Cyclin D3 Is a Cofactor of Retinoic Acid Receptors, Modulating Their Activity in the Presence of Cellular Retinoic Acid-binding Protein II

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Ligand-induced transcription activation of retinoic acid (RA) target genes by nuclear receptors (retinoic acid (RAR) and retinoid X (RXR) receptors) depends on the recruitment of coactivators. We have previously demonstrated that the small 15-kDa cellular RA-binding protein II (CRABPII) is a cofactor present in the RA-dependent nuclear complex. As identifying cell-specific partners of CRABPII might help to understand the novel control of RA signaling, we performed a yeast two-hybrid screen of a hematopoietic HL-60 cDNA library using human CRABPII as bait and have subsequently identified human cyclin D3 as a partner of CRABPII. Cyclin D3 interacted with CRABPII in a ligand-independent manner and equally bound RARα, but not RXRα, and only in the presence of RA. We further show that cyclin D3 positively modulated RA-mediated transcription through CRABPII. Therefore, cyclin D3 may be part of a ternary complex with CRABPII and RAR. Finally, we show that cyclin D3 expression paralleled HL-60 differentiation and arrest of cell growth. These findings led us to speculate that control of cell proliferation during induction of differentiation may directly involve, at the transcriptional level, nuclear receptors, coactivators, and proteins of the cell cycle in a cell- and nuclear receptor-specific manner.

Retinoic acid (RA) plays a pivotal role in the development and homeostasis of vertebrates through its ability to directly control the transcription of target genes involved in the control of cell proliferation, differentiation, and survival. Retinoids mediate transcription through two classes of nuclear receptors, the retinoic acid receptors (RARα, RARβ, and RARγ) and the retinoid X receptors (RXRα, RXRβ, and RXRγ), which bind as RXR-RAR heterodimers to RA-response elements located in the promoter region of RA target genes. Like most nuclear receptors, RARs and RXRs share a highly conserved structure (1), with ligand-binding (LBD) and DNA-binding (DBD) domains. In addition, they possess two autonomous transcription activation functions, AF-1 and AF-2. AF-1, located at the N-terminal end (A/B region), is ligand-independent; in contrast, AF-2, located in the C-terminal E region, is ligand-dependent (1).

Ligand binding induces conformational changes in the LBD involving helix H12, which encompasses the core of AF-2 of the nuclear receptor, resulting in the creation of a new surface for the recruitment of coactivators, such as proteins of the p160 family (SRC-1 (steroid receptor coactivator-1)/NCoA1, TIF2/GRIP-1/SRC-2, and p/CIP/RAC3/ACTR/AIB-1/TRAM-1) and CBP (cAMP-response element-binding protein-binding protein/p300 (2–4). These coactivators are also associated with other large histone acetyltransferase complexes (such as the pCAF complex) that lead to chromatin condensation (5, 6).

Nuclear receptors further recruit an additional complex variously termed TRAP, DRIP, SMCC, or Mediator, which establishes contacts with RNA polymerase II and the general transcription factors (7, 8).

We previously showed that a small protein (15 kDa) belonging to the family of intracellular lipid-binding proteins that bind small hydrophobic molecules such as retinoids and fatty acids (9), cellular retinoic acid-binding protein II (CRABPII), also acts as a coactivator of nuclear retinoid receptors (10). Indeed, CRABPII can be found in the nucleus (10, 11) and more specifically in the RA-dependent nuclear complex (10). Moreover, we (10) and others (12–14) have shown that overexpression of CRABPII enhances transactivation of RA target genes by RXR-RAR heterodimers either in transfected cells or in human hematopoietic cells. This cofactor effect results from a physical interaction of CRABPII with the LBD of RARα or RXRα (15), which releases all-trans-RA from CRABPII to RARα (13). To explain the function of this novel ligand-binding coactivator, we proposed the following scenario (15). First, holocRABPII docks to the apo-receptors bound to their promoters in the nucleus; the docking occurs around key structures of the ligand entrance pockets of CRABPII and the nuclear receptor. This establishes a channel that allows the release of RA from holo-CRABPII to apo-RARα or apo-RXRα. Because the CRABPII-nuclear RAR interaction does not require the presence of RA (10), apo-CRABPII could remain bound to the holoreceptor, preventing dissociation of RA from the nuclear receptor. Thus, CRABPII would increase the stability of the DNA-bound RXR-RAR complex (10), further contributing to the enhancement of RA-mediated transcription.

