Deletion of the Cancer-amplified Coactivator AIB3 Results in Defective Placentation and Embryonic Lethality*

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The amplified in breast cancer-3 (AIB3, ASC-2, RAP250, PRIP, TRBP, NRC, or NcoA6) gene is characterized as a cancer-amplified transcriptional coactivator for nuclear receptors, which include the peroxisome proliferator-activated receptor γ (PPARγ). To assess its biological function, we deleted the AIB3 gene in mice by homologous recombination. AIB3−/− mice are developmentally normal and fertile. AIB3−/− embryos exhibit growth restriction and lethality during 9.75–11.5 days postconception. The embryonic lethality is probably at least in part due to the impairment of maternal blood sinuses, the massive erythrovascular network and cardiac hypoplasia. These defects are similar to those encountered in mice lacking PPARγ or the PPARγ-binding protein (PPB, TRAP220, or DRIP205). In addition, the transcriptional activities of PPARγ are significantly affected in mouse embryonic fibroblasts lacking AIB3. These results suggest that AIB3 is required for PPARγ function in placental development and for normal heart development. These results also indicate that the biological function of AIB3 is not redundant with other classes of nuclear receptor coactivators such as PBP and members of the steroid receptor coactivator family.

The AIB3 gene was initially identified from a highly amplified chromosomal region (20q11–12) in human breast tumor cells (1). In addition to amplification in 10% of breast cancers, AIB3 is amplified in 30% of colon cancers and 13% of lung cancers, suggesting that AIB3 may play an important role in cell growth and tumorigenesis (2, 3). AIB3 was subsequently characterized as a strong transcriptional coactivator for many nuclear receptors, including RXRα, PPARα, PPARγ, TRβ, and TRα, and therefore, designated as ASC-2 (3), RAP250 (4), PRIP (5), TRBP (6), NRC (7), and NcoA6. Apart from nuclear receptors, AIB3 also serves as a coactivator for other classes of transcription factors involved in the regulation of cell survival, proliferation, differentiation, and immune responses such as AP-1, serum response factor (SRF), CREB, C/EBPα, and NF-κB (6, 8, 9). These studies suggest that AIB3 may play important roles in multiple signaling pathways regulated by hormones, growth factors, and cytokines.

AIB3 is a widely expressed nuclear coactivator that mediates transcriptional activities of transcription factors through interaction with proteins including SRC-1, CBP, p300, DRIP130, TBP, and TFIIF (3, 4, 6, 7). SRC-1, CBP, and p300 possess intrinsic histone acetyltransferases and are important components of the coactivator complex that also contains other histone acetyltransferase activities such as pCAF and protein methyltransferases such as CARM1 (10–12). Recruitment of the SRC-1-CBP coactivator complex to the promoter by ligand-bound nuclear receptors facilitates local chromatin remodeling and target gene transcription (10, 11). DRIP130 is a component of the TRAP or DRIP coactivator complex that was thought to coactivate transcription by nuclear receptors and transcription factors through direct contact with general transcription factors (13, 14). Therefore, AIB3 may function through bridging both SRC-1-CBP and TRAP common coactivator complexes to the transcription factors and through interacting with the general transcription machinery (TBP and TFIIF).

Although studies based on protein-protein interactions and transient transfection assays provided basic conceptual knowledge concerning AIB3 function, the results from in vitro experiments may not be easily extrapolated to the in vivo physiological conditions. To study the biological function of AIB3, we have generated and characterized AIB3 null mice. We show that deletion of the AIB3 gene causes abnormal heart morphology, severe defects in placental development and embryonic lethality during 9.75–11.5 dpc, probably due to the impairment of PPARγ function.

