sun, Y., M. Nadal-Vicens, S. Misono, M. Z. Lin, A. Zubiaga, X. Hua, G. Fan, and M. E. Greenberg 2001 Neurogenin promotes neurogenesis and inhibits glial differentiation by independent mechanisms Cell. 104:365-76

256. Swiatek, P. J., C. E. Lindsell, F. F. del Amo, G. Weinmaster, and T. Gridley 1994. Notch1 is essential for postimplantation development in mice Genes Dev. 8:707-19

257. Takke, C., P. Dornseifer, E. v Weizsacker, and J. A. Campos-Ortega 1999. her4, a zebrafish homologue of the Drosophila neurogenic gene E(spl), is a target of NOTCH signalling Development. 126:1811-21

258. Tanaka, Y., I. Naruse, T. Maekawa, H. Masuya, T. Shiroishi, and S. Ishii 1997. Abnormal skeletal patterning in embryos lacking a single Cbp allele: a partial similarity with Rubinstein-Taybi syndrome Proc Natl Acad Sci U S A. 94:10215-20

259. Tapscott, S. J., R. L. Davis, M. J. Thayer, P. F. Cheng, H. Weintraub, and A. B. Lassar 1988. MyoD1: a nuclear phosphoprotein requiring a Myc homology region to convert fibroblasts to myoblasts Science. 242:405-11

260. Taunton, J., C. A. Hassig, and S. L. Schreiber 1996. A mammalian histone deacetylase related to the yeast transcriptional regulator Rpd3p Science. 272:408-11

261. Thai, M. V., S. Guruswamy, K. T. Cao, J. E. Pessin, and A. L. Olson 1998. Myocyte enhancer factor 2 (MEF2)-binding site is required for GLUT4 gene expression in transgenic mice. Regulation of MEF2 DNA binding activity in insulin-deficient diabetes J Biol Chem. 273:14285-92

262. Thomas, T., A. K. Voss, K. Chowdhury, and P. Gruss 2000. Querkopf, a MYST family histone acetyltransferase, is required for normal cerebral cortex development Development. 127:2537-48

263. Ting, C. N., M. C. Olson, K. P. Barton, and J. M. Leiden 1996. Transcription factor GATA-3 is required for development of the T-cell lineage Nature. 384:474-8

264. Tomita, K., K. Moriyoshi, S. Nakanishi, F. Guillemot, and R. Kageyama 2000. Mammalian achaete-scute and atonal homologs regulate neuronal versus glial fate determination in the central nervous system Embo J. 19:5460-72

265. Tournamille, C., Y. Colin, J. P. Cartron, and C. Le Van Kim 1995. Disruption of a GATA motif in the Duffy gene promoter abolishes erythroid gene expression in Duffy-negative individuals Nat Genet. 10:224-8

266. Vidal, M., and R. F. Gaber 1991. RPD3 encodes a second factor required to achieve maximum positive and negative transcriptional states in Saccharomyces cerevisiae Mol Cell Biol. 11:6317-27

267. Vignali, M., A. H. Hassan, K. E. Neely, and J. L. Workman 2000. ATP-dependent chromatin-remodeling complexes Mol Cell Biol. 20:1899-910

268. Wang, A. H., N. R. Bertos, M. Vezmar, N. Pelletier, M. Crosato, H. H. Heng, J. Th'ng, J. Han, and X. J. Yang

1999. HDAC4, a human histone deacetylase related to yeast HDA1, is a transcriptional corepressor Mol Cell Biol. 19:7816-27

269. Wang, A. H., M. J. Kruhlak, J. Wu, N. R. Bertos, M. Vezmar, B. I. Posner, D. P. Bazett-Jones, and X. J. Yang 2000. Regulation of histone deacetylase 4 by binding of 14-3-3 proteins Mol Cell Biol. 20:6904-12

270. Wang, H., Z. Q. Huang, L. Xia, Q. Feng, H. Erdjument-Bromage, B. D. Strahl, S. D. Briggs, C. D. Allis, J. Wong, P. Tempst, and Y. Zhang 2001. Methylation of Histone H4 at Arginine 3 Facilitates Transcriptional Activation by Nuclear Hormone Receptor Science. 31:31

271. Wang, J. C., J. M. Stafford, and D. K. Granner 1998. SRC-1 and GRIP1 coactivate transcription with hepatocyte nuclear factor 4 J Biol Chem. 273:30847-50

272. Warrell, R. P., Jr., L. Z. He, V. Richon, E. Calleja, and P. P. Pandolfi 1998. Therapeutic targeting of transcription in acute promyelocytic leukemia by use of an inhibitor of histone deacetylase J Natl Cancer Inst. 90:1621-5

273. Webster, K. A., G. E. Muscat, and L. Kedes 1988. Adenovirus E1A products suppress myogenic differentiation and inhibit transcription from muscle-specific promoters Nature. 332:553-7

274. Wei, Q., and B. M. Paterson 2001. Regulation of MyoD function in the dividing myoblast FEBS Lett. 490:171-8

275. Weinstein, B. M., D. L. Stemple, W. Driever, and M. C. Fishman 1995. Gridlock, a localized heritable vascular patterning defect in the zebrafish Nat Med. 1:1143-7

276. Weintraub, H., R. Davis, D. Lockshon, and A. Lassar 1990. MyoD binds cooperatively to two sites in a target enhancer sequence: occupancy of two sites is required for activation Proc Natl Acad Sci U S A. 87:5623-7