As identifying cell-specific partners of CRABPII in the RA-dependent nuclear complex may help to understand the novel control of RA signaling, we performed a yeast two-hybrid
screen of a hematopoietic HL-60 cDNA library using human CRABPII as bait and have subsequently identified human cyclin D3 as a novel partner of CRABPII. We found that cyclin D3 interacts with CRABPII in a ligand-independent manner. No interaction was noted with other D-type cyclins (D1 or D2). Interestingly, cyclin D3 was also found to interact with RXRa, but not with RXRb, and only in a RA-dependent manner. Cyclin D3 enhanced RA-mediated transactivation of RA target genes by increasing the interaction of CRABPII with RARs. Furthermore, we show that cyclin D3 expression contributes to the induction of differentiation in HL-60 cells. Our results identify cyclin D3 as a partner of a ternary complex with the coactivator CRABPII and the nuclear receptor RXRa and demonstrate another level of transcriptional control during RA-induced differentiation and arrest of cell growth.

**EXPERIMENTAL PROCEDURES**

**Antibodies and Reagents—**Mouse monoclonal antibodies directed against CRABPII (5CRA3B3) and rabbit polyclonal antibodies directed against the F region of RXRa (RPxRaF) or the A region of RXRb (RPxRbA) (a gift from P. Chambon) were described as were RA (10). Rabbit polyclonal antibodies directed against cyclins D1-D3 (sc-117, sc-181, and sc-182, respectively) and goat polyclonal antibody directed against cyclin D3 (sc-182-G) were from Santa Cruz Biotechnology (Santa Cruz, CA). Rabbit polyclonal antibody directed against actin (A-2066) was from Sigma (St. Quentin Fallavier, France). All-trans-RA and 9-cis-RA were supplied by Hoffman-La Roche (Basel, Switzerland).

**Plasmids—**The expression vectors for RXRα (pSG5-hRARα), RXRβ (pRXRa-STOP-CAT-CL), and CRABPII (pTL1-CRABPII) were provided by P. Chambon. Plasmids encoding cyclins D1-D3 (pRC/CMV-hepcyclinD1, pRC/CMV-hepcyclinD2, and pRC/CMV-hepcyclinD3, respectively) (16) were provided by M. E. Ewen. The hRARβ2-luciferase reporter construct (17) was provided by H. de The Plasmids encoding GST-hRARβ, GST-hRARαDEF, and GST-mRARβ (18, 19) were provided by P. Chambon. The plasmid encoding hRARβ1 was previously described (15). hRARβ1 was amplified by PCR from NC4 cells and cloned into the yeast pAS2-1 plasmid (Clontech), which contains the TRP1 marker and directs synthesis of Gal4DBD fusion proteins. The following primers were used: 5′-CCCGAATTCTAGCTCACTTCGTTCCG3′ (forward) and 5′-AGTG-GATCCATTCACGGCTGAGATGACCT3′ (reverse). hRARβ1 was cloned into the same vector after PCR amplification from pSG5-hRARα using the following primers: 5′-CCCCGAAATTCTAGCTCACTTCGTTCCG3′ and 5′-AGTG-GATCCATTCACGGCTGAGATGACCT3′. All constructs were generated using standard cloning procedures and verified by restriction enzyme analysis and DNA sequencing.

