Akt Participation in the Wnt Signaling Pathway through Dishevelled*

Inactivation of glycogen synthase kinase 3β (GSK3β) and the resulting stabilization of free β-catenin are critical steps in the activation of Wnt target genes. While Akt regulates GSK3α/β in the phosphatidylinositol 3-OH kinase signaling pathway, its role in Wnt signaling is unknown. Here we report that expression of Wnt or Dishevelled (Dvl) increased Akt activity. Activated Akt bound to the Axin-GSK3 complex in the presence of Dvl, phosphorylated GSK3β and increased free β-catenin levels. Furthermore, in Wnt-overexpressing PC12 cells, dominant-negative Akt decreased free β-catenin and derepressed nerve growth factor-induced differentiation. Therefore, Akt acts in association with Dvl as an important regulator of the Wnt signaling pathway.

Wnt signaling regulates several developmental processes in both insects and vertebrates. Aberrant Wnt signaling occurs both in oncogenic processes (1–3) and in some cardiovascular diseases (4–6). The interaction between secreted Wnt glycoproteins and their cognate Frizzled receptors leads to the activation of Dvl1 protein, which transmits the Wnt signal to downstream effectors. By inhibiting phosphorylation of β-catenin by GSK3β, activated Dvl prevents the ubiquitination and subsequent proteosomal degradation of β-catenin. The resulting accumulation of free β-catenin enhances its interaction with transcription factors of the lymphoid enhancer factor-T cell factor (LEF/TCF) family and induces the transcription of target genes such as cyclin D1 and c-myc (1–3). Two mechanisms have been advanced to account for the inhibition of GSK3β by Dvl: 1) the catalytic activity of GSK3β is blocked by serine phosphorylation (1, 7–10); 2) the interaction of GSK3β and β-catenin is disrupted by a conformation change of the Axin-β-catenin-GSK3β-adenomatosis polyposis coli protein complex (Axin complex) (2, 11–13). However, in the first instance, the process whereby Dvl stimulates serine phosphorylation has not been elucidated; nor is it clear whether these two mechanisms function in a concerted manner to promote Wnt signaling.

The serine/threonine kinase Akt (protein Kinase B related to A and protein kinase C) is a major effector of the PI3K pathway and is activated by many polypeptide growth factors (14–16). The recruitment of Akt from the cytoplasm to the plasma membrane by the lipid products of PI3K leads to Akt phosphorylation by 3-phosphoinositide-dependent protein kinases. This phosphorylation of Akt at Thr308 and Ser473 results in its activation. Akt acts in part through its phosphorylation of GSK3α/β, which in turn regulates cell metabolism. Recognizing the pivotal role of GSK3β in Wnt signaling, we tested the hypothesis that Akt functions in this pathway to control GSK3β activity.

EXPERIMENTAL PROCEDURES

Cell Culture—PC12, Int5 and Tni3 cells were cultured as described (17). 293T cells were maintained in Dulbecco’s modified Eagle’s medium (DMEM, Life Technologies, Inc.) supplemented with 10% fetal bovine serum (FBS, Hyclone), 20 mM HEPES (pH 7.35), 1 mM sodium pyruvate, and 1 mM non-essential amino acids (all from Life Technologies, Inc.). NIH-3T3 cells were cultured in DMEM supplemented with 10% FBS.