**EXPERIMENTAL PROCEDURES**

**Construction of Targeting Vector and Homologous Recombination—**

The NoI-HSV.tk-SacII DNA fragment for a negative selection marker was subcloned into the parent plasmid pNTR-LacZ-PGKneo by using a linker with XhoI and SacII sites. The 7-kb AIB3 genomic DNA spanning exons 7–9 (GenBank TM NM_019825: 2718–2997 bp) was amplified by PCR from mouse embryonic stem (ES) cell DNA and inserted into a NotI site between the neo and the tk expression cassettes to serve as the 3′-targeting arm. The 5-kb AIB3 genomic DNA spanning exons 1–3 (GenBank TM NM_019825: 245–454 bp) was also amplified by PCR and subcloned into SalI and XhoI sites located 5′ to LacZ-PGKneo to serve as the 5′-targeting arm (Fig. 1A). The targeting vector was linearized by SotI digestion and electroporated into TC-1 ES cells as described previously (15, 16). Individual clones resistant to G418 and 1-2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodouracil were isolated. Targeted

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cloned by Southern blot using both 5' and 3' probes located in exon 1 (GenBank™ NM_018925: 24–240 bp) and exon 9 (GenBank™ NM_018925: 3001–3417 bp) and used to generate chimeric mice through microinjection as described previously (15, 16).

**Genotyping and Western Blots**—Genomic DNA was extracted from tail tips or yolk sacs. AIB3 wild type and mutant alleles were distinguished by PCR using allele-specific primer pairs (Fig. 1A). PCR with P11 (gctatgcatctctgatttg) and P12 (gctatgcatctctgatttg) amplifies a 262-bp band from the wild type allele, while PCR with P-neo (gctatgcatctctgatttg) and P11 amplifies a 550-bp band from the mutant allele. For Western blot, protein lysates were prepared from 9.5-dpc individual embryos and the amount of 0.1-mg protein for each sample was separated on SDS-PAGE. The blots were analyzed by using polyclonal antibodies against amino acids 714–999 and 1641–2083 of human TRBP (AIB3) (6).

**Histological Analysis and Immunohistochemistry**—Mouse embryos and placentas were fixed in 4% paraformaldehyde at 4 °C overnight and processed for paraffin sectioning at 5 μm for the hematoxylin and eosin staining. To prepare semithin sections, placentas were cut into pieces and fixed in 0.1 x cacodylate buffer (pH 7.4) containing 1.25% glutaraldehyde and 1% formaldehyde overnight at 4 °C, postfixed in the same buffer with 1% OsO₄ for 1 h, and embedded in an Epon mixture. Semithin sections were cut at 0.5 μm and stained with toluidine blue. Immunostaining was performed on rehydrated paraffin sections as described previously (17). The PCRM-1 monoclonal antibody (Phar-Mingen), VEGF-R2 (Flk-1) monoclonal antibody (PharMingen), smooth muscle α-actin monoclonal antibody (Zymed Laboratories Inc.), and phosphohistone H3 polyclonal antibody (Upstate Biotechnology) were applied according to manufacturers’ instructions.

**BrDU Labeling, TUNEL Assay, and In Situ Hybridization**—BrDU (Amersham Biosciences) was injected intraperitoneally into pregnant mice at 9.5 dpc in a dose of 0.5 mg/g body weight. Two hours after injection, mice were sacrificed and placentas processed for paraffin sectioning. A BrDU immunostaining kit (Zymed Laboratories Inc.) and a TUNEL assay kit (Roche Molecular Biochemicals) were used to detect proliferating cells and apoptotic cells, respectively. In situ hybridization was performed on rehydrated mouse placenta and heart sections by using 32P-labeled RNA probes.

**Isolation of Mouse Embryonic Fibroblasts (MEF) and Transient Transfections**—Primary MEFs were isolated from individual embryos at 9.75 dpc following digestion with 0.25% trypsin for 20 min at 37 °C. MEFs were cultured in DMEM with 10% fetal calf serum. Cells were transiently transfected with plasmid DNAs using the FuGENE 6 Transfection Reagent according to the product instruction (Roche Molecular Biochemicals).

