The p62 Scaffold Regulates Nerve Growth Factor-induced NF-κB Activation by Influencing TRAF6 Polyubiquitination*

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Sequestosome 1/p62 is a scaffolding protein with several interaction modules that include a PB1 dimerization domain, a TRAF6 (tumor necrosis factor receptor-associated factor) binding site, and a ubiquitin-associating (UBA) domain. Here, we report that p62 functions to facilitate K63-polyubiquitination of TRAF6 and thereby mediates nerve growth factor-induced activation of the NF-κB pathway. In brain of p62 knock-out mice we did not recover polyubiquitinated TRAF6. The UBA domain binds polyubiquitin chains and deletion of p62-UBA domain or mutation of F406V within the ubiquitin binding pocket of the UBA domain abolished TRAF6 polyubiquitination. Likewise, deletion of p62 N-terminal dimerization domain or the TRAF6 binding site had similar effects on both polyubiquitination and oligomerization of TRAF6. Nerve growth factor treatment of PC12 cells induced TRAF6 polyubiquitination along with formation of a p62-TRAF6-IKKβ-PKCε signal complex, while inhibition of the p62/TRAF6 interaction had an opposite effect. These results provide evidence for a mechanism whereby p62 serves to regulate the NF-κB pathway.

Nuclear Factor κB (NF-κB) plays an important role in the regulation of a number of genes involved in neuronal development and survival, as well as numerous other cellular functions, such as inflammation, immunity, and cellular differentiation (1, 2). Constitutive NF-κB activity is necessary for neuronal survival (3) and neurite outgrowth (4). In its inactive state NF-κB is bound by its inhibitor protein, IκB, in the cytoplasm (1). Once a cell is activated, IκB is phosphorylated by IκB kinase (IKK) and tagged by ubiquitin for proteosomal degradation, freeing NF-κB to enter the nucleus (2). Nerve growth factor (NGF) elicits its biological response by binding to two receptors, TrkA and p75. The p75 receptor activates NF-κB by binding and interacting directly with TRAF6 (5) and a receptor-associated kinase, IRAK (interleukin receptor-associated kinase) (6). Through an adaptor protein, p62, the p75 receptor connects with the atypical protein kinase Cs (aPKCs), which serve as upstream kinases for phosphorylation and activation of IKKβ (7) in NGF and IL-1 signaling (8), suggesting a common and conserved mechanism whereby p62 regulates the NF-κB pathway.

Sequestosome 1/p62 was cloned as the interacting protein of the atypical PKCs (9, 10) and serves as a scaffold comprised of numerous protein interaction modules that allow effector proteins to converge and interact with their substrates, thus passing the signal downstream to activate NF-κB (11, 12). Both the aPKCs, ζ and 4, and tumor necrosis factor receptor-associated factor (TRAF6) specifically interact with p62; aPKC interacts with the PB1 domain (amino acids 3–100), and TRAF6 interacts with the TRAF6 binding domain (amino acids 228–254) (12). The interaction of p62 and TRAF family members is specific to p62 and TRAF6, as neither TRAF5 nor TRAF2 interact with p62 (8). The N terminus of p62 is also necessary for p62 dimerization (13), and p62 also possesses a UBA domain at its C terminus, which allows for interaction with both chains of polyubiquitin, as well as K63-polyubiquitinated proteins (14). Interestingly, mutations within the UBA domain and/or deletion of the UBA domain are implicated in Paget Disease of the Bone (PDB) (15).

We have shown previously that p62 is a necessary component in the activation of IKKβ by NGF (6, 7). Direct phosphorylation of IKKβ by aPKC is sufficient to activate IKK (16), whereby p62 bridges aPKC to IKKβ (17). TRAF6, a member of the RING domain family of E3 ubiquitin ligases (18), directs the synthesis of K63-linked polyubiquitin chains and is itself activated by K63-linked polyubiquitination (19, 20). Interaction of p62 with TRAF6 is essential for NF-κB signaling (8) by enabling TRAF6 to interact with aPKC and IKKβ into the signaling complex (17). In this regard, dominant negative aPKC impairs IKKβ activation (16), and depletion of p62 blocks NGF-induced NF-κB activation (6). Altogether, these findings suggest a possible role for p62 in the regulation of TRAF6 activation, although the biochemical mechanism whereby p62 regulates TRAF6 remains elusive.