**Yeast Two-hybrid Screening—**Yeast reporter strain Y190 (HIS3, lacZ, trp1, leu2, cyr2) was previously described by Harper et al. (20). Transformation was carried out using the lithium acetate procedure (21), and expression of the fusion proteins was checked by immunoblotting. Standard media (Clontech) were used for yeast growth according to the manufacturer’s protocols.

**Two-hybrid Screening—**An HL-60 Gal4ADAD fusion library (a gift from J.-M. Garnier and P. Chambon) was inserted into the pACT2 vector, which contains the LEU2 marker and a cassette expressing nuclear localized Gal4ADAD preceding a polylinker with cloning sites, vector, which contains the sequence encoding human cyclin D3 (accession number M all-RA. We analyzed colonies that grew in the presence or absence of 1 μM all-trans-RA. Bound proteins were recovered in SDS loading buffer, resolved by 12% SDS-PAGE, and analyzed by immunoblotting or blue exclusion dye test.

**RESULTS**

**Identification of Cyclin D3 as a CRABPII-binding Protein in Yeast Two-hybrid Screening—**The yeast two-hybrid system was used to identify proteins that interact with hCRABPII. Gal4DBD fused amino-terminally to hCRABPII in the pAS2-1 vector was expressed in yeast strain Y190, which contains two reporter genes: a HIS3 reporter gene and a lacZ reporter gene, both under the control of Gal4-binding sites. No growth was observed on plates lacking histidine (either in the absence or presence of 3-AT, a competitive inhibitor of the HIS3 gene product), indicating that hCRABPII on its own does not trans-activate the HIS3 gene (data not shown). An HL-60 cDNA library was constructed in the pACT2 vector that directs synthesis of polypeptides fused to Gal4ADAD. Y190 yeast cells expressing hCRABPII were transformed with this library.

Approximately 1.0 × 10^8 Y190 yeast transformants were spread on His− plates containing 25 mg 3-AT in the absence or presence of 1 μM all-trans-RA. We analyzed colonies that grew on selective medium in the presence of 1 μM all-trans-RA and that turned blue when tested in a β-galactosidase assay. Plasmids were recovered from the few positive clones, amplified, subjected to restriction analysis, and sequenced. Sequence comparison with the GenBankTM/EBI Data Bank and the Swiss Protein Database identified one 0.651-kb cDNA insert as the sequence encoding human cyclin D3 (accession number NM_001760). This cDNA fragment depicted the known open reading frame encoded by the cDNA as a Raf substrate.
Cyclin D3 Interacts Specifically with CRABPII and the DEF Regions of RARs in Yeast—To confirm the interaction of cyclin D3 with CRABPII, the Gal4AAD-cyclin D3 hybrid protein was expressed in the Y190 yeast strain in combination with the Gal4DBD-CRABPII hybrid protein. Both proteins interacted as evidenced by growth of colonies on histidine-deficient medium and activation of the HIS3 reporter gene. Area 1, pAS2-1RAR-DEF plus pACT2-cyclinD3; area 2, pAS2-1 plus pACT2-cyclinD3; area 3, pAS2-1CRABPII plus pACT2-cyclinD3. Specific interactions were observed only with the following hybrid pairs: RARs-DEF plus cyclin D3 (area 2) and CRABPII plus cyclin D3 (area 3).

Cyclin D3 Interacts with CRABPII in the Presence or Absence of RA in Vitro—To study further the data obtained with the yeast two-hybrid system, binding assays with human cyclin D3 and hCRABPII were performed in vitro with recombinant proteins. 35S-Labeled cyclin D3 produced by in vitro translation in rabbit reticulocytes was incubated with the GST-hCRABPII fusion protein attached to glutathione-Sepharose beads. Bound cyclin D3 was revealed by autoradiography after SDS-PAGE. In agreement with the two-hybrid data, human cyclin D3 interacted with hCRABPII (Fig. 2). Beads loaded with the control GST protein did not retain cyclin D3 (Fig. 2, lane 2). This interaction occurred either in the presence (data not shown) or absence (Fig. 2, lane 3) of RA. No interactions were identified with various hCRABPII deletion mutants fused to GST corresponding to the nuclear receptor-interacting domains and the LBD of hCRABPII (15) (data not shown), suggesting that the complete structure of hCRABPII is essential for its interaction with cyclin D3. Interestingly, no interactions were observed under the same conditions with cyclins D1 and D2 (Fig. 2), suggesting that CRABPII interacts with only one type of D-type cyclin, cyclin D3.

