Dimerization Choices Control the Ability of Axin and Dishevelled to Activate c-Jun N-terminal Kinase/Stress-activated Protein Kinase*

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Axin and Dishevelled are two downstream components of the Wnt signaling pathway. Dishevelled is a positive regulator and is placed genetically between Frizzled and glycogen synthase kinase-3β, whereas Axin is a negative regulator that acts downstream of glycogen synthase kinase-3β. It is intriguing that they each can activate the c-Jun N-terminal kinase/stress-activated protein kinase (JNK/SAPK) when expressed in the cell. We set out to address if Axin and Dishevelled are functionally cooperative, antagonistic, or entirely independent, in terms of the JNK activation event. We found that in contrast to Axin, Dvl2 activation of JNK does not require MEKK1, and complex formation between Dvl2 and Axin is independent of Axin-MEKK1 binding. Furthermore, Dvl2-DIX and Dvl2-DEP proteins deficient for JNK activation can attenuate Axin-activated JNK activity by disrupting Axin dimerization. However, Axin-MID, Axin-AC, and Axin-CT proteins deficient for JNK activation cannot interfere with Dvl2-activated JNK activity. These results indicate that unlike the strict requirement of homodimerization for Axin function, Dvl2 can activate JNK either as a monomer or homodimer/heterodimer. We suggest that there may be a switch mechanism based on dimerization combinations, that commands cells to activate Wnt signaling or JNK activation, and to turn on specific activators of JNK in response to various environmental cues.

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1 The abbreviations used are: APC, adenomatous polyposis coli; GSK-3β, glycogen synthase kinase-3β; DIX, Dishevelled homologous domain; PDZ, PSD-95/Dlg/ZO-1; DEP, Dishevelled/egl-10/pleckstrin; JNK, c-Jun N-terminal kinase; MEKK, mitogen-activated protein kinase/extracellular signal-regulated kinase kinase; MID, MEKK1-interacting domain; Dvl, Dishevelled; HA, hemagglutinin; GST, glutathione S-transferase; SAPK, stress-activated protein kinase.

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functionally cooperative, antagonistic, or entirely independent in JNK activation. Here, we report that MEKK1 is not involved in Dvl2-mediated JNK, unlike JNK activation by Axin. We examined a possible mutual regulation between the Axin- and Dvl2-mediated JNK signaling pathway, and demonstrate that whereas Dvl2-activated JNK activity is not affected by Axin, Axin-mediated JNK activation may be regulated by Dvl2 through the DIX domain. Dimerization is critical for Axin activation of JNK, whereas it appears to not be requisite for Dishevelled activation of JNK. Our data suggest that dimerization choices determine the ability of Axin and Dishevelled to activate JNK.

MATERIALS AND METHODS

Construction of Plasmids—A series of different constructs of mouse Dvl2 (Fig. 3A) were created using convenient restriction enzyme sites. Briefly, to construct mutants HA-Dvl2-DEP and HA-Dvl2-ΔDIX, the N terminus of wild-type Dvl2 was deleted at the ApalI and XhoI sites, respectively, and fused in-frame to the HA tag. To construct HA-Dvl2-ΔPDZ, wild-type Dvl2 was digested internally at XhoI and ApalI sites, blunted with Klenow fragment, and religated in-frame. To construct HA-Dvl2-ΔDEP, the region between NotI and HpaI of wild-type Dvl2 was released and replaced with a polymerase chain reaction-generated fragment using the primers 5′-GGAAGCAGCGGCCGCCACGC-3′ and 5′-gttaacGGCCATGTCCATGTGGAC-3′ and 5′-gttaacGGCCATGTCCATGTGGAC-3′. Constructs for wild-type Axin, Axin-MID, Axin-3C, and Axin-CT (Fig. 5A) have been previously described (22). Expression vectors for MEKK1, MEKK1-K1255M, and MEKK1-C were gifts from Dr. M. Karin (University of California, San Diego, CA), and HA-Dvl1 was kindly provided by Dr. A. Kikuchi (Hiroshima University School of Medicine, Hiroshima, Japan).