**RESULTS**

**Generation of AIB3 Mutant Mice**—To generate AIB3 mutant mice, a targeting vector was constructed and used to disrupt the AIB3 gene through homologous recombination in ES cells (Fig. 1A). In the targeted allele, expression of the first three exons preceding the deletion region and encoding aa 1–170 is predicted. However, this N-terminal peptide does not contain structural domains for interaction with any transcription factors or for transcriptional activation (3–7). The 21.4-kb DNA region encoding Pro471-Leu496 was deleted by the targeting construct, which was confirmed by Southern blot and real-time RT-PCR (Fig. 1, B and C). The exons located downstream the deletion region for aa 896–2067 were disrupted and transcriptionally terminated by the insertion of the neo cassette with a signaling sequence for transcriptional termination (Fig. 1A), which was confirmed by the absence of the C-terminal domains for interaction with transcription factors, DNA-dependent protein kinases, and other protein complexes (6) in AIB3 knock-out embryos (Fig. 1D and data not shown). On Western blots probed with polyclonal antibodies against aa 714–999 and aa 1641–2063, the AIB3 protein was clearly detected in wild type and AIB3/−/− embryos, but not detected in AIB3/−/− embryos. Collectively, these data demonstrate that the targeted AIB3 allele can not produce any functional proteins.

From a total of 768 examined ES clones, four correctly targeted clones were identified and microinjected into recipient blastocysts to generate chimeric mice. Chimeric founders capable of germ line transmission were obtained from one independent ES clones and were crossed to wild type (AIB3+/+) C57BL/6 females to produce heterozygous (AIB3+/−) and AIB3−/− embryos at 9.5 dpc. One-step Taq-Man real-time RT-PCR was performed using total RNA samples with the ABI7700 Sequence Detection System (Applied Biosystems). Results were normalized to endogenous 18 S RNA amounts. The 3′ primer was gctatgcatctctgatttg, the TaqMan probe is gaattaagactgacagcaac. The 3′ primer was aaggatgtcatctctgatttg. D, Western blots using antibodies against TRBP (AIB3) C terminus (aa 1641–2063) and β-actin (loading control). The C terminus of AIB3 protein was not detectable in tissue lysates of AIB3−/− embryos.

**FIG. 1. Generation of AIB3 mutant mice.** A, structure of the wild type AIB3 allele, targeting vector, and recombinant AIB3 allele. Exons and locations of restriction sites and probes for Southern blot are indicated. Allele-specific PCR primer pairs, P12/P11 and P-neo/P11, were used for genotype analysis. Although the lacZ sequence was kpnI-Rked in the AIB3 locus, no β-galactosidase activity was detected in mutant lines. B, Southern blot using the 5′ probe after digestion of ES cell DNA with BstXI. Hybridization bands for wild type (wt) and knockout (ko) alleles are indicated. Southern blot using Apal digestion and the 3′ probe is not shown. C, relative amounts of AIB3 mRNA molecules in AIB3+/+, AIB3+/−, and AIB3−/− embryos at 9.5 dpc. One-step Taq-Man real-time RT-PCR was performed using total RNA samples with the ABI7700 Sequence Detection System (Applied Biosystems). Results were normalized to endogenous 18 S RNA amounts. The 3′ primer is gctatgcatctctgatttg. E, the TaqMan probe is gaattaagactgacagcaac. The 3′ primer is aaggatgtcatctctgatttg. D, Western blots using antibodies against TRBP (AIB3) C terminus (aa 1641–2063) and β-actin (loading control). The C terminus of AIB3 protein was not detectable in tissue lysates of AIB3−/− embryos.
embryos. However, the atrial and ventricular walls of AIB3−/− hearts were much thinner than those of normal hearts (Fig. 2, C and D). Especially, the compact zone of the ventricular wall was more severely affected. The trabeculae were not only thinner, but also deformed. In addition, a significant portion of the AIB3−/− endocardium was detached from the myocardium (Fig. 2D), suggesting that the requisite intimate interaction between the endocardium and the myocardium was affected.

To elucidate the cellular mechanisms responsible for the heart abnormalities, molecular markers for proliferation and differentiation of the myocardium were examined by performing immunostaining and in situ hybridization. Immunostaining of the Ser10-phosphorylated histone H3, a marker of cell mitosis (18), revealed that the cell proliferation rates of AIB3−/− myocardium were 24.4 ± 3.2% (n = 5 embryos), which was significantly lower than the proliferation rates of wild-type myocardium (36.1 ± 3%, n = 5, p < 0.001 by t test). However, immunostaining showed similar expression patterns of the smooth muscle α-actin in both wild type and AIB3−/− hearts (data not shown). In addition, the myosin light chain 2v (MLC2v), a contractile protein gene expressed in the striated muscle, was also equally expressed in both wild type and AIB3−/− ventricular myocardium (Fig. 2, E and F). These results suggest that the hypoplastic development of AIB3−/− hearts correlates with the decrease in myocardial proliferation. However, AIB3 may not be required for myocardial differentiation.