Cyclin D3 Interacts with the DEF Regions of RARs in the Presence of RA in Vitro—Binding assays with cyclin D3 and the DEF regions of RAR were also performed in vitro. Extracts from COS-6 cells overexpressing the different cyclins (D1–D3) were incubated with the GST-RARs fusion protein attached to glutathione-Sepharose beads in the presence or absence of all-
trans-RA (Fig. 3). Bound cyclins were revealed by immunoblotting. No interaction was detected in the absence of RA (Fig. 3A, lane 2). However, a RA-dependent interaction was observed between RARα and cyclin D3 (Fig. 3A, lane 3). No interaction was detected with cyclins D1 and D2 (data not shown).

To identify which RARα domain is involved in the interaction with cyclin D3, several GST fusion proteins carrying deletions of RARα were tested in the presence or absence of RA. Compared with full-length RARα, RARα with its DBD and LBD deleted (RARαAB) (Fig. 3B) was impaired in its ability to interact with cyclin D3 (Fig. 3C, lanes 5 and 6). In contrast, the LBD of RARα (RARαDEF) retained its capacity to bind cyclin D3 in the presence of RA (Fig. 3C, lanes 7 and 8). Similarly, a RARαDEF mutant bearing an internal deletion of the core motif (RARαDEFΔ(408–416)) (Fig. 3B) involved in the recruitment of coactivators retained the RA-dependent interaction with cyclin D3 (Fig. 3C, lanes 9 and 10). Altogether, these results suggest that the interaction with cyclin D3 involves a motif located in the LBD, distinct from the AF-2 domain core, but whose accessibility depends on RA binding. It must be noted that, under the same conditions, cyclin D3 did not interact with GST-RXRα even in the presence of 9-cis-RA (Fig. 3A, lanes 4 and 5), indicating that cyclin D3 interacts in vitro specifically with RARα.

Human Cyclin D3 Co-immunoprecipitates with Both CRABPII and RARα in Vivo—The interaction of cyclin D3 with CRABPII and RARα was further investigated in co-immunoprecipitation experiments using COS-6 cells overexpressing cyclin D3 either alone or in combination with RARα or CRABPII and treated or not with RA. Extracts were immunoprecipitated with anti-cyclin D3 antibody and analyzed by SDS-PAGE/immunoblotting (Fig. 4).

Anti-cyclin D3 antibody immunoprecipitated both cyclin D3 and RARα from extracts of COS-6 cells cotransfected with the corresponding expression vectors and treated with RA (Fig. 4A). These proteins were not revealed in control immunoprecipitations. Similarly, anti-cyclin D3 antibody co-immunoprecipitated CRABPII when both proteins were coexpressed in COS-6 cells (data not shown). Such a co-immunoprecipitation occurred whether the cells were treated or not with RA, corroborating the results obtained in two-hybrid and GST pull-down assays.

When both RARα and CRABPII expression vectors were cotransfected with cyclin D3 in COS-6 cells, anti-cyclin D3 antibody co-immunoprecipitated the three proteins (Fig. 4B). It must be noted that this co-immunoprecipitation was observed whether or not the cells were treated with RA. Such a ligand-independent co-immunoprecipitation of RARα with cyclin D3 and CRABPII may reflect the RA-independent interaction of the receptor with CRABPII (10, 15). Thus, one can hypothesize that, in vivo, in the absence of RA, CRABPII forms a bridge between RARα and cyclin D3.

