The JNK-interacting Protein-1 Scaffold Protein Targets MAPK Phosphatase-7 to Dephosphorylate JNK*

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The c-Jun N-terminal kinase (JNK) group of mitogen-activated protein kinases (MAPKs) are activated by pleiotropic signals including environmental stresses, growth factors, and hormones. A subset of JNK can bind to distinct scaffold proteins that also bind upstream kinases of the JNK pathway, allowing sequential kinetic activation within a signaling module. The JNK-interacting protein-1 (JIP-1) scaffold protein specifically binds JNK, MAP kinase kinase 7, and members of the MLK family and is essential for stress-mediated JNK activation in neurons. Here we report that JIP-1 also binds the dual-specificity phosphatases MKP7 and M3/6 via a region independent of its JNK binding domain. The C-terminal region of MKP7, homologous to that of M3/6 but not other DSPs, is required for interaction with JIP-1. When MKP7 is bound to JIP-1 it reduces JNK activation leading to reduced phosphorylation of the JNK target c-Jun. These results indicate that the JIP-1 scaffold protein modulates JNK signaling via association with both protein kinases and protein phosphatases that target JNK.

MAPK activity is also regulated by protein phosphatases (2). In unstimulated cells JNK phosphatase activity is required to counteract the basal level of MKK4 and MKK7 activity and suppress JNK activation, whereas following cell stimulation JNK phosphatases can down-regulate JNK activity to basal levels (3–5). Inhibitor studies suggest that tyrosine, serine/threonine, and dual-specificity phosphatases contribute to JNK phosphatase activity (4). A large family of dual-specificity phosphatases (DSPs) has been identified that appear highly specific for MAPKs (2, 6). Over-expression studies have suggested that different dual-specificity phosphatases display different activities toward the MAPKs JNK, p38, and ERK. These experiments show that M3/6 (7), MKP5 (8, 9), and MKP7 (10–12) have higher activity against JNK than p38 or ERK, whereas MKP3 (13), MKP4 (14), and PAC1 (15) appear more specific for ERK. MKP1 appears to have equal activity against JNK, p38, and ERK (16).

Scaffold proteins bind components of MAPK-signaling modules and regulate their activity and intracellular location (17, 18). JNK signaling is controlled by scaffold proteins including both the JIP family and β-arrestin-2 (19–26). JIP-1 and JIP-2 share extensive sequence homology and are mainly expressed in neuronal tissues, testis, and β-cells; however, lower levels are present in many cell types (19, 20, 22). They interact with JNK, MKK7, and MLKs and can enhance signaling by this MAPK module (21, 22). JIP-2 has also recently been reported to interact with isoforms of p38 MAPK (27, 28). The third member of the family, JIP-3, displays no significant sequence homology with JIP-1 or JIP-2, but it also binds to multiple components of JNK-signaling modules (23, 24). In addition to the MLK-MKK7-JNK-signaling module, a number of other proteins have been demonstrated to interact with JIP-1, including hematopoietic progenitor kinase 1 (21), RhoGEF190 (29), β-amyloid precursor protein (30), kinesin light chain (26), and apolipoprotein E receptor-2 (31). The physiological functions of these interactions with JIP-1 remain to be elucidated. Genetic studies indicate a role for JIP-1 in neuronal apoptosis. The targeted deletion of the Jip1 gene in mice results in reduced apoptosis of hippocampal neurones in response to stress, which coincides with reduced JNK activity and reduced phosphorylation of the JNK target c-Jun (32). It has also been reported that JIP-1 may suppress JNK activation in some cell types (33, 34) or play a role in vesicle trafficking (26). In this study we sought to determine whether, in addition to recruiting protein kinase components of JNK-signaling modules, JIP scaffold proteins could recruit DSPs to regulate JNK signaling.

