β-Catenin is a mediator of the Wnt-signaling pathway. In many cancers, β-catenin is stabilized and accumulates in the nucleus where it associates with lymphoid-enhancing factor 1/T-cell transcription factors to activate genes involved in cell transformation. Previously, we showed that adenomatous polyposis coli (APC) protein can regulate β-catenin localization by nuclear export. In this study, we used in vitro transport assays to test whether cellular β-catenin can exit the nucleus independent of APC and the CRM1 export receptor. In digitonin-permeabilized SW480 (APCmut/mut) tumor cells, nuclear β-catenin decreased >60% in export reactions in the absence of exogenous factors. Under similar conditions nuclear c-ABL was only exported after the addition of cytosolic extract, and the export was blocked by the CRM1-specific inhibitor, leptomycin B. The nuclear export of β-catenin was not blocked by leptomycin B treatment, revealing a CRM1- and APC-independent pathway. The export of β-catenin was sensitive to lower temperatures and the removal of ATP, indicating an active process. Ectopically expressed yellow fluorescent protein-β-catenin also displayed CRM1-independent export. Conversely, the overexpression of the CRM1 transporter moderately stimulated export of nuclear β-catenin, confirming that β-catenin exits the nucleus by at least two distinct pathways. The shuttling ability of tumor cell β-catenin has implications for its regulation and its role in transferring signals between the nucleus and plasma membrane.

β-Catenin is a multi-functional protein implicated in several cellular processes including cell-cell adhesion and the transcriptional activation of genes (1–3). β-Catenin was first identified as a component of the adherens junction complex, bound to the intracellular domain of the transmembrane cell adhesion protein, E-cadherin, helping to connect the cell surface with the internal actin cytoskeleton (2, 3). The cadherin-bound form of β-catenin is anchored at the plasma membrane (4). Non-membrane-bound β-catenin, however, has a major function in transducing the Wnt signal from the cell surface to the nucleus (1, 2). In response to Wnt binding at the cell surface, β-catenin is stabilized and actively translocates into the nucleus where it binds to the lymphoid-enhancing factor 1 (LEF-1)1/T-cell transcription factors. Nuclear β-catenin activates LEF-1/T-cell transcriptional activity, thereby inducing the expression of genes involved in cellular transformation and invasion, including c-myc (5), cyclin D1 (6), and matriptin (7).

β-Catenin interacts with multiple proteins and is primarily regulated by degradation. In the cytoplasm, β-catenin binds to the adenomatous polyposis coli (APC) tumor suppressor, which initiates assembly of a degradation complex comprising additional proteins, including Axin, Conductin, and glycogen synthase kinase-3β (GSK-3β) (2, 8–10). GSK-3β phosphorylates β-catenin at the N terminus, marking it for ubiquitination and degradation by the proteasome complex (1, 9). Wnt signaling inhibits this phosphorylation, leading to the stabilization of β-catenin. β-Catenin is also stabilized in different cancers by interference with the degradation pathway resulting from mutations in its own gene (11, 12) or within the APC (1, 2, 8) and Axin (13) genes. When stable β-catenin is overexpressed, very often it accrues in the nucleus (3, 14, 15). Therefore, β-catenin is a common focal point for Wnt growth factor signaling and cancer, and its nuclear accumulation leads to the oncogenic transformation of cells via β-catenin-dependent transcriptional activation (16).

Recently, APC was identified as a nuclear cytoplasmic shuttling protein that contains multiple nuclear export signals (17–19) with evidence supporting the notion that APC can taxi β-catenin from the nucleus to the cytoplasm (17, 20). This activity was shown to stimulate APC-dependent degradation of β-catenin (17, 20). There are other pieces of evidence, however, that suggest an additional nuclear export pathway for β-catenin that is independent to that involving APC. Previously, Prieve and Waterman (21) reported indirect evidence that a form of Xenopus β-catenin with a defective APC-binding domain was able to be exported from the nucleus of transfected lymphocytes after actinomycin D treatment. Also, β-catenin can enter the nucleus independently of soluble transport factors, such as the importin receptors (22), raising the possibility that movement in the reverse direction may also be true. More recently, we compared the rates of β-catenin turnover in SW480 cells transfected with either the degradation complex factors APC or Axin (17). Unlike APC whose effect on β-catenin nuclear export and degradation was blocked by leptomycin B, a specific inhibitor of the CRM1 export receptor (23–27), Axin-induced β-catenin turnover was not blocked by leptomycin B.
How did the β-catenin move from nucleus to cytoplasm to be degraded by Axin? By using an in vitro nuclear transport assay, we examined the ability of endogenous β-catenin to exit the nucleus of semi-permeabilized SW480 colon cancer cells. We show that unlike another oncogenic shuttling protein, c-ABL, cellular β-catenin can exit the nucleus independent of CRM1 and, therefore, represents a unique type of nuclear-cytoplasmic shuttling protein. The ability of β-catenin to exit the nucleus independent of APC suggests that nuclear shuttling is integral to its regulation.