**Defective Placentaion in AIB3−/− Embryos—**Several classes of abnormalities were observed in AIB3−/− placentas. First, the essential labyrinthine layer in AIB3−/− placentas was not successfully developed. In AIB3+/− and AIB3−/− placentas, the labyrinthine layer was formed by 9.5 dpc and further developed into a densely packed thick structure with the fetal vascular network supported by spongiotrophoblasts and surrounded by maternal blood sinuses (Fig. 3, A, C, and E). Between the maternal blood sinuses and the fetal endothelium, the three-cell-layered epithelial barrier characteristic of mouse and human placental was tightly packed to warrant appropriate material exchanges between maternal and fetal blood (Fig. 3G). In contrast, the fetal blood vessels in AIB3−/− placentas did not successfully invade into the presumptive labyrinth, even by 10.5 dpc (Fig. 3, B, D, and F) as demonstrated by a lack of fetal vessels containing nucleated erythrocytes (Fig. 3, compare F with E). Immunostaining of endothelial cell markers, PECAM-1 and VEFG-F-R2, further confirmed that the fetal capillaries in AIB3−/− placentas were poorly developed in the labyrinth (Fig. 3, C and D, and data not shown). Although occasionally, a few AIB3−/− fetal vessels were able to grow into the labyrinthine layer, the invading chorionic villi were surrounded by excessively thickened trophoblast cell layers destroying the characteristic three-cell-layered epithelial barrier required for nutrition and oxygen exchange (Fig. 3H). Second, AIB3−/− maternal blood sinuses, which in normal placentas were compact and well defined (Fig. 3E), were often dilated or ruptured (Fig. 3F), sometimes expanding the entire zone to form huge blood pools in AIB3−/− placentas (not shown). AIB3−/− spongiotrophoblasts lining the wall of maternal blood sinuses were loosely attached or even detached (Fig. 3, compare I with J and see arrows). Third, the erythropoietic activity of spongiotrophoblasts and trophoblast giant cells, which is also an indication of vascular defects, was extremely active in AIB3−/− placentas. A number of maternal erythrocytes were observed in the cytoplasms of many trophoblast giant cells (42%), as demonstrated by in situ hybridization signals (black color) for the MLC2v gene in the ventricular V myocardium. RA and LA, right and left atrial chambers.

**Fig. 2.** A and B, mouse embryos at 10.5 dpc. All AIB3−/− embryos are smaller than AIB3+/− and AIB3−/− embryos at this stage. Large blood pools in hearts (asterisk) and pericardial effusion (arrow) were found in some AIB3−/− embryos (B). C and D, cross-sections of hearts showing abnormal AIB3−/− heart morphologies, including the thin ventricular wall (arrows) and detachment of the endocardium (*). E and F, bright field images showing in situ hybridization signals (black color) for the MLC2v gene in the ventricular (V) myocardium. RA and LA, right and left atrial chambers.

Table I

| Stages | n*   | Genotypes | Resorbed embryos⁴ |
|--------|------|-----------|--------------------|
|        |      | +/− | −/− | −/+ | −/− |
| 8.5 dpc | 48   | 11 | 24 | 10 | 3 (6%)⁵ |
| 9.5 dpc | 165  | 43 | 78 | 33 (1)% | 10 (6%) |
| 9.75 dpc | 125  | 31 | 60 | 26 (4)% | 4 (35)% |
| 10 dpc  | 131  | 33 | 61 | 19 (10) | 8 (6%) |
| 10.5 dpc | 112  | 27 | 57 | 5 (11) | 12 (11)% |
| 11.5 dpc | 64   | 15 | 30 | 2 (7) | 10 (16)% |
| 12.5 dpc | 41   | 9  | 18 | 0 (5) | 9 (22%) |
| Weaning⁵ | 204  | 63 | 141 | 0 | |

* Number of embryos or pups.
⁴ Resorbed embryos were not genotyped.
⁵ The percentile of resorbed to total embryos.
⁶ The number of dead AIB3−/− embryos.
⁷ The weaning was on day 21 after birth.

