Experimental Procedures

Materials, DNA constructs, protein expression and purification. Wild type and mutant variants of MST1 and MST2 cDNAs were previously described (24). The cDNAs encoding human MOBKL1A, MOBKL1B, MOBKL2B, MOB2/HCCA2 and LATS1 were obtained from Origene, those encoding MST3, NDR1 and NDR2 were from the kinase clone set, Institute of Proteomics, HMS. All cDNAs were inserted into the pCMV5 vector and a FLAG and/or HA epitope tag was inserted at the aminoterminus. MOBKL1A, MOBKL1B, MOBKL2B and MOB2/HCCA2 cDNAs were inserted into the pGEX KG and pMal vectors and all constructs were verified by DNA sequence. N-terminally tagged GST- and MBP-fusion proteins were expressed in *E.coli* DH5α, affinity purified on glutathione – Sepharose or amylose resin respectively. Tetracycline - inducible (TetOn) MST2 and MOBKL1A constructs were cloned into pcDNA5/TO(Invitrogen). TetOn shRNA cassette was kindly provided by K. Strebhardt. shRNA against Mobkl1B and Mobkl1A used following oligos, and subcloned into pcDNA5/TO vector. Target sequences are underlined. MOBKL1B forward:
AGCTTGACTATTCTAAAGCGTCTGTTCAAGAGACAGACGCTTTAGAATAGTCTTTT;
MOBKL1B reverse:
CTAGAAAAGACTATTCTAAAGCGTCTGTCTCTTGAACAGACGCTTTAGAATAGTCA;
MOBKL1A forward:
TGCATTTCCATTCAGTGAATGGAGCTTCAAGAGAGCTCCATTCACTGAATGGAAATGCTTTT;
MOBKL1A reverse:
CTAGAAAAGCATTTCCATTCAGTGAATGGAGCTCTCTTGAAGCTCCATTCACTGAATGGAAATGCA
Lentiviral constructs expressing GFP and shRNA against MST2 were made by subcloning the following oligos (target sequences are underlined) into Lentilox 3.5 vector. MST2 forward:

TCGGTCAAGTTGTCGCAATTTTCAAGAGAAATTGCGACAACTTGACCG TTTTTTC;
MST2 reverse:
TCGAGAAAAAACGGTCAAGTTGTCGCAATTTCTCTTGAAAATTGCGACAACT TGACCGA

Okadaic acid was from Calbiochem (San Diego, CA).

Identification of a 25 kDa substrate for MST1 from L1210 cell lysate using KESTREL. L1210 cells were extracted in two steps so both cytoplasmic and nuclear extracts to be obtained. The cells were harvested, washed once in cold PBS and suspended in lysis buffer (10mM HEPES, pH 7.6, 50mM NaCl, 0.25M Sucrose, 0.1mM EGTA, 1mM DTT, 1mM $MgCl_2$, 1mM PMSF, 1mM NaF, proteinase inhibitor tablet (Roche); all procedures thereafter were at 4°C. After a brief sonication sufficient to disrupt >90% of cells, the sample was centrifuged at 1000xg for 10 min to pellet nuclei. This supernatant was centrifuged further at 10 000xg for 15 min. and this supernatant was used as the cytosolic extract. The nuclear pellet was washed once in a low salt buffer (10mM HEPES pH 7.6, 10mM KCl, 1mM $MgCl_2$, 0.1mM EGTA, 1mM DTT, 1mM PMSF 1mM NaF, Roche proteinase inhibitor tablet), resuspended in high salt buffer (10mM HEPES pH 7.6, 0.2% (w/v) Brij 35, 0.5M NaCl, 0.1mM EGTA, 1mM DTT, 1mM PMSF 1mM NaF, Roche proteinase inhibitor tablet), incubated for 15 min at 4^0C with occasional vortexing and subjected to centrifugation at 10 000xg for 15 min. The resultant supernatant was combined with the cytosolic extract (108 mg of total protein) and dialyzed extensively against the column buffer (10mM HEPES pH 7.6, 100mM NaCl, 1mM $MgCl_2$, 0.2% (w/v) Brij 35, 0.1mM EGTA. 0.1% (v/v) β-mercaptoethanol, 1mM NaF, 1mM PMSF). The sample was applied to a 5 ml Hi Trap HP SP column (Amersham Biosciences) equilibrated in the column buffer and the elution was carried out with 20 column volumes of an NaCl gradient from 0.1M to 0.5M. Fractions of 1 ml were collected and aliquots of every third fraction were diluted in kinase buffer (20 mM Tris-HCl pH 7.5, 100 mM NaCl, 20 mM β-glycerophosphate, 10 mM DTT, 0.1 mM EGTA, 1mM Na_3VO_4, 100 nM Calyculin) so that 5.5 μg of each fraction were used in a

