Lymphoid Enhancer Factor-1 Blocks Adenomatous Polyposis Coli-mediated Nuclear Export and Degradation of β-Catenin

REGULATION BY HISTONE DEACETYLASE 1*

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The oncogenic protein β-catenin is overexpressed in many cancers, frequently accumulating in nuclei where it forms active complexes with lymphoid enhancer factor-1 (LEF-1)/T-cell transcription factors, inducing genes such as c-myc and cyclin D1. In normal cells, nuclear β-catenin levels are controlled by the adenomatous polyposis coli (APC) protein through nuclear export and cytoplasmic degradation. Transient expression of LEF-1 is known to increase nuclear β-catenin levels by an unknown mechanism. Here, we show that APC and LEF-1 compete for nuclear β-catenin with opposing consequences. APC can export nuclear β-catenin to the cytoplasm for degradation. In contrast, LEF-1 anchors β-catenin in the nucleus by blocking APC-mediated nuclear export. LEF-1 also prevented the APC/CRLM-independent nuclear export of β-catenin as revealed by in vitro assays. Importantly, LEF-1-bound β-catenin was protected from degradation by APC and axin in SW480 colon cancer cells. The ability of LEF-1 to trap β-catenin in the nucleus was down-regulated by histone deacetylase 1, and this correlated with a decrease in LEF1 transcription activity. Our findings identify LEF-1 as a key regulator of β-catenin nuclear localization and stability and suggest that overexpression of LEF-1 in colon cancer and melanoma cells may contribute to the accumulation of oncogenic β-catenin in the nucleus.

β-Catenin accumulates to excessive levels in different cancers, including melanomas, colon cancer, breast cancer, and hepatocarcinomas (1–3). Whether overexpressed in cancer (2, 3), in transfected cells (4), or in transgenic mice (5), the induced β-catenin accumulates throughout the cell with frequent concentration in the nucleus. β-Catenin is thought to be the key mediator of the Wnt signaling pathway (3), and when overexpressed it can cause cell transformation (6). The oncogenic potential of β-catenin is mediated by its association with a class of related (but not identical) transcription factors that include lymphoid enhancer factor-1 (LEF-1), and the T cell factors including TCF-1, -3, and -4 (3). Of these, LEF-1 is of particular interest as it is overexpressed in colon cancer cell lines (7) and colon tumors (8), and in metastatic melanoma cells (9), and is known to form nuclear β-catenin-LEF-1 complexes in vivo, which activate transcription of various transforming genes, including cyclin D1 (10) and c-myc (11).

β-Catenin overexpression results from stabilizing cancer mutations within the β-catenin gene (see Ref. 2) or in genes that regulate its degradation such as APC and axin (see Ref. 3). Recently, we and others showed that the nuclear build-up of β-catenin is normally prevented by a combination of nuclear export and cytoplasmic distinct degradation (12–14). β-Catenin can exit the nucleus by two distinct pathways: the CRM1 export pathway, which requires its association with the shuttling protein APC (12–14), and an alternative CRM1-independent export route (15, 16). Despite the ability of β-catenin to efficiently exit the nucleus of SW480 colon cancer cells (16), its subcellular distribution is biased toward the nucleus in those cells (16, 17). Therefore, what factors influence nuclear retention of β-catenin?