Overall distributions of the mPL-1-expressing trophoblast giant cells, the 4311-expressing spongiotrophoblasts, and the Mash2-expressing spongiotrophoblasts and labyrinthine trophoblasts in AIB3−/− placentas were similar to those in normal placentas, suggesting that AIB3 is not essential for the determination of trophoblast cell lineages (Fig. 3, M–R). However, a higher number of trophoblast giant cells, a lower number of spongiotrophoblasts, and a much lower number of labyrinthine trophoblasts were observed in AIB3−/− placentas, as reflected by the hybridization signals in AIB3−/− placentas. Accordingly, the proliferation rate of AIB3−/− trophoblast giant cells (42%)
was significantly higher than that of AIB3−/− trophoblast giant cells (27%) (Fig. 3, A and B). In contrast, the 25% proliferation rate of AIB3−/− spongiotrophoblasts was significantly lower than the 52% proliferation rate of AIB3+/+ spongiotrophoblasts (Fig. 3, A and B). These results indicate that the balance of three types of trophoblasts is disrupted in AIB3−/− placentas, and the population of labyrinthine trophoblasts is more severely affected in AIB3−/− placentas.

**Transcriptional Activities of PPARγ Are Attenuated in Cells Lacking AIB3**—To gain insight into the molecular mechanisms responsible for AIB3 function in PPARγ-regulated transcription, we isolated MEFs and assayed transcriptional activities of PPARγ in cells lacking AIB3. The transcriptional activities of PPARγ in AIB3+/+ and AIB3−/− MEFs were increased 20-fold after ligand treatment. However, the transcriptional activities of PPARγ in AIB3−/− MEFs were only increased 10-fold after ligand treatment (Fig. 4). These results suggest that PPARγ function is impaired in AIB3 null cells.

**DISCUSSION**

Recently, a number of coactivators have been shown to enhance transcriptional activation by many nuclear receptors and other transcription factors in a redundant fashion when they are overexpressed in cultured cells (10, 11). A significant challenge is to define the functional relationships among individual coactivators and transcription factors under physiological conditions. Previous studies have demonstrated that the function of coactivators of the SRC family are partially redundant, and mice lacking SRC-1, TIF2, or SRC-3 (p/CIP) are viable although they exhibit distinct phenotypes (15, 16, 19–21). In contrast, mice lacking the cancer-amplified coactivator AIB3 exhibit intrauterine growth restriction, hypoplastic heart development, defective placentation, and embryonic lethality during 9.75–11.5 dpc. These results indicate that AIB3 is essential for embryonic development beyond 9.75 dpc, and it is not functionally redundant with any other classes of coactivators such as the SRC family members.

Noticeably, mice lacking either PPARγ or its binding protein, PBP, are lethal at 10–11.5 dpc, and their lethality is largely attributed to defects in placental development (22, 23). Since AIB3 is highly expressed in the placenta (4), AIB3 serves as a coactivator for PPARγ (5), and AIB3−/− embryos die at a similar stage, we reasoned that AIB3 may play an important role in placentation through mediating PPARγ function. Analyses of placental structure, specific molecular markers for the fetal endothelium and trophoblasts, and PPARγ transcriptional activities in AIB3−/− cells confirmed this prediction and, therefore, provided the first in vivo evidence of AIB3 as a coactivator of PPARγ. Indeed, most histological defects observed in the placenta of AIB3−/− embryos are also observed in PPARγ