Cyclin D3 Enhances the Transactivation of RA Target Genes through CRABPII—We previously demonstrated that CRABPII acts as a coactivator for RA-mediated transactivation of target genes in HL-60 cells through its binding to RARs (10).

Having shown herein that RARα forms a complex not only with CRABPII, but also with cyclin D3, we studied the effects of cyclin D3 on RARα transactivation in either the absence or presence of RA. As shown in Fig. 5, cotransfection of cyclin D3 with RARα was sufficient to allow RA-dependent transactivation of the RARresponsive enhancer of the pRE-luciferase reporter gene (Fig. 5B, lanes 7 and 8). When RARα was cotransfected with cyclin D3 and CRABPII, transactivation of the RARE was increased in the absence of RA (Fig. 5B, lane 9). Together, these results indicated that cyclin D3 enhances the transactivation of RA target genes through CRABPII.
presence of CRABPII. HL-60 cells were transiently transfected with the hRARα and cyclin D3 expression vectors and treated or not with RA. Whole cell extracts were incubated with goat anti-cyclin D3 antibody and then with protein G-Sepharose beads (lanes 3 and 5). Control immunoprecipitations (IP) were performed with anti-cyclin D2 antibody (lanes 2 and 4). The immunocomplexes were resolved by SDS-12% PAGE, transferred to nitrocellulose membranes, and immunoblotted with anti-cyclin D3 or anti-RARα antibody. B, COS-6 cells were cotransfected with the CRABPII, RARα, and cyclin D3 expression vectors and treated or not with all-trans-RA as indicated. Whole cell extracts were immunoprecipitated as described for A and immunoblotted with anti-cyclin D3, anti-RARα, or anti-CRABPII antibody.

Cyclin D3 Stabilizes the CRABPII-RARα Interaction—To investigate further how cyclin D3 enhances the transactivation of RA target genes through CRABPII, in vitro GST pull-down assays were performed. 35S-Labeled RARα produced by in vitro translation in rabbit reticulocytes was incubated with the GST-
hCRABPII fusion protein immobilized on glutathione-Sepharose beads in the presence or absence of COS-6 extracts overexpressing cyclin D3 (Fig. 6). As expected, in the absence of cyclin D3, RARα interacted with CRABPII, independently of RA (Fig. 6, lanes 2 and 3) (10). However, higher amounts of RARα were retained in the presence of cyclin D3 in a RA-independent manner (Fig. 6, lanes 4 and 5). Therefore, cyclin D3 appears to increase the efficiency of the formation of the CRABPII-RAR complexes in vitro. These data confirm the results from the in vivo assay showing the formation of the ternary complex involving RAR, CRABPII, and cyclin D3 (Fig. 4B). Such a process might be required for the increase in the transactivation of RA target genes observed with cyclin D3 in the presence of CRABPII.
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DISCUSSION

In this study, we isolated human cyclin D3 as a CRABPII-interacting protein. A physical RA-independent interaction between cyclin D3 and CRABPII was evidenced both in vitro and in vivo. No interactions were observed with various CRABPII deletion mutants, suggesting that the complete structure of CRABPII is essential for its interaction with cyclin D3. Furthermore, no interactions were identified between CRABPII and cyclin D1 or D2 in vitro. These data suggest that the retinoic acid-independent CRABPII-cyclin D3 interaction is specific for only one member of δ-type cyclins.

Interestingly, we also demonstrated that cyclin D3 interacted with RARα, but not with RXRα. Once again, cyclin D3 was the only δ-type cyclin that could interact with RARα. This interaction involved the DEF region of RARα and was observed in vitro as well as in yeast cells. Although the CRABPII-cyclin...
D3 interaction was RA-independent, the cyclin D3-RARα interaction required the presence of RA both in vitro and in vivo. Although cyclin D3 interacted physically with RARs in a RA-dependent manner, this interaction did not require the AF-2 “core” harboring the LXXLL motif of RARα generally implicated in the ligand-dependent interaction between the nuclear receptors and the LXXLL motifs of their coactivators. RA may, however, be required to induce conformational changes around the AF-2 domain to facilitate the cyclin D3-RARα interaction. Surprisingly, the presence of CRABPII allowed cyclin D3 and RARα to interact in the absence of RA. Because CRABPII interacted with both RARα and cyclin D3 in a RA-independent manner, we hypothesize that CRABPII facilitates the recruitment of cyclin D3 on RARα both in the absence and presence of RA.