In this study, we examine the role of p62 in TRAF6 activation. We find that through polyubiquitin binding to the UBA domain p62 regulates K63-polyubiquitination and oligomerization of TRAF6.

MATERIALS AND METHODS

Reagents—Antibodies against TRAF6, ubiquitin, IKKβ, IκB, HA, and Myc tags were purchased from Santa Cruz Biotechnologies, Inc. (Santa Cruz, CA). Anti-FLAG antibodies coupled to agarose or not were purchased from Sigma. IKKβ was from Upstate Biotechnology (Lake Placid, NY), and aPKC was obtained from BD Transduction Laboratories. NSF was obtained from Bioproducts for Science (Indianapolis, IN), and Δ9/13 NSF was provided by Kenneth Neet, Chicago Medical School. The TRAF6-interacting peptide containing the TRAF6-interacting domain of p62 (in italics) along with hydrophobic sequence (AAVALL-PAVVALLAP-EASAGPSEDPSVNLK) and control peptide (AAVAL-PAVVLALLAP-EASAGSADASVNLK) were synthesized by Alpha Diagnostics (San Antonio, TX).
**p62 Stimulates TRAF6 Activity**

![Image](http://www.jbc.org/)

**FIGURE 1. p62 domains necessary for TRAF6-dependent activation of NF-κB. A**, p62 constructs employed: wild type (WT) p62, full-length p62 aa 1–440; p62ΔN-term, a construct missing amino acids 1–229; p62ΔTRA6, a construct missing the TRAF6 binding site, amino acids 228–254; and p62ΔUBA, a construct missing the UBA domain amino acids 386–440. B, HEK cells were cotransfected with increasing concentrations of p62 and its mutants, along with TRAF6 and ubiquitin (Fig. 1A). Deletion of the N terminus, the TRAF6 domain, or the UBA domain of p62 completely prevented p62-stimulated ubiquitination of TRAF6 (Fig. 1B). These findings suggest that polyubiquitin chains carried by the UBA domain of p62 may be utilized for TRAF6 polyubiquitination. This finding suggests that polyubiquitin chains carried by the UBA domain of p62 may be utilized for TRAF6 polyubiquitination. We have shown that amino acids 406–409, MGF, in the UBA domain serve as a hydrophobic core pocket for polyubiquitin chain binding (14). Mutant 1, L398V, has no effect on the polyubiquitin chain binding ability of the UBA domain (14); however, mutant 2, F406V, in which a critical residue for the hydrophobic core pocket for polyubiquitin chain binding (14) is mutated to a hydrophilic residue, prevents p62 enhancement of ubiquitination of TRAF6. Likewise, deletion of the UBA domain blocked p62-stimulated TRAF6 polyubiquitination. This finding suggests that polyubiquitin chains carried by the UBA domain of p62 may be utilized for TRAF6 polyubiquitination.

**RESULTS**

We have previously shown that p62 is necessary for TRAF6-dependent activation of NF-κB in both the IL-1 and NGF systems (7, 8). To further examine the requirement for each domain of p62 in the NF-κB activation process, deletion constructs of p62, missing the N-terminal PB1 motif, the TRAF6 interaction site, or the UBA domain, were cotransfected into HEK cells, and NF-κB activity was measured by luciferase reporter assay (Fig. 1A). All p62 constructs were expressed (Fig. 1B). Deletion of any one domain of p62 abolished TRAF6-induced NF-κB activity, suggesting that each domain plays a critical non-redundant role in the biochemical mechanism of TRAF6 activation (Fig. 1B).