**Fig. 3.** Defects in the development of AIB3−/− placenta. A–F, placental histology. Genotypes and embryonic stages are indicated. In AIB3−/− placenta, the labyrinth layer (la) is not developed, the maternal blood sinuses (ms) are dilated, and the number of spongiotrophoblast cells (sp) are reduced (compare B with A, D with C, and F with E). A and B were immunostained with BrdUrd antibody and briefly counterstained with hematoxynlin. There are more BrdUrd-labeled trophoblast giant cells (gi) and less labeled spongiotrophoblast (sp) and labyrinthine trophoblast (la) cells in AIB3−/− placentas (B with A). C and D were immunostained with FECAM-1 antibody and counterstained with methyl green. E and F were stained with the hematoxylin and eosin. ch., choric plate. Bars, 100 μm. G–L, toluidine-stained semithin sections of placentas at 9.75 dpc. G and H compare the three-cell-layered (I, II, and III) epithelial barriers formed by labyrinthine trophoblasts between the maternal blood sinuses (ms) and fetal blood vessels (fv) in wild type (G) and AIB3−/− (H) placentas. nu, nucleated fetal erythrocytes; me, maternal erythrocytes; en, fetal endothelium. I and J compare the structure of blood sinuses in wild type (I) and AIB3−/− (J) placentas, showing the loosely attached or detouched syncytiotrophoblasts (arrows) in AIB3−/− placentas. K and L show the active erythrophagocytosis (*) of AIB3−/− trophoblast cells (K) and trophoblast giant cells (gi in L). M–R, in situ hybridization of trophoblast markers at 9.5 dpc. The layer of PL-1-expressing trophoblast giant cells (gi) is thicker in AIB3−/− placenta (N) than in AIB3−/− placenta (M). There are more 4511-expressing spongiotrophoblast cells (sp) in AIB3−/− placenta (O) than in AIB3−/− placenta (P). Mash-2-expressing cells, including spongiotrophoblast and labyrinthine trophoblast (la) cells, are also much less in AIB3−/− placenta (R) than in AIB3−/− placenta (Q).
and/or PBP mutant mice (22, 23), which include: failure of
labyrinth formation, dilation of maternal blood sinuses, and
erythropoagocytosis by trophoblasts. The reproducibility of
the placental phenotypes in AIB3, PBP, and PPARγ knock-out
models strongly suggests that these three proteins function
through a linear signaling pathway in vivo. These data dem-
strate that AIB3 is essential for the development and main-
tenance, since in the developing heart, the failure of the
placenta is a low resistance vascular network. The lack or
reduction of this low resistance vasculature system may cause
an increase in afterload for the developing heart and, therefore,
contribute to the disintegration of myocardial architecture
through a mechanical effect.

However, the defect in the placenta labyrinth alone may not
fully explain the severe growth restriction of AIB3−/− embryos,
because other mouse mutants lacking PPARγ, PBP, and Mash2
with very similar placentaion defects exhibit only mild or no
growth retardation (22, 23, 26). On the other hand, defects in
the yolk sac vasculature frequently cause growth restriction in
fetuses and dilatation of the pericardium. Indeed, about 15–
20% of AIB3−/− embryos exhibit pericardial effusion, suggest-
ing that AIB3 may also play some role in the yolk sac de-
velopment and function. Since PPARγ is not expressed in the
yolk sac, and mice lacking PPARγ and PBP have no yolk sac abnor-
malities (22, 23), the coactivator function of AIB3 in the yolk
sac may be associated with other unknown transcription
factors. Therefore, future studies on other parts of AIB3−/− em-
byros in which PPARγ is not expressed will gain more insight
into the functional relationships between AIB3 and other in-
teractive transcription factors.