kinase assay for 5 min at 30°C with or without active MST1 (200 ng) in the presence of 2 mM $MnCl_2$ and 20 nM [γ-^{32}P] ATP. The reactions were stopped by adding SDS sample buffer and subjected to SDS-PAGE. The dried gels were examined by autoradiography. Fractions containing the 25 kDa MST1 substrate were pooled, dialyzed into gel filtration column buffer (20mM Tris-HCl pH 7.5, 100mM NaCl, 0.1mM EGTA, 0.1% (v/v) β-mercaptoethanol), concentrated and loaded onto Superdex 200 10/300 GL column (Amersham Biosciences). The elution was carried out with 1.5 column volumes and 0.5ml fractions were colleted. Aliquots of each third fraction were again tested as substrates for MST1 as described above. Fractions containing the MST1 substrate were pooled, concentrated, subjected to SDS-PAGE and stained with Coomassie Blue; an aliquot of the pool was phosphorylated by active MST1 in the presence of 2 mM $MnCl_2$ and 20 nM [γ-^{32}P] ATP for 5 min at 30°C. The major protein – staining band in the preparation that co-migrated with the ^{32}P labeled band was excised, digested with trypsin and the peptides analyzed by LC-ESI-MS-MS.

Antibodies. The anti-MST1(Thr183P)/MST2(Thr180P) phosphospecific antibody was previously described (24). The following synthetic peptides coupled to KLH through their aminoterminal or carboxyterminal cysteine, were employed to immunize rabbits:
MST1: CK_{246}LKRQEAQQREVDQDDEENSEEamide;
MST2: CK_{298}AKRHDEQQRELEEEEENamide;
LATS1: K_2RSEKPEGYRQMRPC;
LATS2: CS_{32}SVQGLPAGPNSDTSamide;
LATS1/2 activation loop P-peptide: CQRSLAHS(PO4)LVGTPNamide;
LATS1/2 carboxyterminal P-peptide: CEHAFYEFT(PO4)FRRFFDDamide;
MOBKL1A/B Thr12(PO4)-peptide: CSRSSKT(PO4)FKPKKNamide;
MOBKL1A/B Thr35(PO4)-peptide: CLKHAEAT(PO4)LGSGNamide;
Affinity purification of the antibodies against nonphosphorylated antigens was accomplished by adsorbtion/elution from the peptide antigens coupled to Sulfolink Gel (Pierce). For isolation of the phosphospecific antibodies, the immune serum was first adsorbed with columns containing the unphosphorylated peptide, followed by adsorbtion of the flowthrough to the immobilized P-peptide.

Polyclonal antibody recognizing MOBKL1A/B polypeptides was raised in rabbits against full-length bacterially expressed GST-fusion MOBKL1A. The antiserum was affinity-purified on AminoLink Plus Gel (Pierce), to which full-length bacterially expressed MBP-fusion MOBKL1A had been coupled covalently. Elution of all antibodies was accomplished with glycine at pH2.5 followed by immediate neutralization with Tris base and dialysis against 50% glycerol in PBS.

Secondary goat anti-rabbit/mouse HRP-conjugated antibodies were obtained from Jackson Immunoresearch Laboratories. Anti-FLAG antibody was obtained from Sigma and anti-HA antibody from Covance (Princeton, NJ). Other antibodies were from Cell Signaling Technologies.

Cell culture, transfection and cell synchronization. HEK 293, U2OS and L1210 mouse pre-B-cell leukemia cells were all maintained in Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal bovine serum (FBS) in the presence of 100 units/ml penicillin and 100 μg/ml streptomycin (Invitrogen) at 37^0C in a humidified atmosphere with 5% CO_2 for HEK 293 and U2OS, and 10% CO_2 for L1210 cells. TetOn U2OS cell lines were made by selection of stable transformants expressing pcDNA6/TR (Invitrogen) and pcDNA5/TO based constructs. Stable lines were maintained in medium with 10 μg/ml Blasticidin and 300 μg/ml Hygromycin (InvivoGen). 1 μg/ml or 5 μg/ml Doxycycline (Sigma) was added to induce protein or shRNA expression in stable lines. MST2 shRNA stable clones of U2OS cells were made by selecting single cells expressing GFP out of a pool of U2OS cells infected with lentivirus coding shRNA for MST2. For transient transfection cells were plated 24h before transfection and then transfected with Lipofectamine (Invitrogen) according to the manufacturer's recommendations. U2OS cells were plated one day before the onset of synchronization which was achieved by growing the cells in their complete medium containing 0.4μg/ml Nocodazole (Sigma) for 16h. The rounded U2OS cells were then either collected (shaken off) and used as mitotic samples or washed twice with fresh medium and re-plated for different time points needed for studying the mitotic exit.