**EXPERIMENTAL PROCEDURES**

Plasmids—MKP2, MKP4, MKP7, and PAC1 were amplified by PCR using Turbo Pfu (Stratagene) from expressed sequence tags (Integrated Molecular Analysis of Genomes and their Expression (IMAGE) Consortium identification numbers: 3605895, 3501447, 4400399,

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The abbreviations used are: JNK, c-Jun N-terminal kinase; JIP, JNK-interacting protein; MAPK, mitogen-activated protein kinase; MKK, MAPK kinase; MKKK, MAPKK kinase; MKP, MAPK phosphatase; MLK, mixed lineage kinase; ERK2, extracellular signal regulated kinase 2; JBD, JNK binding domain; GST, glutathione S-transferase; DSP, dual-specificity phosphatase; HA, hemagglutinin; DAPI, 4′,6-diamidino-2-phenylindole.
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and 4297852) and then subcloned into the vectors pCDNA4HIS (Invitrogen) and fused to an N-terminal Xpression/T7 epitope tag or into pCDNA3.1 lacking an epitope tag (Invitrogen). MKP7 deletion constructs were subcloned into pCDNA4HIS fused to an N-terminal Xpression/T7 epitope tag. pMT M3/6 was a gift from Professor Alan Ashworth (Institute of Cancer Research, London, UK). HA-JNK3 was a gift from Dr. Julian Doward (Cancer Research, London, UK), and was subcloned into pCDNA3.1. Mutation of Cys-244 in MKP7 to Ser was performed using the oligonucleotide primer 5'-GATGTTGTTCTAGTGCACAGTTTAGCC-GGATCCCT'c, together with a complementary oligonucleotide and the QuickChange™ kit from Stratagene. Plasmids expressing T7-JIP-1 (21), T7-JIP-2 (22), T7-JIP-3 (23), GST-JIP-1, and JIP-1 deletions (21), HA-JNK2 (22), and HA-MLK3 (21) have been described previously. The construct expressing HA-c-Jun was provided by M. Karin (University of California, San Diego).

Production of Anti-MKP7 Polyclonal Antiserum—Residues 345–465 of MKP7 were expressed from the vector pET28 in the bacterial strain BL21 (DE3). Cell extracts were prepared in 50 mM Tris, pH 8.8, 300 mM NaCl, and 0.5% IGEPAL CA-630, and centrifuged at 14,000 × g for 10 min. The supernatant was discarded and the pellet resuspended in 10 mM Tris, pH 8.0, 8 M urea, and 100 mM NaH2PO4. The MKP7 fragment was bound to Ni-agarose (Quiagen) then eluted in 10 mM Tris, pH 4.5, 6 M urea, and 100 mM NaH2PO4. The final pH was adjusted to pH 7.0, and a rat was immunized at three weekly intervals. The first immunization of 50 μg of MKP7 and Complete Freund’s Adjuvant was via the Peyer’s Patches. The second immunization was also with 50 μg of MKP7 into the Peyer’s Patches but Incomplete Freund’s Adjuvant was used. The third immunization was done intraperitoneally with 80 μg of MKP7 mixed with Incomplete Freund’s Adjuvant. The final immunization was again via the Peyer’s Patches with 50 μg of MKP7 and Incomplete Freund’s Adjuvant. 5 days later the rat serum was collected and used unpurified at a dilution of 1/2000 for immunoblotting or 1/500 for immunoprecipitation.

Cell Culture—293T cells were maintained in Dulbecco’s modified Eagle’s medium (DMEM) supplemented with 10% fetal calf serum. ND7 and N1E-115 cells were maintained in DMEM supplemented with 10% fetal bovine serum. COS-7 cells were maintained in DMEM supplemented with 5% fetal calf serum. Both COS-7 and 293T cells were transfected using LipofectAMINE (Invitrogen) according to the manufacturer’s instructions.

Pull Downs, Immunoprecipitations, and Immunoblots—293T cells were washed once with ice-cold phosphate-buffered saline then lysed in buffer containing 50 mM Tris-HCl, pH 7.5, 150 mM NaCl, 1% IGEPAL CA-630, 5 mM EDTA, and a protease inhibitor mixture (Roche Molecular Biochemicals). After incubation on ice for 10 min, extracts were centrifuged at 14000 × g for 10 min. Supernatants were recovered and combined with an appropriate volume of gel loading buffer (final concentration 50 mM Tris, pH 6.8, 2% SDS, 100 mM dithiothreitol, 4% 6 M urea, and 100 mM NaH2PO4. The final pH was adjusted to pH 7.0, and a rat was immunized at three weekly intervals. The first immunization of 50 μg of MKP7 and Complete Freund’s Adjuvant was via the Peyer’s Patches. The second immunization was also with 50 μg of MKP7 into the Peyer’s Patches but Incomplete Freund’s Adjuvant was used. The third immunization was done intraperitoneally with 80 μg of MKP7 mixed with Incomplete Freund’s Adjuvant. The final immunization was again via the Peyer’s Patches with 50 μg of MKP7 and Incomplete Freund’s Adjuvant. 5 days later the rat serum was collected and used unpurified at a dilution of 1/2000 for immunoblotting or 1/500 for immunoprecipitation.