EXPERIMENTAL PROCEDURES

Cell Culture, Antibodies, and Transfections—SW480 human colon cancer cells are homozygous for truncated mutant APC (amino acids 1–1337) and were cultured in Dulbecco’s modified Eagle’s medium with 10% fetal calf serum. Cells were confirmed mycoplasma negative. The primary antibodies used to detect different cellular proteins are as follows: β-catenin, a monoclonal antibody C19220, which recognizes C-terminal epitope, was from Transduction Laboratories; a rabbit polyclonal antibody H-102, which recognizes C-terminal amino acids 680–781, and a goat polyclonal antibody C-18 were from Santa Cruz Biotechnology; c-ABL, a rabbit polyclonal antibody K-12, which targets amino acids 502–512 in central kinase domain, and a rabbit polyclonal antibody C-19, which recognizes a C-terminal epitope, were from Santa Cruz Biotechnology; and AP2, a rabbit polyclonal antibody C-18, which binds C terminus, was from Santa Cruz Biotechnology. The DNA transfection of cells (usually 2 µg of DNA/2 ml of medium) was performed with FuGene transfection reagent as directed by the supplier (Roche Molecular Biochemicals) using cells at medium density seeded onto coverslips.

Plasmid Construction—The full-length human β-catenin cDNA was excised from the vector pJL-catenin/SKI1+ (supplied by J. Behrens) as a Smal-SalI fragment and cloned into frame in the equivalent sites of a linker-modified eYFP-C1 (CLONTECH) expression vector. The resulting plasmid, pYFP-β-catenin, was checked by restriction mapping and sequencing, and the correct co-expression of both the YFP and β-catenin domains was confirmed in transfected cells by immunofluorescent staining with three different β-catenin antibodies (see above). The construction of the YFP-CRM1 vector was described previously (28).

Preparation of Cytoplasmic Extract—Cells were resuspended in lysis buffer (10 mM Tris-HCL, pH 7.0, 150 mM KCl, 3 mM MgCl2, 1 mM CaCl2, 0.2% bovine serum albumin, 3.5% glycerol, 0.5 mM phenylmethylsulfonyl fluoride and 1 mM dithiothreitol) and lysed on ice following the addition of 0.5% Nonidet P-40. Samples were centrifuged at 1000 rpm for 5 min. The supernatant was then incubated with 0.5% sodium deoxycholate for 10 min on ice and centrifuged 13,000 rpm for 20 min at a cold room. The supernatant was collected as the cytosolic fraction and stored at −70 °C. Protein concentration was determined using the Bio-Rad protein assay kit.

Permeabilized Cell Export Assay Optimization—Digitonin was prepared at a working concentration of 5 mg/ml as described previously by Gorlich et al. (29). An analysis of SW480 cells transfected with different GFP fusion constructs that vary in their capacity for nuclear export (30) showed that doses of 30–50 µg/ml digitonin effectively disrupted the plasma membrane but not the nuclear envelope (data not shown). Cells were also assessed by phase contrast microscopy to ensure histological integrity of the nuclear membrane under these conditions.

Export Assay—The transport assay was performed in principle as described previously (24, 31) but with several modifications. Cells grown on coverslips in Nunc 8-well trays were first washed 3 times with PBS and then incubated on ice for 6 min in 0.5 ml of transport buffer containing 50 mM Tris-HCL, pH 7.5, 5 mM magnesium acetate, 2 mM EGTA, 50 mM potassium acetate, 2 mM dithiothreitol, 50 µM phenylmethylsulfonyl fluoride, 1 mM benzamidine, and 50 µg/ml leupeptin in the presence or absence of digitonin (30–50 µg/ml). After permeabilization of the outer membrane, cells were then washed 3 times in PBS and incubated for 30 min in 0.5 ml of transport buffer +/− energy. +Energy indicates the addition of 1 mM ATP, 0.5 mM GTP, 4 units/ml of creatine kinase, and 10 mM creatine phosphate, whereas −energy samples contained 10 mM sodium azide to deplete ATP. After the transport reaction, cells were washed twice in PBS and fixed in 3% formalin/PBS (Sigma). Transport reactions were performed either in a 30 °C incubator, or at 4 °C, in which case cells were grown on separate trays and all incubations and buffers were chilled on ice at each step. For LMB treatments, high doses (~20 ng/ml) of the export inhibitor were used throughout (confirmed to block CRM1-mediated export in a GFP-based export assay (reviewed in Ref. 30), and cells were preincubated with LMB 30 min before digitonin treatment. All reagents, except LMB, were obtained from Sigma or Roche Molecular Biochemicals (23). Note that the addition of protease inhibitors helps to ensure that the disappearance of nuclear staining is more likely due to nuclear export than nuclear degradation.