Previous studies have shown that the activity of TRAF6 is regulated by polyubiquitination/activation may be stimulated by endogenous factors (20, 21). To examine whether p62 regulates TRAF6 by a similar mechanism, HEK cells were cotransfected with p62, TRAF6, and ubiquitin (Fig. 2A). TRAF6 displayed low basal polyubiquitination; however, when cotransfected with p62, TRAF6 polyubiquitination was dramatically enhanced (Fig. 2A). Under stringent SDS-denaturing immunoprecipitation conditions, TRAF6 did not coimmunoprecipitate p62 as shown by lack of p62 in the TRAF6 immunoprecipitate (data not shown). We observe that p62 knock-out mice exhibit reduced NF-κB activity and diminished IKK phosphorylation (22). To examine whether the loss of p62 affected TRAF6 polyubiquitination, lysates of brain from p62 wild type or knock-out mice were immunoprecipitated for TRAF6, and ubiquitination was examined by Western blotting with anti-ubiquitin antibody (Fig. 2B). The loss of p62 completely eliminated ubiquitination of TRAF6 (Fig. 2A). To examine whether p62 stimulated TRAF6 K63-chain synthesis, mutants of Ub K29R, K48R, and K63R were transfected along with TRAF6 and p62. Mutation of K63R but not K29R or K48R completely eliminated TRAF6 K63-polyubiquitination, thereby demonstrating that p62 selectively stimulated K63-polyubiquitin chain synthesis.

Since all three interaction domains of p62 were necessary for NF-κB activity (Fig. 1A), we sought to evaluate the role each domain has in TRAF6 polyubiquitination. HEK cells were cotransfected with p62 and its mutants, along with TRAF6 and ubiquitin (Fig. 2D). Deletion of the N terminus, the TRAF6 domain, or the UBA domain of p62 completely prevented p62-stimulated ubiquitination of TRAF6 (Fig. 2D). These findings suggest that p62 dimerization through the N terminus is necessary for p62 to stimulate ubiquitination of TRAF6. Likewise, deletion of the UBA domain blocked p62-stimulated TRAF6 polyubiquitination. This finding suggests that polyubiquitin chains carried by the UBA domain of p62 may be utilized for TRAF6 polyubiquitination. We have shown that amino acids 406–409, MGF, in the UBA domain serve as a hydrophobic core pocket for polyubiquitin chain binding (14). Mutant 1, L398V, has no effect on the polyubiquitin chain binding ability of the UBA domain (14); however, mutant 2, F406V, in which a critical residue necessary for chain binding is changed, prevents p62 enhancement of TRAF6 ubiquitination. These findings demonstrate that chain binding by the UBA domain of p62 is necessary for ubiquitination of TRAF6.

Recent studies have shown that TRAF6 is activated via a mechanism employing oligomerization (21). To test whether p62 influences TRAF6 oligomerization, lysates from transfected cells were analyzed by glycerol gradient ultracentrifugation. Equal concentrations of transfected HEK cell lysate, expressing similar amounts of TRAF6 and/or p62 were loaded onto the gradients. For comparison purposes, fractions 9–12 (TRAF6 oligomers) were immunoprecipitated with FLAG, to capture transfected TRAF6, and then Western blotted for FLAG (Fig. 2F). TRAF6 migrated at the bottom of the gradient as oligomers only when cotransfected with full-length p62. Formation of TRAF6 oligomers was significantly reduced when the cotransfection was conducted with either ΔN-term or ΔUBA constructs of p62 and completely eliminated when TRAF6/p62 interaction was blocked. Altogether, these
**FIGURE 2. p62 enhances the E3 ubiquitin ligase activity of TRAF6.** A, HEK cells were cotransfected as shown, and TRAF6 was immunoprecipitated with FLAG followed by Western blotting with HA to detect Ub or FLAG to detect TRAF6. B, brain lysates prepared from wild type (WT) or knock-out (KO) p62 mice were immunoprecipitated with TRAF6 antibody and Western blotted with TRAF6 or p62 antibodies. C, HEK cells were cotransfected as shown and TRAF6 recovered by immunoprecipitation with FLAG antibody followed by Western blotting with HA to detect Ub or FLAG for TRAF6, Myc for p62. D, HEK cells were cotransfected as shown and TRAF6 recovered by immunoprecipitation with FLAG antibody followed by Western blotting with HA to detect Ub, Myc for p62. E, 12 200–μl fractions were collected from the glycerol gradients. Fractions 9–12 of TRAF6 oligomers were pooled and immunoprecipitated with FLAG antibody and Western blotted with FLAG to detect transfected TRAF6. The lysates were blotted with FLAG or Myc/Ha antibodies to examine expression of either TRAF6 or p62. IP, immunoprecipitation; WB, Western blotting.
p62 Stimulates TRAF6 Activity