Plasmid Constructs and Adenoviruses—Mouse Dvl-1, Akt-1, Axin, and rat GSK3β were prepared by reverse transcriptase-polymerase chain reaction (PCR) using the high fidelity thermostable DNA polymerase PfuTurbo (Stratagene). Dvl-1 was subcloned in frame into pcDNA3.1−/−myc-His (Invitrogen) to introduce Myc-His epitope tags at the C terminus. GSK3β was subcloned into pcDNA3.1−/− (Invitrogen). Axin and Akt-1 were subcloned either in frame or with a stop codon into pFLAG-CMV5−/− (Sigma) to yield protein with or without FLAG tag at the C terminus, respectively. Deletion mutants of Dvl-1, N-Dvl-1(4–197), and C-Dvl(369–695) were generated by PCR and subcloned in frame into pcDNA3.1−/−Myc-His. The C-terminal (β-catenin binding) region of E-cadherin (18) was cloned by reverse transcriptase-PCR in frame into pEGEX5-1 (Amersham Pharmacia Biotech) for GST-E-cadherin pull-down assay. Four recombinant first-generation type 5 adenoviruses were used in these studies. Ad.EGFP has been described previously (19). Ad.AAA-Akt and Ad.β-gal.EGFP, which also express EGFP, were constructed using the method described previously (20). The wild type Akt-expressing adenovirus was constructed using Akt-HA (kindly provided by T. Franke) in pAdRVS-4 (kindly provided by D. Dichek) and obtaining homologous recombinants through cotransfection with pM17 (Microbix Biosystems) in 293 cells.

Wnt-3a-conditioned Medium—Wnt-3a- and control-conditioned medium were prepared essentially as described (21). We verified that Wnt-3a medium specifically up-regulated the cellular β-catenin levels in L cells.

Reporter Assays—293T cells were transfected using LipofectAMINE™ (Life Technologies, Inc.) in 6-well plates with 30 ng/well of TOPFlash or FOPFlash luciferase reporter (Upstate Biotechnology) together with effector plasmids or empty pcDNA3 vector (amount added to keep the total DNA content at 1 µg/well) as described in the figure legends. Cell extracts were prepared 24 h after transfection by a deter-
gent lysis method (Promega). Transfection efficiencies were normalized by pCMVβ-gal reporter activity (CLONTECH). Each construct was transfected at least three times in triplicate. Reporter activities (mean ± S.D.) are presented as the -fold increase of TOPFlash activity from the cells transfected with empty vector.

Western Blotting—Cell lysates were prepared in a buffer containing 20 mM Tris, pH 8.0, 140 mM NaCl, 1 mM EGTA, 1.5 mM MgCl2, 10% glycerol, 1% Triton X-100, 2.5 mM sodium pyrophosphate, 1 mM β-glycerophosphate, 1 mM sodium vanadate, dithiothreitol, and protease inhibitors (Complete® without EDTA, Roche). Cell extracts were clarified by centrifugation and subjected to SDS-polyacrylamide gel electrophoresis followed by immunoblotting with indicated antibodies.

Immunoprecipitation and Akt Kinase Activity Assays—Cell lysates were precleared with protein A or G-Sepharose beads (Amersham Pharmacia Biotech or Calbiochem, respectively) for 1 h at 4 °C, and then incubated with the indicated antibody and protein A or G-Sepharose beads for 3.5 h at 4 °C. The immunocomplexes were pelleted and washed three times with cold lysis buffer. The samples were subjected to immunoblotting with the indicated antibodies. Akt activity was measured using an Akt kinase assay kit (New England BioLabs) with recombinant GSK3β as a substrate for immunoprecipitated Akt.

Analysis of Free β-Catenin Levels—Free β-catenin levels were detected by GST-E-cadherin pull-down assay as described (18). GST-E-cadherin fusion protein was expressed in bacteria and purified by binding to glutathione-Sepharose beads (Amersham Pharmacia Biotech). 1 mg of cell lysate was incubated with GST-E-cadherin-beads for 1 h at 4 °C. The beads were collected by centrifugation and washed, and proteins were dissolved in Laemmli buffer and subjected to SDS-polyacrylamide gel electrophoresis followed by immunoblotting with anti-β-catenin antibody.

Neuronal Differentiation—Cells were incubated in differentiation medium (DMEM supplemented with 1% horse serum and 100 ng/ml NGF (Austral Biologicals) or growth medium (DMEM supplemented with 10% horse serum, 5% FBS)). Medium was refreshed every 48 h. Neurite out-growth was defined as a phase dark process with a clearly defined growth cone that was at least 1.5 cell diameters in length. Experiments were carried out in triplicate and repeated at least three times, and in each experiment cells were counted by at least two individuals who were blinded to the groups.