Transient Transfection and Immunoprecipitation—Human embryonic kidney 293T cells were maintained in RPMI 1640 medium supplemented with 10% fetal bovine serum, 100 IU penicillin, 100 μg/ml streptomycin, and 2 mM glutamine. Transfections were performed in 60-mm dishes using Superfect™ according to the manufacturer's instructions (Qiagen). The total amount of transfected DNA was adjusted to 4 μg with the empty vector pcMV5 where necessary. Cells were harvested at 40 h post-transfection and lysed in a lysis buffer (22). FLAG-tagged JNK1 was immunoprecipitated using mouse monoclonal anti-FLAG M2 beads (Sigma), and the kinase activities were determined as described previously using 1 μg of GST-c-Jun (amino acids 1–79; Stratagene) as substrate (22). Fold activation of the kinases was determined by an imaging analyzer (Molecular Dynamics model 425E) and normalized to their expression levels. Data are expressed as -fold kinase activation compared with vector-transfected cells, and the values represent the mean ± S.E. from three separate experiments. Total cell lysates were probed with anti-HA to detect the expression of HA-MEKK1 (lanes 3 and 4) and HA-MEKK1-K1255M (lanes 5 and 6) in the presence (lanes 4 and 6) or absence (lanes 3 and 5) of Dvl2. B, Dvl2 does not form a complex with MEKK1. Cells were transfected with 1.5 μg of HA-Dvl2 plus 1.5 μg of either Myc-MEKK1 or Myc-MEKK1-C, cell lysates were immunoprecipitated (IP) with anti-HA for Dvl2, anti-MEKK1 for MEKK1, or control IgG. The immunoprecipitates and cell lysates were then analyzed by immunoblotting separately using anti-HA and anti-Myc for Dvl2 and MEKK1, respectively.

RESULT

Dvl2 Activation of JNK Does Not Require MEKK1 and Binding of Dvl2 to Axin Is Independent of the Axin-MEKK1 Interaction—We have previously demonstrated that MEKK1 binds Axin and is critical for Axin activation of JNK (22). Because Dishevelled possesses the ability to activate JNK (25, 26), we asked whether MEKK1 played a role in JNK activation by Dvl2. 293T cells were separately cotransfected with Dvl2, FLAG-JNK1, and wild-type HA-MEKK1 or its kinase-inactive mutant HA-MEKK1-K1255M, and assayed for their abilities to activate JNK. Similar kinase assays were performed on cells cotransfected with Axin as control. As expected, Dvl2 and MEKK1 each activated JNK by about 4- and 8-fold, respectively (Fig. 1A). Coexpression of Dvl2 with MEKK1 further elevated JNK activity (∼12-fold), but the kinase-inactive form of MEKK1, which reduced Axin activation of JNK (22), did not appear to alter Dvl2 activation of JNK (Fig. 1A). These results

Distinct Mechanisms of JNK Activation by Axin and Dvl

Fig. 1. Dvl2 activation of JNK is independent of MEKK1. A, kinase-inactive form of MEKK1 does not abolish Dvl2 activation of JNK. Cells were transiently transfected with 1 μg of FLAG-JNK1 plus 2 μg of either HA-MEKK1 or HA-MEKK1-K1255M in the presence (dark columns) or absence (light columns) of 1 μg of HA-Dvl2. Following immunoprecipitation of FLAG-JNK1, their kinase activities were assayed using GST-c-Jun as substrate. The amount of the kinase in each immunoprecipitate was quantified by immunoblotting. Data are expressed as -fold kinase activation compared with vector-transfected cells. The values represent the mean ± S.E. from three separate experiments. Total cell lysates were probed with anti-HA to detect the expression of HA-MEKK1 (lanes 3 and 4) and HA-MEKK1-K1255M (lanes 5 and 6) in the presence (lanes 4 and 6) or absence (lanes 3 and 5) of Dvl2. B, Dvl2 does not form a complex with MEKK1. Cells were transfected with 1.5 μg of HA-Dvl2 plus 1.5 μg of either Myc-MEKK1 or Myc-MEKK1-C, cell lysates were immunoprecipitated (IP) with anti-HA for Dvl2, anti-MEKK1 for MEKK1, or control IgG. The immunoprecipitates and cell lysates were then analyzed by immunoblotting separately using anti-HA and anti-Myc for Dvl2 and MEKK1, respectively.
suggest that MEKK1 does not play a role in Dvl2-mediated activation of JNK. In agreement with our above observations, we did not detect any interaction between Dvl2 and full-length MEKK1 or the C terminus of MEKK1 (MEKK1-C) in coinmunoprecipitation assays (Fig. 1B). We also addressed whether the dominant negative forms of other upstream activators of JNK such as TAK1-K63W, ASK1-K709M, Cdc42N17, and RacN17 could block Dvl2-mediated JNK activation. We found that Dvl2-induced JNK activation was significantly suppressed by dominant negative Cdc42N17 and RacN17, in agreement with a report on the involvement of Rac1 and Cdc42 in Dvl1-induced JNK activation (26). In contrast, we did not see any apparent change in Axin-mediated JNK activation in the presence of dominant negative Cdc42N17 and RacN17, suggesting that the JNK pathways activated by Axin and Dvl2 are distinct.