As we have previously identified a coactivator function of CRABPII for the nuclear RA-RAR complexes, the interaction between cyclin D3, CRABPII, and RARα led us to investigate the role of cyclin D3 in RA-mediated transactivation. On its own, cyclin D3 had no effect on RA-mediated transactivation. By contrast, CRABPII and CRABPII and enhances the cyclin D3 coactivator transactivation activity.

This is the first study demonstrating that cyclin D3 is involved in nuclear receptor transcriptional regulation. Another α-type cyclin (D1) has been described as a bridging factor between the estrogen receptor and its coactivators to positively regulate nuclear receptor-mediated transactivation. Similar functions can be found between cyclins D1 and D3, as cyclin D1 binds estrogen receptor-α in the absence of ligand and enhances estrogen-dependent transactivation (16, 26, 27) and the estrogen receptor and one of its coactivators, SRC-1 (28). Cyclin D1 may also promote or stabilize the interaction between the estrogen receptor and p/CAF, thereby increasing the histone acetyltransferase activity of the transcriptional machinery (29). Conversely, cyclin D1 has also been reported to bind the androgen receptor through the N-terminal domain and to inhibit transactivation by directly competing for p/CAF binding (30, 31). Apart from being specific for RARα, cyclin D3 has other distinct features. In contrast to the interaction between cyclin D1 and SRC-1, which involves the LXXLL motif of cyclin D1 and the LXXLL motif of SRC-1 (32), the interaction between cyclin D3 and CRABPII is different, as cyclin D3 does not harbor any LXXLL motif and thus will not bind potential or candidate coactivators through their LXXLL motifs. Interestingly, CRABPII does not have a LXXLL motif, strongly suggesting that, for its interaction with cyclin D3, other recognition motifs are involved.

Therefore, the involvement of a α-type cyclin in the transcriptional control of ligands directly implicated in cell growth and differentiation provides a new concept in which cell cycle regulatory proteins could play a dual function. Indeed, although α-type cyclins are essential regulatory subunits of the cyclin-dependent kinases (33–35) and operate in mid-to-late G1 to allow cell progression in S phase (34, 36–38), the transactivation function of cyclin D1 was shown to be independent of CDK4 and Rb phosphorylation (16, 26, 27). Although cyclins D1 and D2 have been extensively studied, few reports are available for cyclin D3. Structurally related to cyclins D1 and D2, cyclin D3 appears nevertheless to be more ubiquitously expressed. Furthermore, although its role in cell proliferation is clearly evidenced in lymphocytes, it is mainly shown to accumulate in terminally differentiated tissues (23). This characteristic was corroborated in vitro during differentiation of rodent myoblasts in which cyclin D3 expression was induced and reported to play an important role in irreversible cell cycle arrest of differentiated myocytes (39–41). In this study, we confirm and extend previous data on HL-60 myeloid or F9 teratocarcinoma cells. Although all three cyclins could be detected in the nuclear compartment of different hematopoietic cells (HL-60, NB4, and U-937), only cyclin D3 expression paralleled the acquisition of differentiation features and the arrest of cell growth, as previously noted (23, 24). Retinoids act as regulators of cell growth, differentiation, and apoptosis and have been shown to specifically arrest myeloid cells in the G1 phase of the cell cycle (42). In the ML-1 myeloid cell line, the cell cycle arrest associated with all-trans-RA-induced differentiation involves regulation of the expression of cyclin D3 and cyclin kinase inhibitors (p18 and p21), affects the phosphorylation status of cyclin-dependent kinases, and ultimately triggers dephosphorylation of the Rb protein (43). Thus, in RA-mediated myeloid differentiation, the increased levels of cyclin D3 contrast with the cells’ progressive arrest in G1 and point to a distinct effect on the establishment and/or maintenance of the differentiated status of the cell. The former may be explained by titration of cyclin D3 by either the cyclin D3-RAR or CRABPII-cyclin D3 interaction, whereas the latter may be related to cyclin D3 transcription activity on RA target genes involved in either differentiation (RAR, CRABPII, CD11b, Hox, and granulocyte colony-stimulating factor genes (G-CSF)) and/or cell cycle inhibition (p21 and p27 genes) (44).