Fluorescence-activated cell sorter (FACS) analysis. U2OS cells were trypsinized, and rinsed once in DMEM, 10% FBS, once in PBS and fixed in 70% ethanol. Fixed cells

were washed twice in PBS, 1% BSA, and then suspended in 500 μl staining solution, which contains 0.05% Triton X-100, 50 μg/ml Prodium Iodide (PI), 0.1 mg/ml RNase A in PBS. Cells were stained at 37 ^{o}C for 30 min, then analyzed by using a FACSCalibur system (BD Biosciences).

In vitro kinase assays. All recombinant kinases were expressed as FLAG-tagged proteins in HEK 293. The cells were lysed in 1% Triton X-100 lysis buffer containing 30mM HEPES pH 7.4, 20mM β-glycerophosphate, 20mM KCl, 1mM EGTA, 1mM NaF, 1mM DTT, 1mM PMSF, 1mM Na_3VO_4, 100 nM Calyculin, proteinase inhibitor tablet (Roche) and the recombinant kinases were immunoprecipitated on FLAG sepharose and eluted off the beads using 0.1 mg/ml FLAG peptide in lysis buffer. MST1, MST2 and MST3, immobilized on the FLAG sepharose beads, were preactivated by incubation in kinase buffer (20mM Tris-HCl pH 7.5, 100mM NaCl, 20mM β-glycerophosphate, 10mM DTT, 0.1mM EGTA, 1mM Na_3VO_4, 100nM Calyculin) supplemented with 10mM $MgCl_2$ and 250μM ATP (5 times in excess of the approximate EC50 ATP ~50μM) at 30^{o}C for 30 min. The sepharose beads were then washed 3 times in lysis buffer and preactivated kinases were eluted with FLAG peptide. Aliquots of these preparations were used in the substrate studies.

To measure the fractional activation of endogenous MST1 and MST2 kinases, each enzyme was immunoprecipitated out of either exponentially growing or Nocodazole - arrested U2OS cells. The immunoprecipitated MST1 and MST2 proteins were eluted from the beads at 4°C by addition of 3 volumes of lysis buffer containing 0.25 mg/ml of MST1 or MST2 peptide, with occasional vortexing. Each eluate was divided into two aliquots; one was subjected to preactivation in vitro as described above and the other incubated in parallel without ATP. The ATP concentrations were then equalized at 10 μM by dilution into the appropriate mixture containing γ32P-ATP; the kinase activity was determined under conditions that do not permit significant autoactivation in vitro (10mM $MgCl_2$, 10 μM ATP for 2 min at 30^{0}C) using 1 mg/ml MBP (myelin basic protein) as a substrate. The reactions were terminated by adding SDS sample buffer, separated by SDS/PAGE and analyzed by phosphoimaging. The resultant 32P-MBP

expressed in arbitrary units are identified as “basal activity” for non-preactivated samples and “maximal activity” for preactivated samples.

Supplementary Figures:

Figure S1. The amino acid sequences of the human MOBKL polypeptides was assembled and aligned using ClustalW. An * indicates identity in the amino acid at that site, whereas : and . indicate sequence conservation of a progressively lesser extent. The sites of MST1/2-catalyzed phosphorylation on MOBKL1A/B (threonines 12 and 35) and the corresponding sites on MOBKL2A/B/C are in bold. In addition to MOBKL1A and 1B, several other genes encoding MATS-related polypeptides are found in the human genome. Three genes (MOBKL2A, Chr19p13.3; MOBKL2B, Chr9p21.2; MOBKL2C, Chr1p33) encode polypeptides that are each nearly 70% identical to each other, approximately 50-60% identical to MOBKL1A and all three contain potential phosphorylation sites corresponding to MOBKL1A/B Thr12 and Thr35. More distant are the polypeptides encoded by MOB2/HCCA2 (Chr11p15.5) and MOB3/phocein (Chr2q33.1), which are approximately 40% and 25% identical to MOBKL1A/B respectively, however both lack potential phosphorylation sites corresponding to those phosphorylated in MOBKL1A/B by MST1.