Selective Binding of JIP-1 and JIP-2 to the Dual-specificity Phosphatases MKP7 and M3/6—Sub-populations of JNK bind to scaffold proteins, therefore we asked whether distinct phosphatases regulate these distinct pools of JNK. MKP7 and M3/6 are DSPs that preferentially target JNK compared with other MAPKs (7, 10–12). We examined whether these DSPs could associate with the JIP family of scaffold proteins to regulate JNK activity. We co-expressed epitope-tagged JIP-1, JIP-2, and JIP-3 with either MKP7 or M3/6 and examined JIP precipitates for the presence of the DSPs using appropriate polyclonal antibodies. JIP-1 and JIP-2, but not JIP-3, associated with MKP7 (Fig. 1A, compare lanes 6, 9, and 12) and M3/6 (Fig. 1B, compare lanes 2, 4, and 6), suggesting that these phosphatases interact with a specific subset of JNK scaffold proteins. To determine whether the JIP proteins selectively interacted with MKP7 and M3/6 compared with other DSPs, we co-expressed GST-tagged JIP-1 and epitope-tagged versions of the DSPs in cells. Co-precipitation analysis demonstrated that MKP7 was detected in JIP-1 precipitates (Fig. 1C, lane 8). In contrast we detected no interaction with the DSPs MKP2, MKP4, and PAC1 (Fig. 1C, lanes 2, 4, and 6) or with MKP1 and MKP6.2 Our data therefore show that JIP-1 binds to a restricted set of DSPs including MKP7 and M3/6.

In Vivo Association of JIP-1 with MKP7 and M3/6—JIP-1 is strongly expressed in neuronal cells (26, 29, 32), whereas MKP7 is reported to be abundantly expressed in brain (11). Using appropriate antibodies, we sought to establish whether endogenous complexes of JIP-1 and MKP7 or M3/6 are present in neuronal cells. Antiserum against M3/6 (5) and a JIP-1 monoclonal antibody (22) have been described previously. We generated polyclonal antiserum against MKP7, which recognized exogenously expressed T7-tagged MKP7 on immunoblots of total COS-7 cell extracts (Fig. 2A) and recognized an endogenous protein corresponding to the size of MKP7 in extracts of the neuronal cell line N1E-115 (Fig. 2B). The MKP7 antiserum also immunoprecipitated the T7-tagged MKP7 from COS-7 extracts (Fig. 2A), indicating its suitability for co-immunoprecipitation experiments.