Statistics—Where indicated, comparisons between groups were made by factorial analysis of variance followed by Scheffe’s test (Fig. 1B) or by unpaired Student’s t test (Fig. 5C) when appropriate. Significance was accepted at p < 0.05.

RESULTS

Wnt Signaling Induces Phosphorylation and Activation of Akt—We first explored the possibility that Wnt signaling stimulates Akt activity. In a Wnt-1-overexpressing PC12 cell line (Int5) (17), but not in either the parental PC12 or in an anti-sense Wnt-1-expressing PC12 cell line (Tni3), Akt was phosphorylated at both Thr308 and Ser473 (Fig. 1A). The phosphorylation of both residues is necessary and sufficient for full Akt activation (16). Accordingly, Akt activity, measured by its ability to phosphorylate recombinant GSK3β, was much higher in Int5 cells than in control cells (Fig. 1A). Furthermore, phosphorylation of GSK3β at Ser9, which results in its inactivation (10), was higher in Int5 than in control cells (Fig. 1, A and B). Phosphorylation of Akt and GSK3β was inhibited by the Wnt antagonist-secreted Frizzled-related protein-1 (sFRP-1) (Fig. 1C) accompanied by a reduction in free β-catenin as we showed previously (22). These results indicated that phosphorylation of Akt and GSK3β, and free β-catenin levels in Int5 cells, were dependent on secreted Wnt-1 protein. To extend these observations to other cells, we also analyzed Akt phosphorylation in NIH-3T3 cells transiently transfected with Wnt-1, Dvl-1, and a β-catenin mutant (S37A β-catenin). Previous studies had shown that overexpression of these gene products cause an increase in free β-catenin, indicative of Wnt signaling (2, 8, 23–25). Transient expression of Wnt-1 or Dvl-1, but not S37A β-catenin, increased Akt phosphorylation (Fig. 1D). These results indicated that Akt activation is a consequence of Wnt signaling that occurs downstream of Dvl.

Dominant-negative Akt Inhibits Wnt Signaling Pathway—To determine whether activated Akt is required for the canonical Wnt signaling, we used a dominant-negative form of Akt (AA-Akt) (26). Int5 cells infected with an adenovirus expressing AAA-Akt (Ad.AAA-Akt) showed reductions in phosphorylated GSK3β and free β-catenin protein levels (Fig. 2A). These changes did not occur in cells infected with control virus (Ad.EGFP). In transient transfection assays using 293T cells, Wnt-1, Dvl-1, and S37A β-catenin each enhanced TCF-binding site reporter gene activity (TOPFlash) (Fig. 2B). AAA-Akt suppressed TOPFlash activity induced by Wnt-1 or Dvl-1 but did not affect the S37A β-catenin induced activity (Fig. 2B). The activity of the mutated TCF-binding site reporter (FOPFlash) was not affected in these experiments (data not shown and Fig. 3B). These results implied that Akt is involved in Wnt signaling, functioning at a point in the pathway between Dvl and β-catenin.

Akt Up-regulates Free β-Catenin Levels and Wnt Target Gene Expression in the Presence of Dvl—to test whether Akt activity is sufficient to stimulate an increase in free β-catenin, we infected Int5 and Tni3 cells with either an adenovirus-expressing wild type Akt (Ad.Akt) or a control adenovirus (Ad.EGFP). Although the amount and activity of Akt are similarly increased in both lines infected with Ad.Akt, a rise in free β-catenin levels was seen only in the Int5 cells (Fig. 3A). These results demonstrated that Akt activity was not sufficient to up-regulate free β-catenin but that it could augment the activity of a Wnt stimulus.

Recalling that a dominant-negative form of Akt inhibited Wnt signaling induced by Dvl, we postulated that Akt might
Akt expression increases free β-catenin levels in Int5 cells. Int5 cells were infected with the control adenovirus Ad.β-gal.EGFP or Ad.AAA-Akt at a multiplicity of infection (MOI) of 50 and harvested after 48 h. Proteins were analyzed as described for Fig. 1. B, dominant-negative Akt suppresses the expression of Wnt target gene. 293T cells were transfected with TOPFlash luciferase reporter together with AAA-Akt, Wnt-1 (330 ng), Dvl-1 (170 ng), S37A β-catenin (S37A) (8 ng), or empty pcDNA3 vector.