In summary, we have identified in this study a novel level of molecular control associating three distinct partners of RA-mediated transcription (cyclin D3, CRABPII, and RARα) that connects three key cellular processes: the cell cycle, ligand bioavailability, and gene expression. From our results and other published data (10, 15, 45), we may establish a physiological model (Fig. 8). After binding to RA, CRABPII translocates from the cytoplasm to the nucleus (45). Holo-CRABPII then docks to the apo-nuclear receptors bound to their promoters. Cyclin D3 forms a ternary complex and allows the stability of the CRABPII-RAR-R interaction to increase and thus to enhance the transactivation activity of the complex.

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REFERENCES

1. Chambon, P. (1996) FASEB J. 10, 940–954
2. Glass, C. K., and Rosenfeld, M. G. (2000) Genes Dev. 14, 121–141
3. Hermanson, O., Glass, C. K., and Rosenfeld, M. G. (2002) Trends Endocrinol. Metab. 13, 55–60
4. McKenna, N. J., and O’Malley, B. W. (2002) Cell 108, 465–474
5. Narlikar, G. J., Fan, H. Y., and Kingston, R. E. (2002) Cell 108, 475–487
6. Dihlworth, F. J., and Chambon, P. (2001) Oncogene 20, 3047–3054
7. Woychik, N. A., and Hampsky, M. (2002) Cell 108, 453–463
8. Malik, S., and Roeder, R. G. (2000) Trends Biochem. Sci. 25, 277–283
9. Napoli, J. L. (1999) Biochim. Biophys. Acta 1440, 139–162
10. Delva, L., Bastie, J.-N., Rochette-Egly, C., Krausa, B., Baltriraud, N., Despoy, G., Chambon, P., and Chomienne, C. (1999) Mol. Cell. Biol. 19, 7158–7167
11. Gaub, M. P., Lutz, Y., Ghyselfinck, N. B., Scheuer, I., Pfister, V., Chambon, P., and Rochette-Egly, C. (1999) J. Histochem. Cytochem. 46, 1103–1111
12. Jing, Y., Waxman, S., and Mira-y-Lopez, R. (1997) Cancer Res. 57, 1668–1672
13. Dong, D., Ruuska, S. E., Levinthal, D. J., and Noy, N. (1999) J. Biol. Chem. 274, 26395–26398
14. Wolf, G. (2000) Natu. Rev. 58, 151–153
15. Bastie, J.-N., Despoy, G., Baltriraud, N., Rochette-Egly, C., Chomienne, C., and Delva, L. (2001) FEMS Lett. 507, 67–73
16. Neuman, E., Lauha, M. H., Lin, N., Upton, T. M., Miller, S. J., DiBenno, J., Pestell, R. G., Hinds, P. W., Dowdy, S. F., Brown, M., and Ewen, M. E. (1997) Mol. Cell. Biol. 17, 5338–5347
17. de Thé, H., Vivanco-Ruiz, M. M., Tollius, P., Stunnenberg, H., and Dejean, A.
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(1990) Nature 343, 177–180
18. von Baur, E., Zechem, C., Heery, D., Heine, M. J., Garnier, J.-M., Vivat, V., Le Douarin, B., Gronemeyer, H., Chambon, P., and Losson, R. (1996) EMBO J. 15, 110–124