Despite the many nuclear proteins with which β-catenin associates (18), β-catenin nuclear retention is most often correlated with binding to LEF-1 (4, 7, 19–22). Some reports suggest that LEF-1 can compete directly with APC and with E-cadherin for the mutually exclusive binding to the armadillo repeat domain of β-catenin in vitro (23) or in vivo (20, 23). On the other hand, Neufeld et al. (13) proposed that APC binding is dominant and that APC can displace nuclear β-catenin from LEF-1 complexes and subsequently export β-catenin to the cytoplasm. Given the well documented role of β-catenin-LEF-1 transcription complex activity in cell signaling and cancer (1–3), we have investigated the mechanism by which LEF-1 acts to retain β-catenin in the nucleus. We confirmed that LEF-1 and APC do compete for nuclear β-catenin; however, APC did not remove β-catenin once it was bound to LEF-1. In fact, LEF-1 effectively blocked APC-mediated nuclear export of β-catenin in vivo and blocked APC-independent export of β-catenin in vitro. Unexpectedly, LEF-1-bound β-catenin was highly protected in the nucleus from destruction by overexpressed APC and axin. We conclude that the β-catenin-LEF-1 interaction is not one-sided and that while β-catenin can activate transcriptionally silent LEF-1, and LEF-1 in turn functions to trap and stabilize β-catenin in the nucleus.

MATERIALS AND METHODS

Cell Culture and Treatments—NIH 3T3 mouse fibroblasts and SW480 colon carcinoma cells were cultured in Dulbecco’s modified Eagle’s medium with 10% fetal calf serum and were confirmed free of line; YFP, yellow fluorescent protein; Ab, antibody; TCF, T cell factor; NES, nuclear export signal.

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mycoplasma. Leptomycin B was added to a final concentration of 6 ng/ml. MG132 (Calbiochem) was used at a final concentration of 20 μM. DNA transfection of cells (typically 1 μg of DNA/2 ml of medium) was performed with LipofectAMINE reagent as directed (Invitrogen), using cells at medium density seeded onto coverslips.

**Plasmid Construction**—The pAPC-YFP fusion vector is based on the pCMV-APC vector (25) and contains yellow fluorescent protein (YFP) positioned at the C terminus of APC. We previously found that YFP was not properly expressed when inserted at the N terminus of APC, presumably due to folding constraints (data not shown). To construct pAPC-YFP, the pCMV-APC plasmid was first cut with AvaII at a unique C-terminal restriction site, and a modified PCR-amplified C-terminal fragment was then inserted to create the vector pCMV-APC(MCS). This plasmid was checked by DNA sequencing. The PCR primers used to amplify the APC C terminus were as follows: forward primer (FW-DAYR, 5'-TTAATTACAACCCAAG-3') and reverse primer (REVNOT1, 5'-CCATTCTCTAGTTATATCGATGCGGCCGCAACAGATGTCACAAGG-3'). The modified APC C terminus was engineered to incorporate the unique restriction sites NotI and ClaI just prior to the translation stop site, enabling the in-frame insertion of a NotI fragment containing the YFP cDNA. The resulting vector, pAPC-YFP, was confirmed by restriction mapping, and expression of both the APC and YFP domains was confirmed in transfected cells by immunostaining with the APC antibodies Ab7 (recognizes the N terminus, Oncogene Research) and C-20 (recognizes the C terminus, Santa Cruz Biotechnology).

**Luciferase Assay**—SW480 or NIH 3T3 cells were transfected with 0.5 μg of the luciferase reporter plasmids pGL3-OT or pGL3-OF (provided by Dr. B. Vogelstein), in addition to 0.5 μg of various APC plasmid DNAs, or 0.5/2.5 μg of histone deacetylase 1 cDNA (pCDNA3-HDAC1; kind gift of Dr. D. Ayer). The pGL3-OT promoter contains three LEF-1/TCF binding sites, whereas pGL3-OF contains mutated inactive TCF sites and is a negative control (11). Reporter gene activity was determined 48 h post-transfection with the luciferase assay system (Promega). Luciferase activity of APC-transfected samples was normalized for transfection efficiency by scoring for APC-positive SW480 cells in duplicate samples (immunostained with APC Ab7, Oncogene Research). Final luciferase activity values were arrived at by subtracting background (including the pGL3-OF value) and determining the mean ± S.D. from three experiments (in duplicate), where the pGL3-OT sample was set to 100%.