We performed co-immunoprecipitation analysis using the MKP7 and M3/6 antisera, and we detected endogenous JIP-1 in both MKP7 and M3/6 precipitates from extracts of the neuronal cell lines ND7 and N1E-115, respectively (Fig. 2, C and D). These data indicate that endogenously expressed JIP-1 can associate with MKP7 and M3/6. Previously, JIP-1 has been demonstrated to reside in the cytoplasm of N1E-115 cells and to be concentrated at the tips of the neurites (29). Both exogenously expressed and endogenous MKP7 have been reported to be cytoplasmic (10–12), although there is evidence that it is a nuclear shuttle protein (11). We therefore investigated whether JIP-1 and MKP7 co-localized in N1E-115 cells. As shown in Fig. 2E, JIP-1 immunostaining is present in the cell...
MKP7 Binds to JIP-1 Independently of JNK Binding—It has previously been demonstrated that immunoprecipitates of MKP7 with monoclonal JIP-1 antibody. A control IP was performed using rat immunoglobulin. For comparison, 20 μg of the original extract (Total Extract) was loaded on the gel. D, extracts of N1E-115 cells (0.5 mg) were subject to immunoprecipitation with a rabbit anti-M3/6 polyclonal antiserum. The presence of JIP-1 in the precipitates was examined by immunoblot with a monoclonal JIP-1 antibody. For comparison, 20 μg of the original extract (Total Extract) was loaded on the gel. E, detection of endogenous JIP-1 (green) and MKP7 (red) expression in N1E-115 cells by immunofluorescence analysis. The nucleus was detected by staining DNA with DAPI (blue). F, double-label immunofluorescence analysis of JIP-1 (green) and MKP7 (red) in N1E-115 cells. The images were overlaid (Merge) to demonstrate co-localization (yellow). The nucleus was detected by staining DNA with DAPI (blue).
over-expressed MKP7 (10, 11) and M3/6 (5) contain JNK and that JIP-1 can directly bind to JNK (19, 21). The formation of complexes between JIP-1 and MKP7 or M3/6 might therefore be mediated by an interaction of the phosphatase with JNK. To examine this question, co-immunoprecipitation analysis was used to determine the ability of MKP7 and M3/6 to bind to a JIP-1 mutant with a deletion in the JNK binding domain (JIP-1 ΔJBD) (Fig. 3, A and B). MKP7, but not JNK, bound to JIP-1 ΔJBD, indicating that MKP7 can bind to JIP-1 independently of JNK (Fig. 3B, lane 3). Similar results were obtained for M3/6 binding to JIP-1 ΔJBD.2 We further demonstrated that MKP7 could not bind to the N-terminal region of JIP-1 that includes the JNK binding domain (residues 1–282) but did bind to a C-terminal fragment of JIP-1 (residues 282–707) that does not associate with JNK (Fig. 3B, lanes 4 and 5). Very weak binding of a shorter C-terminal fragment of JIP-1 (amino acids 471–707) to MKP7 was also detected (Fig. 3B, lane 6). These results indicate that C-terminal regions of JIP-1 are required for binding MKP7 and that MKP7 forms a stable interaction with JIP-1 in the absence of JNK binding. However, it does not rule out the possibility that interactions between MKP7 and JNK may help to stabilize MKP7 binding to JIP-1.

We next sought to identify the region of MKP7 that mediates its binding to JIP-1. We performed co-precipitation analysis of MKP7 deletion mutants with JIP-1 (Fig. 3, C and D). An MKP7 deletion mutant containing amino acids 1–394 did not bind to JIP-1, whereas a mutant containing amino acids 1–443 did bind JIP-1, albeit more weakly than full-length MKP7 (Fig. 3D, compare lanes 1, 5, and 7). These experiments identify the sequence between amino acids 394 and 443 as important for
binding. There was increased binding to JIP-1 of an MKP7 mutant containing amino acids 1–552 (Fig. 3D, lane 11), indicating that additional sequences within the C terminus also contribute to binding. The C terminus of MKP7 is homologous to that of M3/6 but not to other DSPs, which probably explains the selective binding of MKP7 and M3/6 by JIP-1. The binding of JIP-1 to the C-terminal region of MKP7 is distinct from the JNK-binding region located in the N terminus of MKP7 (10), providing additional evidence that MKP7 binding to JIP-1 is independent of JNK binding. Interestingly, an MKP7 mutant lacking the extended C terminus, and therefore unable to bind to JIP-1, is significantly more active against JNK in co-expression studies than wild-type MKP7. This suggests that the C terminus of MKP7 may perform a regulatory function, and this in part may be mediated by binding to regulatory proteins such as JIP-1.

**MKP7 Blocks JIP-1 Enhanced Activation of JNK and c-Jun Phosphorylation**—JIP-1 binds to JNK, MKK7, and MLKs resulting in enhanced activation of JNK (21). We therefore tested the possibility that the interaction of MKP7 with JIP-1 would enhance the ability of this phosphatase to dephosphorylate the pool of JNK associated with the JIP-1 scaffold. As previously demonstrated, co-expression of full-length JIP-1 with MLK3 and JNK significantly enhanced the phosphorylation of JNK by MLK3 (Fig. 4A, compare lanes 5 and 8). The expression of MKP7 at a level that did not block JNK activation by MLK3 in the absence of JIP-1 was nevertheless able to completely block the ability of JIP-1 to enhance JNK activation by MLK3 (Fig. 4A, compare lanes 6 and 9). This effect of MKP7 depended upon its phosphatase activity. A catalytically inactive mutant of MKP7 (MKP7 CS) that still binds JIP-1 did not block the JIP-1-mediated enhancement of JNK activation (Fig. 4A, lane 10). These data demonstrate that the ability of MKP7 to dephosphorylate JNK is greatly enhanced by the JIP-1 scaffold protein.