To delineate the mechanism of Akt and Dvl signal transduction, we investigated their interaction with the Axin complex. Others have shown that activated Dvl binds Axin and recruits GSK3β-binding protein to the Axin complex. This binding induces a conformational change in the complex, resulting in the inhibition of GSK3β phosphorylation of β-catenin (2, 12, 13). We first investigated the association between endogenous Akt and Axin. Similar to Wnt-1, Wnt-3a-conditioned medium induces the canonical Wnt signaling pathway (2, 9, 12, 13). We also examined total GSK3β, anti-Akt, anti-phospho-GSK3β antibodies. C, a Dvl mutant, which does not bind to Axin, cannot induce Akt association with the Axin complex. 293T cells were transfected with Axin-FLAG, Akt, and Dvl-Myc, C-Dvl-(369–695)-Myc, or N-Dvl-(1–497)-Myc as indicated. Immunoprecipitation and immunoblotting were performed as described above. D, Akt levels are correlated with GSK3β levels in the Axin complex. 293T cells were transfected with Dvl-Myc and Akt and with GSK3β and/or Axin-FLAG as indicated. Immunoprecipitation and immunoblotting were performed as described above.

Fig. 3. Akt enhances Wnt signaling in the presence of Dvl. A, Akt expression increases free β-catenin levels in Int5 cells but not in Tn3 cells. Tn3 and Int5 cells were infected with Ad.EGFP or Ad.Akt, and cells were harvested after 3 days. The cell lysates were probed with anti-Akt antibody. B, Akt increases the expression of a Wnt target gene in the presence of Dvl. 293T cells were transfected with the TOPFlash or the FOPFlash reporter together with plasmids of Akt and Dvl-1 (170 ng/well) or pcDNA3 as indicated. TOPFlash (closed bars) or FOPFlash (open bars) reporter activities are presented as the -fold increase ofTOPFlash activity from the cells transfected with empty vector.

Akt Interacts with the Axin Complex in the Presence of Dvl—To delineate the mechanism of Akt and Dvl signal transduction, we investigated their interaction with the Axin complex. Others have shown that activated Dvl binds Axin and recruits GSK3β-binding protein to the Axin complex. This binding induces a conformational change in the complex, resulting in the inhibition of GSK3β phosphorylation of β-catenin (2, 12, 13). We first investigated the association between endogenous Akt and Axin. Similar to Wnt-1, Wnt-3a-conditioned medium induces the canonical Wnt signaling pathway (2, 9, 12, 13). We also examined total GSK3β, anti-Akt, anti-phospho-GSK3β antibodies. C, a Dvl mutant, which does not bind to Axin, cannot induce Akt association with the Axin complex. 293T cells were transfected with Axin-FLAG, Akt, and Dvl-Myc, C-Dvl-(369–695)-Myc, or N-Dvl-(1–497)-Myc as indicated. Immunoprecipitation and immunoblotting were performed as described above. D, Akt levels are correlated with GSK3β levels in the Axin complex. 293T cells were transfected with Dvl-Myc and Akt and with GSK3β and/or Axin-FLAG as indicated. Immunoprecipitation and immunoblotting were performed as described above.