**Permeabilized Cell Nuclear Export Assay**—Nuclear export of endogenous cellular β-catenin in SW480 cells was assessed using the digito-nin permeabilized cell assay, as recently described in detail (16). Export reactions were performed at 30 °C for 30 min in transport buffer containing 50 mM Tris-HCl, pH 7.5, 5 mM magnesium acetate, 2 mM EDTA, 50 mM potassium acetate, 2 mM dithiothreitol, 50 μg/ml phenylmethylsulfonyl fluoride, 1 mM benzamidine, and 50 μg/ml leupeptin in the presence or absence of digitonin (50 μM). All reactions included an energy-regenerating system comprising 1 mM ATP, 0.5 mM GTP, 4 units/ml of creatine kinase, and 10 mM creatine phosphate. Cells were immediately fixed and processed for immunostaining following the export reactions.

**Immunofluorescence Staining, Fluorescence Microscopy, and Imaging**—Cells were grown on glass coverslips, fixed in 3% formalin/PBS for 30 min, followed by permeabilization with 0.2% Triton X-100/PBS for 10 min. Cells were preblocked in 3% bovine serum albumin/PBS for 30 min, incubated 50 min with primary antibody (diluted 1:70 in blocking solution), and washed three times with PBS. Primary antibodies were used as follows: β-catenin (monoclonal antibody C19220 from Transduction Laboratories) and rabbit polyclonal antibody H-102 from Santa Cruz Biotechnology), FLAG-axin (anti-FLAG monoclonal antibody M2 from Sigma), HA-LEF-1 (rabbit polyclonal HA-probe Y-11 from Santa Cruz), and APC (monoclonal antibody Ab7 from Oncogene Research). Cells were then incubated with a secondary antibody (1:120 dilution of a fluorescein isothiocyanate- or Texas Red conjugated anti-rabbit or anti-mouse antibody from Sigma) prior to mounting on slides with Vectashield (Vector Laboratories, Burlingame, CA) and fluorescence microscopy. Processing was at room temperature. Cells were analyzed and scored on an Olympus fluorescence microscope at ×400 magnification, and digital images were captured using an OptiScan confocal microscope at ×600 magnification. Quantification of fluorescence images was performed using the NIH Image software as described previously (12). Cell fractionation and Western blot analysis were performed for transfected SW480 cells as described previously (24).

**RESULTS**

**LEF-1 Induces Nuclear Accumulation of β-Catenin**—In mouse NIH 3T3 fibroblasts, cellular β-catenin is localized mainly at the plasma membrane (Fig. 1A). Prior to testing for regulation by LEF-1, we first confirmed that endogenous β-catenin is regulated by nuclear export and degradation in NIH 3T3 cells, by comparing the effects of drugs that block CRM1-specific nuclear export (leptomycin B, LMB) and proteasome-dependent degradation (MG132). We observed that a 16-h treatment with MG132 induced a stronger induction (9-fold) of nuclear β-catenin than did leptomycin B (4-fold), following immunostaining and confocal scanning microscopy (see images and fluorescence quantification in Fig. 1A). Thus, β-catenin accumulates in the nucleus of 3T3 cells following inhibition of the major nuclear export and degradation pathways.

Previous studies reported an increase in nuclear β-catenin following the transient overexpression of LEF-1 (4, 19, 20). We
investigated this further and discovered that endogenous nuclear β-catenin (see confocal images in Fig. 1B) increased in proportion to the amount of ectopically expressed LEF-1, as revealed by quantitative imaging of β-catenin/LEF-1 nuclear fluorescence and linear regression analysis (Fig. 1B). LEF-1 had a similar effect on ectopically expressed β-catenin (data not shown), and unlike the previous study of Hsu et al. (21), the positive effect of LEF-1 was not dependent on co-expression of Wnt-1 protein. As a specificity control, overexpression of nuclear p53 had little effect on nuclear β-catenin (data not shown). We next tested whether co-expression of wild-type APC, or mutant APC-(1–1309) that binds but does not degrade β-catenin, caused a reduction in the effect of LEF-1. As shown in Fig. 1C, both forms of APC did reduce the LEF-1-dependent induction of nuclear β-catenin (although somewhat modestly), suggesting that LEF-1 and APC can compete for nuclear β-catenin in vivo. This finding significantly extends earlier experiments that demonstrated an in vitro competition for β-catenin between LEF-1 and subfragments of APC (23).