One of the major targets of the JNK-signaling pathway is the transcription factor c-Jun (1). JNK phosphorylates c-Jun at Ser-63 and Ser-73 leading to an increase in its transcriptional activity (1). Previous genetic studies (32) have indicated that JIP-1-signaling complexes are involved in transducing JNK signaling to the c-Jun transcription factor. We therefore determined the effect of MKP7 on the ability of JIP-1 to enhance JNK-mediated c-Jun phosphorylation. Co-expression of JIP-1 with MLK3, JNK, and c-Jun significantly enhanced c-Jun phosphorylation (Fig. 4B, compare lanes 3 and 5). The expression of MKP7 impairs the ability of JIP-1 to enhance JNK-mediated c-Jun phosphorylation (Fig. 4B, compare lanes 5 and 6). Taken together, these results provide evidence that MKP7 can be recruited to the JIP-1 complex to down-regulate JNK signaling, leading to reduced phosphorylation of the JNK target c-Jun.

**DISCUSSION**

A number of scaffold proteins that regulate the activities of MAPK pathways have recently been characterized (17, 18). Our data provides the first evidence that MAPK scaffold proteins can recruit protein phosphatases to modulate MAPK activity. The JIP group of scaffold proteins regulates the activity of the JNK MAPK-signaling pathway by binding to the MLK-MKK7-JNK-signaling module (21–23). We have demonstrated that the JIP family proteins JIP-1 and JIP-2 also selectively associate with the DSPs M3/6 and MKP-7 (Figs. 1–3), and this can lead to the dephosphorylation and inactivation of JNK and reduced phosphorylation of c-Jun (Fig. 4).

Our results suggest a model whereby MKP7 and M3/6 are recruited to JIP scaffold proteins to dephosphorylate and inactivate JNK. However, the precise mechanism by which this occurs is unclear. One possibility is that these DSPs act to continually suppress the activation of JNK through the JIP-1 scaffold protein. This raises the possibility that inhibition of phosphatase action, either by inhibition of enzymatic activity or disruption of the interaction of the phosphatase with JIP-1, could contribute to the activation of JNK by JIP-1. Alternatively, phosphatase activity could be required at some specific point in the cycle of JIP-1 function. For example, the phosphatase may act to suppress inappropriate JNK activation, either by particular stimuli or at particular cell locations. The fact that in resting neuronal cells only a fraction of endogenous JIP-1 forms a stable complex with MKP7 and M3/6 (Fig. 2, C and D) suggests that the recruitment of the DSPs may not be a general mechanism for keeping JIP-mediated JNK signaling repressed in the absence of signal. This is supported by co-localization studies that demonstrate that the patterns of JIP-1 and MKP7 immunostaining in N1E-115 cells are overlapping but also distinct (Fig. 2, E and F). It is possible therefore that DSPs are recruited to JIP proteins at a particular cell location (e.g. in the cytoplasm of the cell body) or following stimulation of cells. Our preliminary experiments demonstrate that JIP-1 binding to MKP7 is not affected by oxidative stress, but future studies will be aimed at determining whether this interaction can be regulated either positively or negatively by other signals.

In the future it will be of interest to determine whether other regulators of MAPK pathways recruit specific protein phosphatases to down-regulate these pathways. It seems likely that the targeting of DSPs to specific JNK-signaling modules may be a common theme. Recently a novel DSP, SAPK pathway-regulating phosphatase 1, was described, which when over-expressed can bind to MKK7 and apoptosis signal-regulating kinase 1, potentially acting as a type of scaffold protein itself (35, 36). Expression of SAPK pathway-regulating phosphatase 1 specifically blocked JNK activation by tumor necrosis factor-α (tumor necrosis factor-α), indicating that the formation of this complex may have a distinct function in cells (35, 36).

Although the binding of protein phosphatases to regulators of MAPK-signaling pathways is a novel finding, there are precedents from other signaling systems for the recruitment of protein kinases and protein phosphatases to the same regulatory protein. For example, some members of the protein kinase A anchoring protein (AKAP) family of cAMP-dependent protein kinase-binding proteins also associate with protein phosphatases, thereby co-localizing both positive and negative regulators of a common substrate at distinct locations in cells (37). Such recruitment of positive and negative regulators of signaling pathways by scaffolding or anchoring proteins may therefore be a common mechanism for achieving signaling specificity in cells and permitting the rapid modulation of the activities of target proteins by phosphorylation and dephosphorylation.

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