Because Axin binds MEKK1-C and Dvl-2 is capable of binding Axin (Fig. 2), we asked if Dvl2 would affect the binding of MEKK1-C and Axin. In the presence of Axin, MEKK1-C was detected in the Dvl2 immunoprecipitate (Fig. 2), albeit in lower amounts. Reciprocal coimmunoprecipitation studies revealed a similar result (Fig. 2), indicating that the binding of Dvl2 to Axin did not affect the interaction of Axin with MEKK1-C.

**Dvl2-DIX and Dvl2-DEP Proteins Deficient for JNK Activation Inhibit Axin-activated JNK Activity by Disrupting Axin Dimerization**—Dvl1, a Dishevelled family member, has been shown to interact with Axin, and the interaction is thought to be via their DIX domains, which are also capable of mediating oligomerization to form homo-oligomers (24). We investigated if there was cross-talk between Axin- and Dvl2-activated JNK. First, we asked whether oligomerization of Dvl2 was required for JNK activation. Dishevelled is known to possess multiple domains: DIX, PDZ, and DEP (3, 4, 15). We generated a series of deletion mutants of HA-tagged Dvl2 and assayed for their

![Fig. 2. Binding of Dvl2 and Axin does not affect the interaction between Axin and MEKK1-C.](image)

![Fig. 3. Oligomerization is not needed for Dvl2 activation of JNK.](image)

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abilities to activate JNK. As shown in Fig. 3B, the DEP domain, but not the N-terminal DIX and PDZ domains, was sufficient for the JNK activating activity of Dvl2, similar to studies performed on Dvl1 (25, 26). We asked whether the DEP domain played a role in dimerization of wild-type Dvl2. We found that Dvl2-DEP did not complex with wild-type Dvl2 even though Dvl2 was capable of self-interaction (Fig. 3A). These results suggest that oligomerization is not a requisite for Dvl2 to activate JNK.

Because Dvl2-DIX and Dvl2-DEP exhibited diminished JNK activation activity compared with wild-type Dvl2 (Fig. 3B), we cotransfected 293T cells with Axin and either of these