**APC Regulates β-Catenin/LEF-1 Transcriptional Activity by Nuclear Sequestration**—The overexpression of wild-type APC is known to inhibit β-catenin/LEF-1 transcriptional activity in APCmut/mut SW480 colon cancer cells (17). This inhibitory action is likely to involve competition with LEF-1/TCF factors for binding to β-catenin. Interestingly, Neufeld et al. (13) reported that an export-defective form of APC could also disrupt β-catenin transcriptional activity. Our laboratory identified the same two N-terminal nuclear export signals (NESs; Ref. 12) as did Neufeld and colleagues, and using a luciferase reporter assay we also found that APC isoforms containing mutations in NES1, or in both NES1 and NES2, effectively reduced β-catenin/LEF-1 transcription activity (see Fig. 2). Since these full-length APC NES mutants retain the β-catenin degradation sequences, however, we also tested a cancer mutant form of APC-(1–1309) which can bind and export nuclear β-catenin (12), but cannot degrade it (17). As shown in Fig. 2, APC-(1–1309) reduced promoter/luciferase activity by ~50%, and this was unaffected by mutation of NES1, which is the dominant export signal in APC (24). These results suggest that the ability of APC to inhibit β-catenin/LEF-1 transcription activity primarily involves nuclear sequestration of β-catenin, but is more efficient when APC retains the ability to export/degrade β-catenin.

**LEF-1 Blocks APC-mediated Nuclear Export of β-Catenin**—Can LEF-1 block APC-mediated nuclear export of β-catenin? To address this question without the complication of β-catenin degradation, we again employed the APC-(1–1309) mutant (25). We tested the ability of ectopic APC-(1–1309) to shift β-catenin from nucleus to cytoplasm in transfected SW480 cells, in the absence or presence of co-transfected LEF-1. As shown in the confocal images of Fig. 3, transient expression of the mutant APC re-located β-catenin from nucleus to cytoplasm in 73% of transfected cells expressing cytoplasmic APC. However, the co-expression of LEF-1 caused nuclear retention of β-catenin in 85% of APC-transfected cells (see images and graphs in Fig. 3). The co-expression of ectopic APC and LEF-1 was very efficient, with >95% of APC-transfected cells also expressing recombinant LEF-1 (data not shown). The results demonstrate nuclear retention of β-catenin by co-expressed LEF-1 and indicate that APC is incapable of removing β-catenin from LEF-1 nuclear complexes. This contrasts with the recent prediction that APC might displace β-catenin bound to LEF-1 (15). Interestingly, LEF-1 did not affect APC localization, confirming that binding to β-catenin by LEF-1 and APC is mutually exclusive in vivo.