Fig. 4. Akt interacts with the Axin complex in the presence of Dvl. A, endogenous Akt and Axin associate in Wnt-3a-treated cells. 293T cells were cultured in Wnt-3a-conditioned medium or control medium for 24 h, which was refreshed every 6 h. Cell lysates (5 mg) were immunoprecipitated with an anti-Akt antibody (1:100). The immunoprecipitates and cell lysates were probed with anti-Axin, anti-phospho-Akt (Ser473; P-Akt), anti-Akt, anti-phospho-GSK3β (Ser9; P-GSK3β), and anti-GSK3β antibodies. IB, immunoblot; IP, immunoprecipitation. B, Akt associates with the Axin complex only in the presence of Dvl-1. 293T cells were transfected with Axin-FLAG, Dvl-Myc, Akt, or pcDNA3 as indicated and harvested after 24 h. For immunoprecipitation, the cell lysates (1 mg protein) were incubated with 5 μg of anti-FLAG (Sigma). The immunoprecipitates and cell lysates were probed with anti-phospho-Akt (Ser473; P-Akt), anti-Akt, anti-phospho-GSK3β (Ser9; P-GSK3β), anti-GSK3β, anti-FLAG, or anti-Myc antibodies. C, a Dvl mutant, which does not bind to Axin, cannot induce Akt association with the Axin complex. 293T cells were transfected with Axin-FLAG, Akt, and Dvl-Myc, C-Dvl-(369–695)-Myc, or N-Dvl-(1–497)-Myc as indicated. Immunoprecipitation and immunoblotting were performed as described above. D, Akt levels are correlated with GSK3β levels in the Axin complex. 293T cells were transfected with Dvl-Myc and Akt and with GSK3β and/or Axin-FLAG as indicated. Immunoprecipitation and immunoblotting were performed as described above.
Akt increased the amount of phosphorylated GSK3β in the Axin complex (Fig. 4B, IP). These results suggested that Dvl was necessary for Akt-dependent phosphorylation of GSK3β in the Axin complex. Furthermore, phosphorylated Akt was included in the Axin complex only in the presence of Dvl (Fig. 4B).

Dvl protein family members contain three highly conserved domains: an N-terminal DIX (Dishevelled-Axin) domain, a central PDZ (PSD-95/Discs-large-ZO-1) domain, and a C-terminal DEP (Dishevelled-EGL-10-Pleckstrin) domain (13, 27). Although the roles of each domain have not been elucidated completely, either the DIX or PDZ domain is sufficient for Axin binding (11). To confirm that Dvl binding to Axin is necessary for Akt involvement in the Axin complex, Dvl mutants were generated. Consistent with previous reports (11, 28), C-Dvl-(369–695), which lacks both the DIX and PDZ domains, did not bind to Axin, whereas N-Dvl-(1–497), which lacks the C-terminal region adjacent to the DEP domain, bound to Axin (Fig. 4C). Full-length Dvl and N-Dvl-(1–497), but not C-Dvl-(369–695), induced Akt interaction with the Axin complex (Fig. 4C). Although the magnitude of Akt association with the Axin complex induced by N-Dvl (1–497) was less than that seen with full-length Dvl-1, this difference was consistent with the relative amounts of the recombinantly expressed Dvl proteins (Fig. 4C). C-Dvl(369–695) and N-Dvl-(1–497) were expressed at similar levels (Fig. 4C), indicating that the absence of Akt in the Axin complex is not due to reduced C-Dvl-(369–695) expression levels. These results suggest that the N-terminal region of Dvl, which can bind to Axin, is required to induce Akt association with the Axin complex.

Akt did not interact directly with Axin or Dvl (Fig. 4B and data not shown). However, Akt binding to the Axin complex may be mediated by GSK3β, judging from the correlation of Akt and GSK3β levels in the complex (Fig. 4D). As shown in Fig. 4D, the amount of GSK3β and Akt protein in the Axin complex was higher in GSK3β-overexpressing cells than in control cells. Taken together, our results indicate that Dvl binding to the Axin complex enables Akt to associate with and to phosphorylate GSK3β in the complex.