19. Bommer, M., Benecke, A., Gronemeyer, H., and Rochette-Egly, C. (2002) J. Biol. Chem. 277, 37961–37966
20. Harper, J. W., Adami, G. R., Wei, N., Keyomarsi, K., and Elledge, S. J. (1993) Cell 75, 805–816
21. Giertz, D., St. Jean, A., Woods, R. A., and Schiestl, R. H. (1992) Nucleic Acids Res. 20, 1425
22. Rousselot, P., Hardas, B., Patel, A., Guidez, F., Gaken, J., Castaigne, S., Dejean, A., de Thé, H., Dégou, L., Farzaneh, F., and Chomienne, C. (1994) Oncogene 9, 545–551
23. Bartkova, J., Lukas, J., Strauss, M., and Bartek, J. (1996) Oncogene 17, 1027–1037
24. Li, Y., Glozak, M. A., Smith, S. M., and Rogers, M. B. (1999) Exp. Cell Res. 253, 372–384
25. Kizaki, M., Ireda, Y., Tanosaki, R., Nakajima, H., Morikawa, M., Sakashita, A., and Koeffler, H. P. (1993) Blood 82, 3592–3599
26. Zwijsen, R. M., Wientjens, E., Klomp, R., van der Sman, J., Bernards, R., and Michalides, R. J. (1997) Cell 88, 405–415
27. Lamb, J., Ladha, M. H., McMahon, C., Sutherland, R. L., and Ewen, M. E. (2000) Mol. Cell. Biol. 20, 8667–8675
28. Ratajczak, T. (2001) Reprod. Fertil. Dev. 13, 221–229
29. McMahon, C., Suthiphongschai, T., DiRenzo, J., and Ewen, M. E. (1999) Proc. Natl. Acad. Sci. U. S. A. 96, 5382–5387
30. Petre, C. E., Wetherill, Y. B., Danielsen, M., and Knudsen, K. E. (2002) J. Biol. Chem. 277, 2207–2215
31. Reuten, A. T., Plu, M., Wang, C., Albanese, C., McPhaul, M. J., Sun, Z., Balk, S. P., Janne, O. A., Palivo, J. J., and Pestell, R. G. (2001) Mol. Endocrinol. 15, 797–811
32. Zwijsen, R. M., Buckle, R. S., Hjimans, E. M., Loomans, C. J., and Bernards, R. (1998) Genes Dev. 12, 3488–3498
33. Pines, J. (1995) Biochem. J. 308, 697–711
34. Sherr, C. J. (1996) Science 274, 1672–1677
35. Sherr, C. J. (1994) Cell 79, 551–555
36. Bartek, J., Bartkova, J., and Lukas, J. (1996) Curr. Opin. Cell Biol. 8, 805–814
37. Weinberg, R. A. (1995) Cell 81, 323–330
38. Sherr, C. J., and Roberts, J. M. (1992) Genes Dev. 6, 1501–1512
39. Jahn, L., Sadoshima, J., and Izumo, S. (1994) Exp. Cell Res. 212, 297–307
40. Kiess, M., Gill, R. M., and Hamel, P. A. (1995) Oncogene 10, 159–166
41. Rao, S. S., and Kohitz, D. S. (1995) J. Biol. Chem. 270, 4093–4100
42. Dimberg, A., Bahram, F., Karlberg, I., Larsson, L. G., Nilsson, K., and Oberg, F. (2002) Blood 99, 2199–2206
43. Shimizu, T., Awai, N., and Takeda, K. (2000) Oncogene 19, 4640–4646
44. Melnick, A., and Licht, J. D. (1999) Blood 93, 3167–3215
45. Budhu, S. A., and Noy, N. (2002) Mol. Cell. Biol. 22, 2632–2641
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