**LEF-1 Blocks Degradation of β-Catenin Mediated by APC or Axin**—The striking ability of LEF-1 to block nuclear export of β-catenin by APC-(1–1309) suggested that LEF-1 might also protect β-catenin from degradation by APC. To test this, we first transfected SW480 cells with plasmid encoding full-length untagged APC (pCMV-APC) and observed a total loss of β-cate-
nin in ~60% of transfected cells (see Fig. 4A). This was accompanied by an overall 90% reduction in nuclear β-catenin fluorescence in APC-transfected cells (Fig. 4C). When co-expressed with LEF-1, however, APC no longer exported and promoted degradation of β-catenin. In SW480 cells co-transfected with pHA-LEF-1 and pCMV-APC, nuclear β-catenin fluorescence levels decreased by only 5% in a randomly selected population of transfected cells (Fig. 4C), although many transfected cells did show a reduction in cytoplasmic β-catenin (see images in Fig. 4A). To confirm these findings, we transiently expressed a full-length APC-YFP fusion vector in SW480 cells and stained these cells with a different β-catenin antibody (monoclonal Ab C19220) to that used above (rabbit polyclonal H-102). As expected, LEF-1 reduced the ability of APC-YFP to export and degrade cellular β-catenin (Fig. 4B). Quantitative imaging revealed that APC-YFP reduced β-catenin nuclear fluorescence...
by 92% in the absence of LEF-1, but only by 36% in the presence of LEF-1 (Fig. 4C). Moreover, Western blot analysis of nuclear fractions prepared from SW480 cells untransfected or transfected with APC-YFP ± LEF-1 showed that LEF-1 reduced the disappearance of nuclear β-catenin caused by APC (Fig. 4D). Collectively, these findings demonstrate for the first time that LEF-1 can inhibit APC-mediated degradation of β-catenin by protecting it in the nuclear compartment.

The overexpression of axin, a key component in the cytoplasmic β-catenin degradation complex, is also known to induce β-catenin degradation when overexpressed in cells (26), by a mechanism thought to require the APC/CRM1-independent nuclear export of β-catenin (15, 16). As we observed with APC, co-expression of axin with LEF-1 efficiently blocked the axin-dependent degradation of β-catenin in SW480 cells and caused β-catenin sequestration in the nucleus (Fig. 5).

Inhibition of CRM1-independent β-Catenin Nuclear Export by LEF-1—We recently showed that endogenous β-catenin can exit the nucleus of semipermeabilized SW480 cells independent of APC and the CRM1 export receptor (16). In this in vitro assay, cells are treated with the detergent digitonin, which permeabilizes the plasma membrane but leaves the nuclear envelope intact. The export reaction is unidirectional in that β-catenin can exit the nucleus, but is washed away before it re-enters the nucleus (see confocal images in Fig. 6A, top panel). We transfected SW480 cells with LEF-1 and performed the in vitro export reactions in transport buffer containing an energy-regenerating system (see “Materials and Methods”). As shown in the confocal images, export of β-catenin (detected with monoclonal antibody C19220 and Texas Red secondary antibody) was fully blocked in cells transfected with pHA-LEF-1 (detected with anti-HA antibody Y-11 and fluorescein secondary conjugate). B, quantification of nuclear fluorescence in confocal images confirmed that ectopically expressed LEF-1 prevented loss of nuclear β-catenin. This experiment was performed twice with similar results.

Histone Deacetylase 1 Reduces LEF-1-dependent Nuclear Localization of β-Catenin and Transcriptional Activity—We next addressed possible mechanisms by which nuclear LEF-1-β-catenin complexes might be regulated in cells. Recently, histone deacetylase 1 (HDAC1) was found to interact with LEF-1 or with β-catenin (but apparently not both simultaneously) and caused transcriptional repression of a LEF-1-responsive pro-
Histone deacetylase 1 reduces the effect of LEF-1 on β-catenin nuclear retention and transcription activation. A. NIH 3T3 cells were transfected with expression plasmids encoding LEF-1 (1 µg of DNA), plus or minus HDAC1 (2 µg of DNA). After 48 h, cells were immunostained for cellular β-catenin (antibody C19220) or ectopic LEF-1 (anti-HA antibody Y11). As shown by confocal microscopy, co-expression of HDAC1 reduced the nuclear retention of β-catenin by LEF-1. B, quantitation of β-catenin nuclear fluorescence (confocal cross-sections) in random samplings of transfected cells confirmed that HDAC1 significantly reduced nuclear β-catenin induction. C, NIH 3T3 cells were transiently transfected with 0.5 µg of DNA for the LEF-1-responsive promoter pGL3-OT or the mutant promoter pGL3-OF. Some samples were co-transfected with pHA-LEF-1 (0.5 µg) and pcDNA3-HDAC1 (0.5 or 2.5 µg). After 48 h, luciferase activities were assayed. As shown, co-expression of HDAC1 reduced LEF-1 transcriptional activation. Values shown are means (±S.E.) from two experiments, and similar results were obtained in three different experiments, in the presence or absence of exogenous β-catenin.