Figure S2. Binding of MOBKL1A/B to MST1/2 and ndr family kinases.

(A) Multiple endogenous kinases bind to overexpressed recombinant MOBKL1A. Flag MOBKL1A or empty Flag vector were expressed transiently in 293 cells; the Flag-sepharose pull-downs were eluted with Flag peptide and the eluates were immunoblotted with the anti-LATS1, LATS2, MST1 and MST1 antibodies, as shown. In addition, a Coomassie-blue stained band of ~60kDa seen only in the Flag-MOBKL1A immunoprecipitate was analyzed by LC/MS/MS and found to contain NDR1 and NDR2.

(B) MOBKL1A phosphorylation promotes its binding of LATS1, NDR1 and NDR2 in vitro. Top two panels: Fifty ng of GST, GST-MOB1A wildtype or GST-MOBKL1A mutants immobilized on GSH-sepharose were preincubated at 30^0C for 20 min with 20 ng of preactivated MST2, with (five right-most lanes) or without MgCl2 (10 mM) and ATP (100 μM). The beads were then washed five times and 150 μg of a 293 cell lysate expressing recombinant Flag-LATS1 was added. After one hour at 4°C the beads were again washed five times, eluted into SDS sample buffer and examined, after SDS-PAGE, by immunoblot with anti-LATS1 and anti-GST antibodies.

Lower three panels: As in the top two panels, except the 293 lysate added contained recombinant Flag-NDR1 (third panel from top) or Flag-NDR2 (fourth panel from top) instead of Flag-LATS1.

Figure S3. Characterization of the phosphospecific MOBKL1A/B and LATS1/2 antibodies.

(A) Specificity of anti-P-MOBKL1A/B antibodies. 293 cells were transfected with Flag-MST1 (lane 2), Flag-MST2 (lanes 3-6) or empty Flag vector (lane 1) together with Flag-MOBKL1A wildtype (lanes 1,2,3) Flag-MOBKL1A(Thr12Ala) (lane 4), Flag-MOBKL1A(Thr35Ala) (lane 5), or Flag-MOBKL1A(Thr12/35Ala) (lane 6). Extracts were subjected to SDS-PAGE and immunoblot using anti-Flag and anti-MOBKL1A/B

phosphospecific antibodies, as indicated. Note that mutation of Thr35 to Ala greatly reduces Thr12 phosphorylation.
(B) Immunoblot of 293 cell extracts with anti-P-MOBKL1A/B antibodies. Extracts were prepared from untreated (left) or okadaic acid-treated (right, 1μM for 30 min.) 293 cells. Immunoblots of the cell lysate (25μg polypeptide/lane) with anti-MOBKLIA/B(Thr12P) and (Thr35P) are shown.
(C) Specificity of the LATS1/2 phosphospecific antibodies. 293 cells were transfected with Flag-LATS-1WT, LATS1(Ser909Ala) or LATS1(Thr1079Ala); some of the cells were treated with okadaic acid (1uM for 30') prior to harvest. Extracts were subjected to SDS-PAGE followed by immunoblot with anti-LATS1(Thr1079-PO4) upper panel; anti-LATS1(Ser909-PO4) middle panel; anti-FLAG, lowest panel. Note that okadaic acid treatment greatly increases the LATS1 reactivity with the phosphospecific antibodies, and that mutation of Thr1079 to Ala greatly inhibits Ser909 phosphorylation.

Figure S4. Effects of recombinant MST2(K56R) on ERK and JNK and recombinant MST2 wildtype of MOBKL1A/B and LATS1/2 phosphorylation.
(A) H2O2 induced phosphorylation on ERK and JNK is not affected by expression of kinase-dead MST2. The experiment is that shown in Figure 4B, except the extracts were immunoblotted for endogenous ERK and JNK polypeptides and their subsets exhibiting activation loop phosphorylation.
(B) Overexpression of wildtype MST2 increases basal and H2O2 stimulated MOBKL1A phosphorylation. The experiment was performed exactly as in Figure 4B, however the U2OS cells employed contain tetracycline-inducible Flag-MST2 wildtype rather than the inactive MST2(K56R). Note that in contrast to (B), the basal and H2O2 stimulated MOBKL1A and LATS1 phosphorylations are slightly enhanced.