277. Weintraub, H., R. Davis, S. Tapscott, M. Thayer, M. Krause, R. Benezra, T. K. Blackwell, D. Turner, R. Rupp, S. Hollenberg, and *et al*. 1991. The myoD gene family: nodal point during specification of the muscle cell lineage Science. 251:761-6

278. Weintraub, H., V. J. Dwarki, I. Verma, R. Davis, S. Hollenberg, L. Snider, A. Lassar, and S. J. Tapscott 1991. Muscle-specific transcriptional activation by MyoD Genes & Development. 5:1377-86

279. Weintraub, H., and M. Groudine 1976. Chromosomal subunits in active genes have an altered conformation Science. 193:848-56

280. Weintraub, H., S. J. Tapscott, R. L. Davis, M. J. Thayer, M. A. Adam, A. B. Lassar, and A. D. Miller 1989. Activation of muscle-specific genes in pigment, nerve, fat, liver, and fibroblast cell lines by forced expression of MyoD Proceedings of the National Academy of Sciences of the United States of America. 86:5434-8

281. Winandy, S., L. Wu, J. H. Wang, and K. Georgopoulos 1999. Pre-T cell receptor (TCR) and TCR-controlled checkpoints in T cell differentiation are set by Ikaros J Exp Med. 190:1039-48

282. Winandy, S., P. Wu, and K. Georgopoulos 1995. A dominant mutation in the Ikaros gene leads to rapid development of leukemia and lymphoma Cell. 83:289-99.

283. Wolffe, A. P., and D. Guschin 2000. Review: chromatin structural features and targets that regulate transcription J Struct Biol. 129:102-22

284. Woronicz, J. D., B. Calnan, V. Ngo, and A. Winoto 1994. Requirement for the orphan steroid receptor Nur77 in apoptosis of T- cell hybridomas Nature. 367:277-81

285. Yamada, M., S. Tsuji, and H. Takahashi 2000. Pathology of CAG repeat diseases Neuropathology. 20:319-25

286. Yamagata, T., K. Mitani, H. Oda, T. Suzuki, H. Honda, T. Asai, K. Maki, T. Nakamoto, and H. Hirai 2000. Acetylation of GATA-3 affects T-cell survival and homing to secondary lymphoid organs Embo J. 19:4676-87

287. Yang, X. J., V. V. Ogryzko, J. Nishikawa, B. H. Howard, and Y. Nakatani 1996. A p300/CBP-associated factor that competes with the adenoviral oncoprotein E1A Nature. 382:319-24

288. Yao, T. P., S. P. Oh, M. Fuchs, N. D. Zhou, L. E. Ch'ng, D. Newsome, R. T. Bronson, E. Li, D. M. Livingston, and R. Eckner 1998. Gene dosage-dependent embryonic development and proliferation defects in mice lacking the transcriptional integrator p300 Cell. 93:361-72.

289. Yuan, W., G. Condorelli, M. Caruso, A. Felsani, and A. Giordano 1996. Human p300 protein is a coactivator for the transcription factor MyoD Journal of Biological Chemistry. 271:9009-13

290. Zhang, C. L., T. A. McKinsey, and E. N. Olson 2001. The transcriptional corepressor MITR is a signal-responsive inhibitor of myogenesis Proc Natl Acad Sci U S A. 5:5

291. Zhang, W., and J. J. Bieker 1998. Acetylation and modulation of erythroid Kruppel-like factor (EKLF) activity by interaction with histone acetyltransferases Proc Natl Acad Sci U S A. 95:9855-60

292. Zhang, W., S. Kadam, B. M. Emerson, and J. J. Bieker 2001. Site-specific acetylation by p300 or CREB binding protein regulates erythroid Kruppel-like factor transcriptional activity via its interaction with the SWI-SNF complex Mol Cell Biol. 21:2413-22

293. Zhou, Q., S. Wang, and D. J. Anderson 2000. Identification of a novel family of oligodendrocyte lineage-specific basic helix-loop-helix transcription factors Neuron. 25:331-43

294. Zhuang, Y., P. Soriano, and H. Weintraub 1994. The helix-loop-helix gene E2A is required for B cell formation Cell. 79:875-84

295. Zisman, A., O. D. Peroni, E. D. Abel, M. D. Michael, F. Mauvais-Jarvis, B. B. Lowell, J. F. Wojtaszewski, M. F. Hirshman, A. Virkamaki, L. J. Goodyear, C. R. Kahn, and B. B. Kahn 2000. Targeted disruption of the glucose transporter 4 selectively in muscle causes insulin resistance and glucose intolerance Nat Med. 6:924-8

296. Zuccato, C., A. Ciammola, D. Rigamonti, B. R. Leavitt, D. Goffredo, L. Conti, M. E. MacDonald, R. M. Friedlander, V. Silani, M. R. Hayden, T. Timmusk, S. Sipione, and E. Cattaneo 2001. Loss of Huntingtin-Mediated BDNF Gene Transcription in Huntington's Disease Science. 14:14

Key Words: Chromatin Remodeling, Acetylation, Acetyltransferases, Deacetylases, Cell Differentiation, Human Diseases, Review

Send correspondence to: Dr Vittorio Sartorelli" Laboratory of Muscle Biology, Muscle Gene Expression Group, NIAMS-IRP,National Institutes of Health, Bethesda, Maryland 20892, Tel: 301-435-8145 Fax: 301-435-8136 E-mail: sartorev@mail.nih.gov

Dr. Pier Lorenzo Puri, The Salk Institute for Biological Studies, Peptide Biology Laboratory, La Jolla, California 92093, Tel: 858-453-4100 ext.1190, E-mail: plorenzo@salk.edu