DISCUSSION

There is strong evidence linking the stabilization of β-catenin with its nuclear accumulation. For instance, nuclear levels of β-catenin are enhanced by its overexpression in transgenic mice (5), by proteasome blockade (Ref. 20 and this study; Fig. 1A), and by mutations in the β-catenin, APC, or axin genes (1–3). In this study, we showed that LEF-1 can trap β-catenin in the nucleus and stabilize it against cytoplasmic destruction by APC-axin complexes, providing an additional mechanism by which cancer cells can elevate β-catenin and its transforming activity within the nucleus.

Given that β-catenin can associate with several nuclear proteins including the chromatin remodelling factor BRG1 (29), the histone deacetylase HDAC1 (28), and the transcription coactivator p300/CBP (30, 31), it is likely that additional factors will contribute to its nuclear retention in mammalian cells. Indeed, we observed that co-expression of HDAC1 diminished the ability of LEF-1 to sequester β-catenin in the nucleus and to stimulate transcription of a LEF-1 responsive promoter (Fig. 7). Therefore, the modulation of β-catenin nuclear transport or retention by protein co-factors may reflect a common cellular mechanism for regulating its oncogenic transcription function. This is supported by the finding that the Xenopus TCF-3 protein can block nuclear export of β-catenin in microinjected Xenopus oocytes (15).

The LEF-1 gene is under positive feedback control by β-catenin-LEF-1-TCF transcription complexes (8), providing one explanation for the elevated expression of LEF-1 in colon tumor cell lines (7), colon tumors (8), and malignant melanoma cells (9). LEF-1 forms active complexes with β-catenin in vivo in colon cancer cells (7). We propose that enhanced LEF-1 levels provide an alternative mechanism for stabilizing β-catenin in cells. This may be of particular relevance in cancers where elevated nuclear β-catenin does not correlate with known gene mutations (32, 33). The ability of LEF-1 to stabilize β-catenin is highly consistent with a positive feedback model that favors accumulation of transcriptionally active and oncogenic β-catenin/LEF-1 complexes. In future experiments it will be of interest to identify additional factors and signaling pathways that modulate the stability/dissociation of LEF-1-β-catenin complexes. The ability to regulate the nuclear activity or nuclear exclusion of β-catenin has implications for potential anticancer therapies.