FIGURE 3. NGF induces TRAF6 polyubiquitination and NF-κB activation in a p62-dependent manner. A, PC12 cells were treated with 50 ng/ml Δ9/13 NGF as shown, followed by immunoprecipitation of TRAF6 and Western blotting for Ub. B, PC12 cells were transfected with various p62 mutants as shown followed by stimulation with Δ9/13 NGF for 5 min. Lysates were prepared and immunoprecipitated for TRAF6 and Western blotted for Ub. C, NF-κB activity in transfected PC12 cells treated with 50 ng/ml Δ9/13 NGF was measured by luciferase assay (X ± S.E.). IP, immunoprecipitation; WB, Western blotting.

FIGURE 4. p62 serves as a scaffold for formation of a xB-signal complex. A, PC12 cells were treated with 50 ng/ml Δ9/13 NGF as shown, followed by immunoprecipitation of p62 and Western blotting with antibody to IKKβ, aPKC, TRAF6, or p62. B, PC12 cells were treated with TRAF6 inhibitory or control peptide for 5 h, stimulated with 50 ng/ml Δ9/13 NGF for 5 min, followed by immunoprecipitation of TRAF6 and Western blotted for Ub. The lysates were diluted with Triton lysis buffer and immunoprecipitated for TRAF6 and Western blotted for IKKβ, aPKC, or p62. The lysates were blotted for IKKβ, TRAF6, p62, or phospho-IκB as shown. IP, immunoprecipitation; WB, Western blotting.

findings suggest that p62 induces TRAF6 oligomerization and polyubiquitination.

NGF activation of NF-κB is p62-dependent (7). Since TRAF6 lies upstream in this signal cascade, we hypothesized that NGF might be a natural inducer of TRAF6 polyubiquitination. Furthermore, NGF/NF-κB activation occurs primarily through the p75 receptor, and this response is attenuated by TrkA receptor activation (6). Therefore, PC12 cells were stimulated with NGF Δ9/13, which selectively activates p75 neurotrophin signaling (23), resulting in potent stimulation of TRAF6 polyubiquitination (Fig. 3A). To examine the requirement for p62 and its interaction domains in this process, PC12 cells were transiently transfected with various p62 constructs, stimulated with NGF Δ9/13, followed by immunoprecipitation of TRAF6 and Western blotted with ubiquitin. Acting as dominant negative, deletion of p62 N-term, TRAF6, or UBA domains completely blocked ligand-stimulated polyubiquitination of TRAF6 (Fig. 3B), as well as NGF-induced NF-κB activity (Fig. 3C). Altogether, these findings underscore the critical and important role that p62 plays as a regulator in neurotrophin-mediated activation of TRAF6.

To examine the formation of the endogenous signal complex, PC12 cells were treated with Δ9/13 NGF over the course of the same time period used for the study of TRAF6 polyubiquitination (Fig. 3A). NGF treatment leads to transient formation of a p62 complex that consisted of IKKβ, aPKC, and TRAF6 (Fig. 4A). Interestingly, IKKβ, aPKC and TRAF6 were recruited simultaneously into the signal complex. To determine whether TRAF6 interaction with p62 was necessary for formation of the signal complex and activation of the NF-κB pathway, we used an inhibitory peptide that blocks p62-TRAF6 binding (14). The p62 sequence has a TRAF6 binding site, amino acids 228–254, and peptides to the core sequence (PSEDPS) have been shown to block TRAF6 signaling (24). Both control and inhibitory TRAF6 peptides were synthesized with a leader sequence added to impart cell permeability. PC12 cells were then treated with peptide for 5 h prior to stimulation with Δ9/13 NGF and immunoprecipitation of TRAF6. Treatment with the inhibitory peptide blocked NGF-induced TRAF6 polyubiquitination (Fig. 4B). The inhibitory peptide provided a tool to assess which proteins were recruited into the signal complex in a TRAF6 polyubiquitin chain-dependent manner. Therefore, interactions between p62 and components of the signal complex in the presence or absence of peptide were also examined (Fig. 4B). In addition to blocking polyubiquitination of TRAF6 (Fig. 4B), the inhibitory peptide blocked interaction of p62/TRAF6, recruitment of IKKβ and aPKC, and inhibited NF-κB activation, as assessed by lack of IκB phosphorylation in the lysates. Collectively, these results reveal that TRAF6 interaction with p62 leads to TRAF6 activation along with formation of a TRAF6 signal complex consisting of p62-TRAF6-IKKβ-aPKC.