**FIG. 4.** Axin activation of JNK is inhibited by Dvl2. A, Dvl2-DIX or Dvl2-DEP inhibits Axin activation of JNK, and inhibition is in a dose-dependent manner. Cells were transfected with 1 µg of FLAG-JNK1, plus 1 µg of Myc-Dvl2-DIX or Myc-Dvl2-DEP in the presence of 1 µg of HA-Axin. Immunokinase assays were performed and are presented as described in the legend to Fig. 1. For dose-dependent studies, cells were transiently transfected with 1 µg of HA-Axin and 1 µg of FLAG-JNK1 together with increasing amounts of Myc-Dvl2-DEP as indicated. Total cell lysates were probed with anti-HA and anti-Myc for the expression of Axin and Dvl2-DEP, respectively. Immunokinase assays were performed and are presented as described in the legend to Fig. 1. B, heterodimerization of Dvl2-DEP and Axin reduces Axin self-association. Cells were transfected with 1 µg each of FLAG-Axin and Myc-Axin in the absence or presence of HA-Dvl2-DEP at 1 or 2 µg. Cell lysates were immunoprecipitated (IP) with anti-HA, anti-FLAG, anti-Myc, or control IgG. The immunoprecipitates and cell lysates were then analyzed by immunoblotting separately using anti-HA for Dvl2-DEP and anti-Myc and anti-FLAG for the Axin proteins. C, Dvl2-DEP but not Dvl2-DEP forms a complex with wild-type Axin. Cells were transfected with 2 µg of Myc-Axin together with 2 µg of either HA-Dvl2-DEP or HA-Dvl2-DEP. Cell lysates were immunoprecipitated (IP) with anti-Myc, anti-HA, or control IgG. The immunoprecipitates and cell lysates were then analyzed by immunoblotting separately using anti-Myc and anti-HA for Axin and the Dvl2 proteins, respectively. D, Dvl2-DEP binds to the C terminus of Axin. Cells were transfected with 2 µg of HA-Dvl2-DEP together with 2 µg of either Myc-Axin-ΔC or Myc-Axin-CT. Cell lysates were immunoprecipitated (IP) with anti-HA, anti-Myc, or control IgG. The immunoprecipitates and cell lysates were then analyzed by immunoblotting separately using anti-HA and anti-Myc for Dvl2-DEP and the Axin proteins, respectively.
Dvl2 mutants and asked if JNK activation by Axin would be affected. Overexpression of Axin alone robustly activated JNK (~9-fold) as seen previously (22), and this activity was increased to ~12-fold in the presence of wild-type Dvl2 and Dvl2-DEP. However, coexpression with either Dvl2-DIX or Dvl2-DEP significantly diminished the Axin-induced JNK activity in a dose-dependent manner (Fig. 4A), suggesting that Dvl2 mutants deleted for the DEP domain can regulate Axin activation of JNK, in which case they may bind Axin. To test this association, we performed immunoprecipitation assays using proteins tagged with different epitopes. Western blot analysis revealed that Myc-Axin coprecipitated with HA-Dvl2-ΔDEP but not HA-Dvl2-DEP (Fig. 4C). Conversely, only HA-Dvl2-ΔDEP coprecipitated with Myc-Axin. We noted that the complex formation between Axin and Dvl2-DEP reduced the homodimer formation between Axin itself (Fig. 4B). The association between Myc-Axin and HA-Dvl2-DIX was also detected in similar immunoprecipitation assays, albeit with lower affinity (data not shown). HA-Dvl2-ΔDEP was capable of interacting with Axin at the C terminus (Myc-Axin-CT), which includes the dimerization domain, and removal of this C-terminal domain from Axin (Myc-Axin-ΔC) impaired its ability to associate with Dvl2 (Fig. 4D). Taken together, these results suggest that the N terminus of Dvl2, which includes DIX and PDZ domains, can complex with the C-terminal region of Axin and regulate Axin-mediated JNK activity by disrupting the homo-oligomerization of Axin, which is prerequisite for JNK activation.

Axin-ΔMID, Axin-CT, and Axin-ΔC Proteins Deficient for JNK Activation Do Not Interfere with Dishevelled-activated JNK Activity—We have previously shown that mutant Axin proteins without the MID domain (Axin-ΔMID), the N terminus (Axin-CT), or the C terminus including the DIX domain (Axin-ΔC) are deficient for JNK activation (22). We next examined whether Axin could regulate Dvl2-induced JNK activity. Cells were transfected with Dvl2 alone or together with each of these mutant Axin proteins and assayed for their JNK kinase activities. As shown in Fig. 5A, coexpression with either Myc-Axin-ΔMID or Myc-Axin-CT did not alter the level of JNK activated by Dvl2, despite their abilities to form complex with HA-Dvl2 (Fig. 5B). Myc-Axin-ΔC, which also did not affect Dvl2 activation of JNK (Fig. 5A), did not bind Dvl2 (Fig. 5B). We obtained similar results when the same experiments were carried out with Dvl1 (Fig. 5A). Taken together, these data suggest that the Dishevelled-mediated JNK pathway is not regulated by Axin, and homodimerization is not requisite for Dishevelled activation of JNK.

**DISCUSSION**

It is most intriguing that Axin and Dishevelled, two critical factors that function as negative and positive regulators, respectively, in the same Wnt signaling pathway can activate a common kinase, JNK. The present study has examined if they activate JNK independently or cooperatively. We show that, whereas MEKK1 plays a critical role in JNK activation by Axin, it is not involved in Dvl2 activation of JNK, indicating that Axin and Dvl2 activate JNK through different mechanisms. Moreover, whereas Axin requires self-dimerization to activate JNK, Dvl2 does not. Heterodimerization between Axin and Dvl2 appears not to affect the ability of Dvl2 to activate JNK, yet it abolishes Axin activation of JNK.