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REFERENCES

1. Kinzler, K. W., and Vogelstein, B. (1996) Cell 87, 159–170
2. Marin, P. J. (1999) Bioessays 21, 1021–1030
3. Polakis, P. (2000) Genes Dev. 14, 1387–1391
4. Behrens, J., von Kries, J. P., Kuhl, M., Bruhn, L., Wedlich, D., Grosschedl, R., and Birchmeier, W. (1996) Nature 383, 638–642
5. Harada, N., Tamai, Y., Ishikawa, T.-O., Sauer, B., Takaku, K., Oshima, M., and Taketo, M. M. (1999) EMBO J. 18, 5931–5942
6. Aoki, M., Hecht, A., Kreuse, U., Klemm, R., and Vogt, P. K. (1999) Proc. Natl. Acad. Sci. U. S. A. 96, 139–144
7. Porfiri, E., Rubinfeld, B., Albert, I., Hovanes, K., Waterman, M., and Polakis, P. (1997) Oncogene 15, 2833–2839
8. Hovanes, K., Li, T. W. H., Muñoz, J. E., Truong, T., Milewskovic, T., Marsh, J. L., Holcombe, R. F., and Waterman, M. L. (2001) Nat. Genet. 28, 53–57
9. Murakami, T., Toda, S., Fujimoto, M., Ohtsuki, M., Byers, H. B., Etoh, T., and Nakagawa, H. (2001) Biochem. Biophys. Res. Commun. 288, 8–15
10. Tetsu, O., and McCormick, F. (1999) Nature 396, 422–426
11. He, T. C., Sparks, A. B., Rago, C., Hermeking, H., Zavel, L., da Costa, L. T., Morin, P. J., Vogelstein, B., and Kinzler, K. W. (1998) Science 281, 1509–1512
12. Henderson, B. R. (2000) Nat. Cell Biol. 3, 653–660
13. Neufeld, K. L., Zhang, F., Cullen, B., and White, R. L. (2000) EMBO Rep. 1, 519–523
14. Rosin-Arbesfeld, R., Townsley, F., and Biezns, M. (2000) Nature 406, 1009–1012
15. Wiechens, N., and Fagotto, F. (2001) Curr. Biol. 11, 18–27
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16. Eleftheriou, A., Yoshida, M., and Henderson, B. R. (2001) J. Biol. Chem. 276, 25883–25888
17. Munemitsu, S., Albert, I., Souza, B., Rubinfeld, B., and Polakis, P. (1995) Proc. Natl. Acad. Sci. U. S. A. 92, 3046–3050
18. Sharpe, C., Lawrence, N., and Martinez Arias, A. (2001) Bioessays 23, 311–318
19. Huber, O., Korn, R., McLaughlin, J., Ohnogi, M., Herrman, B. G., and Kemler, R. (1996) Mech. Dev. 59, 3–10
20. Simcha, I., Shrutman, M., Salomon, D., Zhurinsky, J., Sadot, E., Geiger, B., and Ben-Zeév, A. (1998) J. Cell Biol. 141, 1433–1448
21. Hsu, S.-C., Galceran, J., and Grosschedl, R. (1998) Mol. Cell. Biol. 18, 4897–4818
22. Prieve, M. G., and Waterman, M. L. (1999) Mol. Cell. Biol. 19, 4503–4515
23. Orsulic, S., Huber, O., Aberle, H., Arnold, S., and Kemler, R. (1999) J. Cell Sci. 112, 1237–1245
24. Galea, M. A., Eleftheriou, A., and Henderson, B. R. (2001) J. Biol. Chem. 276, 45833–45839
25. Smith, K. J., Levy, D. B., Maupin, P., Pollard, T. D., Vogelstein, B., and Kinzler, K. W. (1994) Cancer Res. 54, 3672–3675
26. Hart, M. J., de los Santos, R., Albert, I. N., Rubinfeld, B., and Polakis, P. (1998) Curr. Biol. 8, 573–581
27. Lee, E., Salic, A., and Kirschner, M. W. (2001) J. Cell Biol. 154, 983–993
28. Billin, A. N., Thirwell, H., and Ayer, D. E. (2000) Mol. Cell. Biol. 20, 6882–6890
29. Barker, N., Hurtlestone, A., Musisi, H., Miles, A., Bienz, M., and Clevers, H. (2001) EMBO J. 20, 4835–4843
30. Sun, Y., Kolligs, F. T., Hettinger, M. O., Mosavin, R., Fearon, E. R., and Nabel, G. J. (2000) Proc. Natl. Acad. Sci. U. S. A. 97, 12613–12618
31. Takemaru, K.-i., and Moon, R. T. (2000) J. Cell Biol. 149, 249–254
32. Rimm, D. L., Caca, K., Hu, G., Harrison, F. B., and Fearon, E. R. (1999) Am. J. Pathol. 154, 325–329
33. Omholt, K., Platz, A., Ringborg, U., and Hansson, J. (2001) Int. J. Cancer 92, 839–842
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