Figure S5. Nocodazole-induced MOBKL1A/B and LATS1 phosphorylation in U2OS cells expressing Lentiviral encoded shRNA directed against MST2.
Three lentiviral MST2 shRNA U2OS stable clones as well as U2OS cells infected with the empty lentiviral vector were harvested during exponential growth (cycling, C) or by shake-off after an overnight nocodazole-induced arrest in metaphase (mitotic, M). Aliquots of total cell lysates containing equal protein were subjected to SDS-PAGE and immunoblot for endogenous MST1, MST2, MST1/2(Thr183P/180P), MOBKLA/B(T35P), MOBKL1A/B, Histone 3(T10P), LATS1/2(S909P), LATS1/2(T1079P), LATS1 and tubulin. Although there is an apparent gradient in the level of MST2 knock down from clone 1 (~30% reduction of MST2) to clone 2 (~80% reduction of MST2) to clone 3 (a >95% decrease of MST2 protein), a substantial decrease in nocodazole-induced MOBKL1A/B phosphorylation (and reduced LATS1(Thr1079) phosphorylation) is evident only with clone 3, in the left panel.

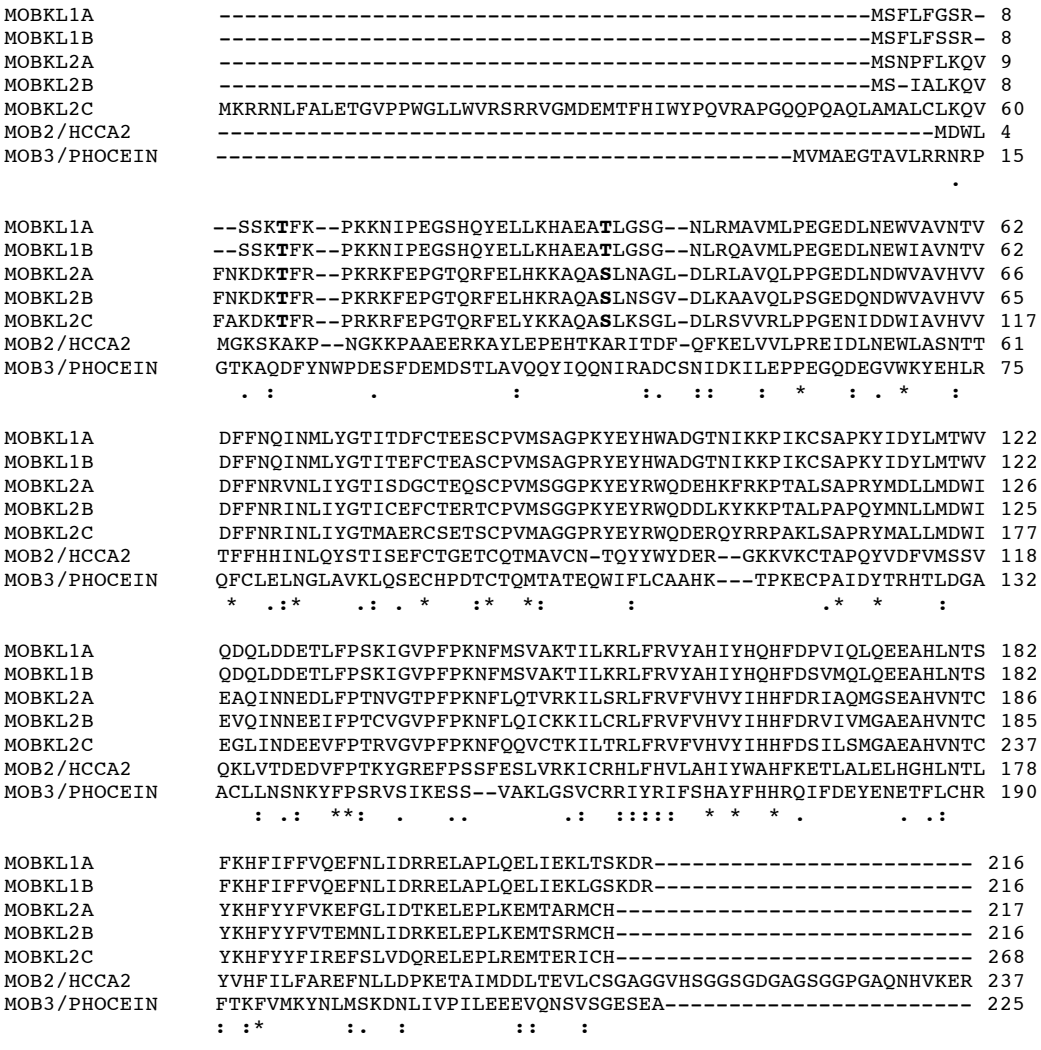
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Fig.S1