Immunofluorescence Microscopy and Image Quantification—For indirect immunofluorescence analysis, cells (on coverslips) were fixed in 3% formalin/PBS for 20 min and then permeabilized with 0.2% Triton X-100/PBS for 10 min. Samples were pre-blocked with 3% bovine serum albumin/PBS for 30 min, incubated with primary antibodies (diluted 1:80 in blocking solution), and washed in PBS. The cells were then incubated with secondary antibody (1:120 dilution of a fluorescein isothiocyanate-conjugated or Texas Red-conjugated anti-rabbit or antimouse antibody from Sigma) and subsequently mounted on slides with Vectorshield (Vector Laboratories) for fluorescence microscopy. Cells were processed at room temperature. Cells transfected with GFP or YFP-fusion constructs were fixed and mounted directly and scored visually for nuclear staining (or cellular distribution) using an Olympus BX40 fluorescence microscope. For quantitation of nuclear fluorescence of immunostained cells, slides were scanned with an Optiscan confocal microscope at ×600 magnification, and several fields from each slide were collected for quantitation. Within each experiment, images from different slides were processed identically to enable accurate quantitative comparison. Hundred fields of individual cells on each sample were identified for nuclear fluorescence using the NIH image software as described previously (17).

RESULTS

Overexpression of Axin Induces β-Catenin Relocalization and Degradation Independent of CRM1—β-Catenin accumulates in nuclei of SW480 colon tumor cells, and recently, we showed that the overexpression of APC enhanced the nuclear export and degradation of β-catenin in transfected SW480 cells (17). APC-dependent relocalization of β-catenin requires the CRM1 export receptor (17, 18) and is blocked by the CRM1-specific inhibitor, leptomycin B (17, 20). Previously, we noted that the ectopic expression of Axin, a key β-catenin degradation factor, resulted in the disappearance of β-catenin from the nucleus and its cytoplasmic degradation, but that this was not blocked by leptomycin B (17). Upon a more detailed examination (see Fig. 1), we confirmed that when β-catenin is released from an MG132-dependent block to degradation, there is a partial but distinct shift from the nucleus to cytoplasm wherein β-catenin is degraded by Axin complexes (only in Axin-transfected cells). However, in contrast to APC, Axin localization was not affected by leptomycin B but remained in the cytoplasm or the perinuclear zone (see confocal images in Fig. 1). The apparently fixed location of Axin suggests that β-catenin itself must be capable of exiting the nucleus via a pathway insensitive to leptomycin B treatment and, therefore, is independent of CRM1 and APC.

Rapid Nuclear Export of Cellular β-Catenin Does Not Require CRM1 or Other Cytosolic Factors—To test for CRM1-independent nuclear export of β-catenin, we used a semi-permeabilized cell assay to assess the ability of nuclear β-catenin to exit the nucleus of SW480 cells. In the absence of digitonin, immunofluorescence microscopy detected β-catenin staining in both the nucleus and cytoplasm (Fig. 2). Treatment with 50 µg/ml digitonin, which selectively permeabilizes the plasma membrane and not the nuclear envelope (see under “Experimental Procedures”) (32), followed by a 30-min incubation in transport buffer caused the near-complete disappearance of endogenous β-catenin (Fig. 2). The same result was obtained using two different antibodies (Mab C19220 and rabbit polyclonal H-102). Quantitation of nuclear fluorescence from confocal images revealed a 65% loss of nuclear β-catenin (see graph in Fig. 2).

The nuclear export of β-catenin was only modestly enhanced (~10%) by the addition of cytoplasmic (Fig. 2) or nuclear extract (data not shown). More important, the addition of high doses of leptomycin B did not significantly block in vitro export.
higher temperature (30 °C), most β-catenin nuclear staining disappeared after digitonin treatment in the presence of an energy-regenerating system. Removal of ATP at this temperature partially blocked the export, decreasing nuclear staining by 40%. Thus, β-catenin nuclear export appears to be an active process. These results also confirm that the presence of digitonin does not interfere with the cell-staining method used in this assay.