Axin and Dishevelled proteins possess the conserved DIX domain, whose structural and functional importance has been revealed by several recent studies. Both a yeast two-hybrid interaction screen and in vitro binding studies demonstrate that Axin can bind itself through the DIX domain at the C terminus (14, 22–24, 27). Similarly, the N-terminal DIX domain of Dishevelled is necessary for self-interaction or the formation of heterodimers either among different Dishevelled family members or between Axin and Dishevelled proteins (24, 28). These biochemical interactions are supported by distribution studies in Xenopus embryos that show colocalization of Dishevelled and Axin within bright vesicular structures in the cytoplasm (8, 29). However, the significance of such homo- and heterodimer formation in the functions of Axin and Dishevelled remains to be clarified. Whereas it is known in Xenopus that removal of the DIX domain of Dishevelled results in total loss of the axis-inducing activity of Dishevelled (30), removal of the DIX domain of Axin does not affect its ability to ventralize frog embryos (8). We have recently shown Axin also has a functional role in activating the JNK signaling pathway and attributed the homo-oligomerization of wild-type Axin to be critical for JNK activation (22). Our results here clearly show that Dvl2-
ΔDIP forms a heterodimer with wild-type Axin, thereby abolishing Axin-mediated JNK activation. This suggests the formation of Axin homo- and heterodimers may provide a mode of regulation for Axin activation of JNK in that homodimers would favor JNK activation, whereas heterodimers would suppress JNK activation (Fig. 6).

On the other hand, Dv12 activation of JNK appears to be independent of the formation of homodimers/heterodimers, based on the observations (i) Dv12-DEP, which lacks the ability to complex with wild-type Dv12, still retains the capacity to activate JNK; and (ii) Axin mutants, which lack the MID domain or possess only the C terminus and are deficient for JNK activation, do not affect Dv12 activation of JNK even though they are fully capable of complexing with Dv12. Thus Dv12 oligomerization may not be critical for activating JNK, in contrast to the strict requirement of Axin oligomerization for JNK activation. This accords future studies to address how Axin and Dishevelled attain balances between homodimerization and heterodimerization. One intriguing possibility is that this balance may be regulated by Wnt signal. Axin is thought to be dephosphorylated and destabilized upon activation of the Wnt pathway (31). It is likely that the lowered abundance of Axin may favor its heterodimerization with Dishevelled, thereby deactivating Axin-JNK. It is equally possible that other factor(s) may be recruited to fine tune Axin function. In particular, with the advent of casein kinase as one of the major players in the Wnt pathway (32, 33), the regulatory signal may arise from factors other than the Wnt ligands.

The functional significance of the preferential inhibition of Axin-JNK by Dv1 is not immediately clear. In our study, overexpression of Axin alone is likely to mimic a situation whereby Axin is in high abundance over Dishevelled when Wnt signals are absent, favoring the homodimerization of Axin. Coexpression of Axin with Dishevelled may represent a scenario in which Dishevelled delivers Wnt signals through interaction with the Axin-GSK-3β complex. Although this process is not entirely clear, recent work indicates Dv11-Axin binding is necessary for the ability of Dv11 and Axin to regulate the stability of β-catenin (24), suggesting that the activated Wnt cascade favors the heterodimerization of Axin and Dishevelled. Activation of JNK is mediated via many signaling cascades and has been implicated in numerous cellular physiological processes, including morphogenesis, cell proliferation, and survival or cell death (34–37). Dishevelled activation of JNK in *Drosophila* plays a critical role in planar polarity signaling, in which cells determine their orientation in the plane of the epithelium and reorganize their cytoskeletons in a polarized array (15, 20, 25). Our finding that JNK activation by Dishevelled cannot be regulated by Axin suggests that planar polarity is separate from Axin function. However, it is unclear what the functional role of JNK activation of Axin is. The ubiquitous expression of Axin in almost all tissues from early embryonic development through to adult stage raises the possibility that Axin has a general role in regulating cell signaling, in addition to its well established role in embryonic axis formation. Our preliminary data suggest JNK activation by Axin may lead to apoptotic cell death. Work by Adachi-Yamada et al. (38) indicates that distortion of positional information in *Drosophila* during normal wing morphogenesis leads to JNK-dependent apoptosis of aberrant wing cells. It is possible that apoptosis caused by Axin may arise in those cells under conditions where the Axin to Dishevelled ratio is abnormally high. Dishevelled may be predicted to provide a means of controlling this Axin-JNK function, and the regulation is unique in that Dishevelled has the capacity to attenuate Axin-JNK, whereas Axin is unable to regulate Dv1-JNK.

In conclusion, our biochemical data strongly indicate that dimerization choices determine the ability of Axin and Dishevelled to activate JNK. The dimerization combination is likely to be determined by some switch mechanism that mediates which of the two should activate JNK under a given physiological situation and that commands cells to respond to various environmental cues.

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