Dominant-negative Akt Restores Neuronal Differentiation of Int5 Cells—Wnt signaling frequently is responsible for changes in cell morphology and differentiation (1–3). For instance, the Wnt-overexpressing Int5 cells have a flat shape and do not differentiate with NGF treatment, whereas the parental PC12 cells are round and differentiate readily in response to NGF (17). sFRP-1-treated Int5 cells differentiated in response to NGF (Fig. 5A); this implies that the phenotype of Int5 cells depends on Wnt signaling. To test the impact of Akt on this Wnt-dependent cellular phenotype, we infected Int5 cells with either a dominant-negative Akt (Ad.ΔA-Akt) or a control (Ad.β-galEGFP) adenovirus. In contrast to the cells treated with control virus, Int5 cells infected with Ad.ΔAA-Akt had a more differentiated appearance with extensive neurite outgrowth in response to NGF (Fig. 5B and C). Neuronal differentiation of Int5 cells was confirmed by changes in peripherin levels. Consistent with a previous report (29), in response to NGF, Wnt-1-overexpressing PC12 cells (Int5) did not up-regulate peripherin protein expression, whereas parental PC12 cells did (Fig. 5D). However, Ad.ΔAA-Akt-infected Int5 cells exhibited increased levels of peripherin when cultured in differentiation medium (Fig. 5D). Increased levels of peripherin are the result of Int5 cell differentiation but not of a direct effect of ΔAA-Akt, because peripherin levels of PC12 and Int5 cells in growth medium were not enhanced by Ad.ΔAA-Akt infection (Fig. 5D, growth). These results demonstrated that inhibition of Akt activity reversed the Wnt-dependent phenotype of Int5 cells, reinforcing the evidence that Akt has an important role in the Wnt signaling pathway.

**DISCUSSION**

Here we show that Wnt signaling stimulates Akt and that activated Akt, in association with Dvl, enhances the phosphorylation of GSK3β in the Axin complex. The concerted action of Dvl and Akt is a distinctive feature of Wnt signaling, which targets phosphorylation of the GSK3β pool that is directly responsible for phosphorylation of β-catenin and its subsequent rapid degradation. This finding explains why other factors, such as insulin and epidermal growth factor, that stimulate Akt through the PI3K pathway but do not activate Dvl fail to cause an increase in cytosolic β-catenin (30, 31). We believe that Dvl interaction with Axin induces a conformational change, allowing Axin-bound GSK3β to be phosphorylated by Akt. This phosphorylated GSK3β cannot modify β-catenin efficiently, which consequently accumulates in the cytosol and translocates to the nucleus where it combines with LEP/TCF family members to up-regulate Wnt-dependent gene expression.

Past reports have suggested that Akt is not involved in Wnt signaling (30, 32). Similar to these accounts, we observed that Akt by itself was not sufficient to mimic a Wnt signal. Also consistent with this literature, constitutively active membrane-bound forms of Akt (14) did not enhance TOPFlash activity, even in the presence of Dvl overexpression (data not shown). Presumably, membrane-anchored Akt is unable to interact with the Axin complex in the cytosol and consequently cannot regulate GSK3β activity in this critical pool. In contrast to these constitutively active forms, wild type Akt is activated at the plasma membrane and then translocates to the cellular interior (15). Previous studies did not detect Akt activation and...
resulting GSK3β phosphorylation at Ser9 when cells were treated with Wnt/Wg-conditioned medium for short time periods, whereas free β-catenin was accumulated immediately by this treatment (8, 31). In contrast, we documented Akt activation and involvement in Wnt signaling using models characterized by either prolonged or constitutive Wnt stimulation. Our data may suggest that the contribution of Akt is to sustain or enhance, but not initiate, the signaling process.

It is still unclear how Akt is activated by a prolonged Wnt stimulus. Recently, integrin-linked kinase was reported to interact with activated Dvl (33), to phosphorylate Akt (34), and to induce Wnt target genes (34, 35). Future studies will determine whether Dvl activates Akt through the integrin-linked kinase pathway.

Acknowledgments—We thank M. E. Greenberg and A. E. West for PC12 cells, G. M. Shackleford for Int5 and Tni3 cells, H. Band for 293T cells, J. R. Woodgett for the AAA-Akt expression plasmid, S. W. Byers for the S37A β-catenin expression plasmid, K. Willert and R. Nusse for the anti-Axin antibody, and S. Takada for the pPGKWnt-3aneo expression plasmid.

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J. Biol. Chem. 2001, 276:17479-17483.
doi: 10.1074/jbc.C000880200 originally published online March 9, 2001

Access the most updated version of this article at doi: 10.1074/jbc.C000880200

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