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REFERENCES
1. Guan, X. Y., Melzter, P. S., Dalton, W. S., and Trent, J. M. (1994) Nat. Genet.
8, 155–161
2. Guan, X. Y., Xu, J., Anzick, S. L., Zhang, H., Trent, J. M., and Melzter, P. S.
(1996) Cancer Res. 56, 3446–3450
3. Lee, S. K., Anzick, S. L., Choi, J. E., Bubendorf, L., Guan, X. Y., Jung, Y. K.,
Kallioniemi, O. P., Kanonan, J., Trent, J. M., Ansatsu, D., Ihn, B. H.,
Cheong, J. H., Lee, Y. C., Melzter, P. S., and Lee, J. W. (1999) J. Biol. Chem.
274, 34283–34289
4. Carra, P., Antonsson, P., Feljo-Huikkko, M., Treuter, E., and Gustafsson, J. A.
(2000) J. Biol. Chem. 275, 5308–5317
5. Zhu, Y., Kan, L. Q., Kanwar, Y. S., Yeildanda, A. Y., Rao, M. S., and Reddy,
J. K. (2000) J. Biol. Chem. 275, 13510–13516
6. Ke, L., Cardina, G. R., and Chin, W. W. (2000) Proc. Natl. Acad. Sci. U. S. A.
97, 6212–6217
7. Mahajan, M. A., and Samuelis, H. H. (2000) Mol. Cell. Biol. 20, 5048–5063
8. Lee, S. K., Na, S. Y., Jung, S. Y., Choi, J. E., Ihn, B. H., Cheong, J. Melzter,
P.S., Lee, Y. C., and Lee, J. W. (2000) Mol. Endocrinol. 14, 915–925
9. Hong, S., Lee, M. Y., and Cheong, J. (2001) Biochem. Biophys. Res. Commun.
282, 1257–1262
10. Xu, J., and O’Malley, B. W. (2002) Rev. Endocr. Metab. Disord. 3, 183–190
11. McKenna, N. J., and O’Malley, B. W. (2002) Cell 108, 465–474
12. Koh, S. S., Chen, D., Lee, Y. H., and Stallcup, M. R. (2001) J. Biol. Chem.
276, 1089–1098
13. Fondell, J. D., Ge, H., and Roeder, R. G. (1996) Proc. Natl. Acad. Sci. U. S. A.
93, 8282–8283
14. Bachr, C., Sudfan, Z., Ward, J., Chang, C. P., Burakov, D., Erdjument-
Bromage, H., Tempst, P., and Freedman, L. P. (1998) Genes Dev. 12,
1787–1800
15. Xu, J., Qiu, Y., DeMayo, F. J., Tsai, S. Y., Tsai, M. J., and O’Malley, B. W.
(1998) Science 279, 1922–1925
16. Xu, J., Liao, L., Ning, G., Yoshida-Komiya, H., Deng, C., and O’Malley, B. W.
(2000) Proc. Natl. Acad. Sci. U. S. A. 97, 6378–6384
17. Yuan, Y., Liao, L., Tulsia, D. A., and Xu, J. (2002) Circulation 105, 2653–2659
18. Ajiro, K., Yoda, K., Usami, K., and Nishikawa, Y. (1996) J. Biol. Chem.
271, 12397–12301
19. Qi, C., Zhu, Y., Pan, J., Yeildanda, A. Y., Rao, M. S., Maeda, N., Subharao, V.,
Pulkuri, S., Hashimoto, T., and Reddy, J. K. (1999) Proc. Natl. Acad. Sci.
U. S. A. 96, 1588–1590
20. Gehin, M., Mark, M., Mannfeldt, C., Dierich, A., Gronemeyer, H., and
Chambon, P. (2002) Mol. Cell. Biol. 22, 5923–5937
21. Wang, Z., Rose, D. W., Hermanson, O., Liu, F., Herman, T., Wu, W., Sato, D.,
Gleiserman, A., Krones, A., Pratt, K., Rosenfeld, R., Glass, C. R., and
Rosenfeld, M. G. (2000) Proc. Natl. Acad. Sci. U. S. A. 97, 13549–13554
22. Barak, Y., Nelson, M. C., Ong, E. S., Jones, Y. Z., Ruiz-Lozano, P., Chien, K. R.,
Koder, A., and Evans, R. M. (1999) Mol. Cell 4, 585–595
23. Zhu, Y., Qi, C., Jia, Y., Nye, J. S., Rao, M. S., and Reddy, J. K. (2000) J. Biol.
Chem. 275, 14779–14782
24. van Lijnschoten, G., Arends, J. W., and Geraedts, J. P. (1994) Am. J. Obstet.
Gynecol. 170, 1534–1542
25. Kress, C., Macara, L. M., Leiser, R., Bowman, A. W., Greer, I. A., and
Kinghorn, J. C. (1996) Am. J. Obstet. Gynecol. 175, 1534–1542
26. Guillenet, F., Nagy, A., Auerbach, A., Rossant, J., and Jeynor, L. (1994)
Nature 371, 333–336
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