**c-ABL Nuclear Export Is CRM1-dependent in the Permeabilized Cell Assay**—To ensure that CRM1-dependent nuclear export can be clearly detected in this assay system, we tested the effect of leptomycin B on nuclear export of c-ABL, a known shuttling protein that contains a CRM1-responsive nuclear export signal (30, 35). In contrast to β-catenin, nuclear c-ABL levels did not decrease in digitonin-treated SW480 cells incubated in transport buffer alone for 30 min at 30 °C (Fig. 4).

Nuclear export of c-ABL required the addition of cytoplasmic extract, and the extract-induced export was inhibited either by lower temperatures or by leptomycin B treatment (Fig. 4). Similar results were obtained with two different c-ABL antibodies (C19 and K12, see Fig. 4). These results demonstrate that c-ABL nuclear export requires exogenous soluble factors, particularly CRM1, and highlight the unique nature of the β-catenin export pathway.

**Cellular and Ectopic β-Catenin Exit the Nucleus by Two Distinct Pathways**—We next showed that ectopically expressed β-catenin also displays rapid and CRM1-independent nuclear export. In _in vitro_ nuclear export activities of YFP or YFP-β-catenin and YFP-CRM1 fusion proteins were compared in transfected SW480 cells. As shown in Fig. 5A, the β-catenin fusion protein exited the nucleus of digitonin-treated cells more efficiently than did the CRM1 export receptor and almost as
It was shown that independently shuttle between the nucleus and cytoplasm. Previously, it was shown that β-catenin can enter the nucleus independent of the CRM1 export receptor. This discovery reveals that human β-catenin can exit the nucleus of tumor cells by a pathway distinct from that recently shown to require an association with the APC tumor suppressor (17–20). Thus, in contrast to previous claims (19), β-catenin is not trapped in the nucleus of tumor cells that express APC mutations.

During the preparation of this manuscript, Wiechens and Fagotto (37) reported that labeled recombinant β-catenin is also exported independent of CRM1 following microinjection into the nuclei of *Xenopus laevis* oocytes. The two studies, which focus on different forms of β-catenin in different species, together demonstrate conservation in the nuclear transport of β-catenin and challenge the notion that monomeric β-catenin transfers a unidirectional signal to the nucleus after Wnt binding at the plasma membrane (1). Instead, the shuttling of β-catenin suggests a more intricate regulatory circuit initiated by Wnt signaling and present in cancer cells, with the possibility of some type of feedback control.

We studied human SW480 colon tumor cells that carry an inactivating and truncating mutation in APC and consequently express high levels of β-catenin in the nucleus and cytoplasm. The ability of endogenous β-catenin to quickly exit the nucleus of SW480 cells without the addition of exogenous transport factors is unusual, as illustrated by the fact that the nuclear export of another oncogenic protein, c-ABL, was strictly dependent on the addition of CRM1-containing cytosolic extract in this system (Fig. 4). The recent study of Wiechens and Fagotto (37) reveals that the nuclear export of recombinant *Xenopus* β-catenin can occur independent of CRM1 and of APC.
CRM1-independent Nuclear Export of β-Catenin

Fig. 5. Evidence for two distinct β-catenin nuclear export pathways in SW480 cells. A, CRM1-independent export of ectopic β-catenin. SW480 cells were transfected with pEYFP-C1 (YFP) or YFP-β-catenin and YFP-CRM1 fusion vectors permeabilized with 0, 30, or 50 μg/ml digitonin and then incubated in transport buffer (+ energy) for 30 min at 30 °C. After 48 h, cells were fixed, and the number of cells with nuclear fluorescence visible by fluorescence microscopy was scored (total cells counted are shown in brackets). Similar to cellular β-catenin, the ectopic YFP-β-catenin very efficiently exits the nucleus in the absence of added soluble factors. B, SW480 cells transfected with YFP-β-catenin or p19ARF-GFP (a protein usually restricted to the nucleus/nucleus) were treated with 50 μg/ml digitonin and examined for export. YFP-β-catenin nuclear export was partially blocked (10% more cells retained nuclear staining) in the presence of LMB. p19ARF-GFP was not exported in permeabilized cells. The results from a typical experiment are shown with similar results obtained in at least two experiments. C, effect of CRM1 overexpression on nuclear β-catenin. SW480 cells were transfected with YFP or the YFP-CRM1 fusion, and after 48 h, cells were stained for β-catenin localization. As shown in the confocal images and graphs, transient expression of the export receptor had a small but specific effect on cellular β-catenin, causing its movement out of the nucleus.