DISCUSSION

Mutations in the UBA domain of Sequestosome 1/p62 have been recently liked to familial PDB (15). Several types of mutations have been
observed: 1) those that affect polyubiquitin binding, such as those of the hydrophobic surface patch involved in ubiquitin interaction, 2) mutations which encode premature stop codon(s) that produce a protein lacking a UBA domain, or 3) mutations that do not affect polyubiquitin chain binding. Our findings reveal that mutations that are within the hydrophobic surface patch are likely to affect NF-κB activation, since chain binding is necessary for TRAF6 activation. Likewise, deletion of the UBA domain results in a loss of function phenotype. On the other hand, mutations that have no effect on polyubiquitin chain binding may result in a gain of function phenotype. If so, this would be in keeping with our observation that the P392L Pagetic mutation results in hyperactivation of aPKC (31). Constitutive NF-κB has recently been identified as a novel protein that recruits TRAF6 to the actin cytoskeleton, a pathway that enables chain binding by the UBA domain. Further structural studies will be needed to assess the relationship between genotype and phenotype and the biochemical function of p62 in relation to PDB.

Previous studies have shown that TAB2 can enhance TRAF6 polyubiquitination through ubiquitin binding (20, 21). In addition, BARD1 can stimulate the E3 ubiquitin ligase activity of BRCA1 some 20-fold (25, 26). Likewise, activity of the RING Ub ligase, Mdm2, can be enhanced though interaction with MdmX (27). Thus, interaction of E3 ligases with their respective scaffold may serve as a conserved mechanism for their activation. There likely exist discrete sites for assembly of E3 signaling complexes within the cell. In this regard, we observed sites of punctate TRAF6/p62 colocalization in HEK cells treated with IL-1 (8) or PC12 cells treated with NGF (28). Moreover, the ability of p62 to recruit TRAF6 to these sites is dependent upon interaction of TRAF6 with p62 (8) or a functional UBA domain (14). Interestingly, although p62-UBA domain non-selectively binds K48 and K63 ubiquitin chains (29), p62 selectively stimulates K63-polyubiquitination chain synthesis as a function of interaction with the E3, TRAF6. These findings suggest the scaffolding function of p62 may regulate K63-polyubiquitination of target substrates brought into the p62/TRAF6 complex. Moreover, since loss of p62 interaction/dimerization influences TRAF6 K63-polyubiquitination, binding of TRAF6 to p62 probably induces a p62 conformation that enables chain binding by the UBA domain. Further structural studies will be needed to directly test this idea.

Activation of IKK through the TAK1-TAB1-TAB2 kinase complex requires polyubiquitination of TRAF6 (21, 30). Both TAB1 and TAB2 bind K63-polyubiquitin chains leading to the activation of TAK1 and subsequent phosphorylation of IKKβ in the activation loop (20). We propose that this activation scenario may be conserved and that p62 recruits TRAF6 and activates aPKCζeta/zeta, to initiate the signaling cascade with phosphorylation of IKKβ by aPKC (16). This would be in keeping with the observation that removal of p62 inhibits IKKβ phosphorylation and activation by NGF (7) and our findings herein demonstrating that removal of p62 and its interaction domains, or TRAF6/p62 interaction, blocks TRAF6 polyubiquitination and impairs formation of the NF-κB signal complex and activation of NF-κB. Interestingly, Ajuba has recently been identified as a novel protein that recruits TRAF6 to p62 and may stabilize the interaction of these two proteins influencing activation of aPKC (31). Constitutive NF-κB activity is necessary for neuronal survival (3). We are currently characterizing the neuronal phenotype of the p62 knock-out mice and observe significant neurodegeneration.3 Two naturally occurring isoforms of p62 are known: one lacks a TRAF6 binding site (32) and another lacks a UBA domain (33). Thus, p62 may regulate TRAF6 activation in a tissue and context-specific manner depending upon the expression of various p62 isoforms.

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