Ran-GTP and involves N-terminal and C-terminal sequences that bear no resemblance to known nuclear transport motifs. Interestingly, complete nuclear export of recombinant β-catenin in the microinjected Xenopus eggs required up to 6 h (37), whereas the near-complete nuclear export of cellular β-catenin that we observed occurred within 30 min of digitonin treatment of human cells (Fig. 2). The slower transport kinetics observed in injected frog nuclei may reflect saturation of the system, as it was proposed that some “unidentified” factor required for β-catenin export was present in limiting amounts (37).

Previously, our laboratory (17) and others (18, 19) demonstrated nuclear cytoplasmic shuttling of the β-catenin-binding protein, APC. Based on evidence from cell transfection experiments, it was proposed that APC (bound to the CRM1 export receptor via its nuclear export signals) can carry β-catenin from the nucleus to the cytoplasm (17, 19, 20). This pathway is likely to be more important in cells where the β-catenin degradation pathway is intact. In such cells, there is little uncomplexed β-catenin, and its localization will be determined primarily by its binding partners. For instance, when β-catenin is bound to E-cadherin, it is anchored at the plasma membrane (4). LEF-1-bound β-catenin is anchored in the nucleus (reviewed in Ref. 38 and data not shown), whereas APC-bound β-catenin can potentially move between the nucleus and cytoplasm. Because the main N-terminal nuclear export signals of APC are well removed from the β-catenin binding sites (17, 18), it is reasonable to propose that APC-β-catenin complexes preassemble in the nucleus (17, 20) and then translocate to the cytoplasm where they associate with other factors (e.g. Axin and GSK-3β) required for β-catenin turnover.

In many tumor cells where the β-catenin degradation pathway is impaired by mutations in the APC, β-catenin, or Axin genes, β-catenin is quite stable and can accumulate to very high levels in both the nucleus and cytoplasm (3, 13, 39). In SW480 cells, which express mutated APC, endogenous β-catenin is expressed well in excess of APC and, to a large extent, is present in a free form uncomplexed with other proteins (33, 34). The identification of a CRM1-independent export pathway (as described in this study and in Ref. 37) suggests that APC would have little impact, unless overexpressed, on the transport or localization of β-catenin in these cells. Therefore, we speculate that APC-dependent export of β-catenin is dominant in normal cells, whereas the high levels of free β-catenin in tumor cells exit the nucleus independent of APC and the CRM1 exporter. Given that β-catenin can efficiently exit the nucleus, why is it so often detected in the nucleus? When β-catenin was overexpressed in Xenopus cells, it did not accumulate well in the nucleus (37). In mammalian cells, however, many studies have reported nuclear staining of β-catenin when it is stabilized (3, 15) or overexpressed (14, 15). Indeed, the transient expression of a YFP-β-catenin fusion displayed strong nuclear and cytoplasmic staining in different cell lines (data not shown). The nuclear accumulation of overexpressed β-catenin may reflect a combination of nuclear retention and possibly a higher rate of nuclear import relative to export. This balance would change in cells where the ratio of APC to β-catenin molecules is much higher and where APC contributes to the export/degradation of β-catenin.

β-Catenin behaves not unlike nuclear transporter molecules in its ability to freely translocate across the nuclear membrane in either direction. Whereas this movement seems to be independent of the importin, CRM1, and Ran nuclear transport factors, the data from competition experiments suggest that another factor may be required for the nuclear export of β-catenin (37). There are some structural similarities between repeat sequences in β-catenin and the importin-β nuclear import receptor (40), and interestingly, importin-β was also found to exit the nucleus independent of the Ran-GTPase (41). Although there is no clear evidence that β-catenin can act as a transporter of other molecules, its ability to rapidly move around the cell and associate with different partners may be integral to its role as a signaling intermediate in the Wnt pathway (1–3). It is
possible that GSK-3β-mediated phosphorylation of β-catenin (targets β-catenin for ubiquitination) is a cytoplasmic event, and that nuclear shuttling allows for the rapid modification of both nuclear and cytoplasmic β-catenin in the cell. Alternatively, β-catenin may be modified in the nucleus, thus altering its activity or ability to associate with specific binding partners in the cytoplasm. The constant cycling of β-catenin in tumor cells means that it will seek out and bind any partners (e.g. E-cadherin, LEF-1, retinoic acid receptor (see Ref. 42)) regardless of their location within the cell. It will now prove important to define precisely how the dynamic intracellular trafficking of β-catenin impacts on its regulation and function.

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Nuclear Export of Human β-Catenin Can Occur Independent of CRM1 and the Adenomatous Polyposis Coli Tumor Suppressor
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