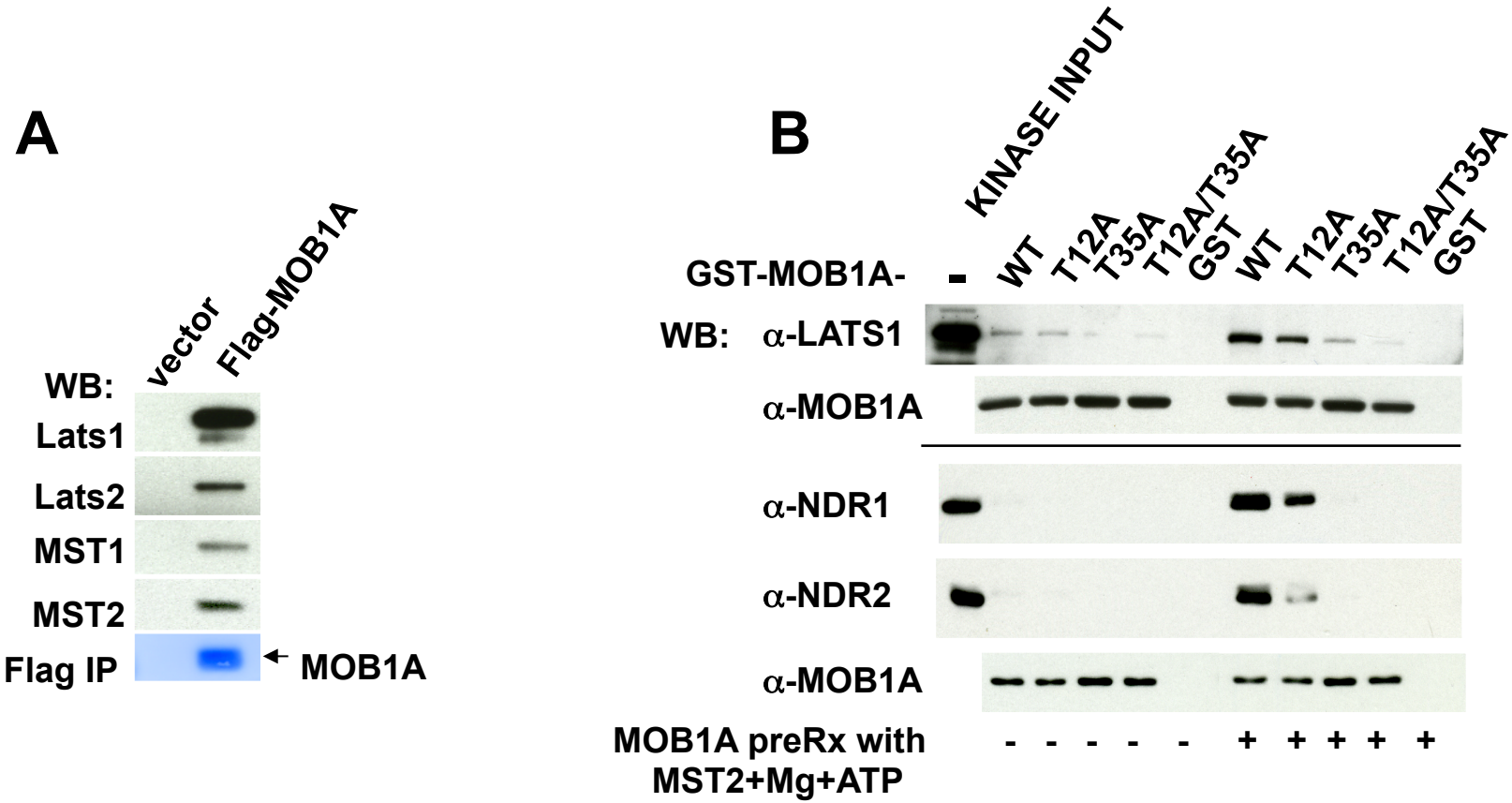
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Fig.S2

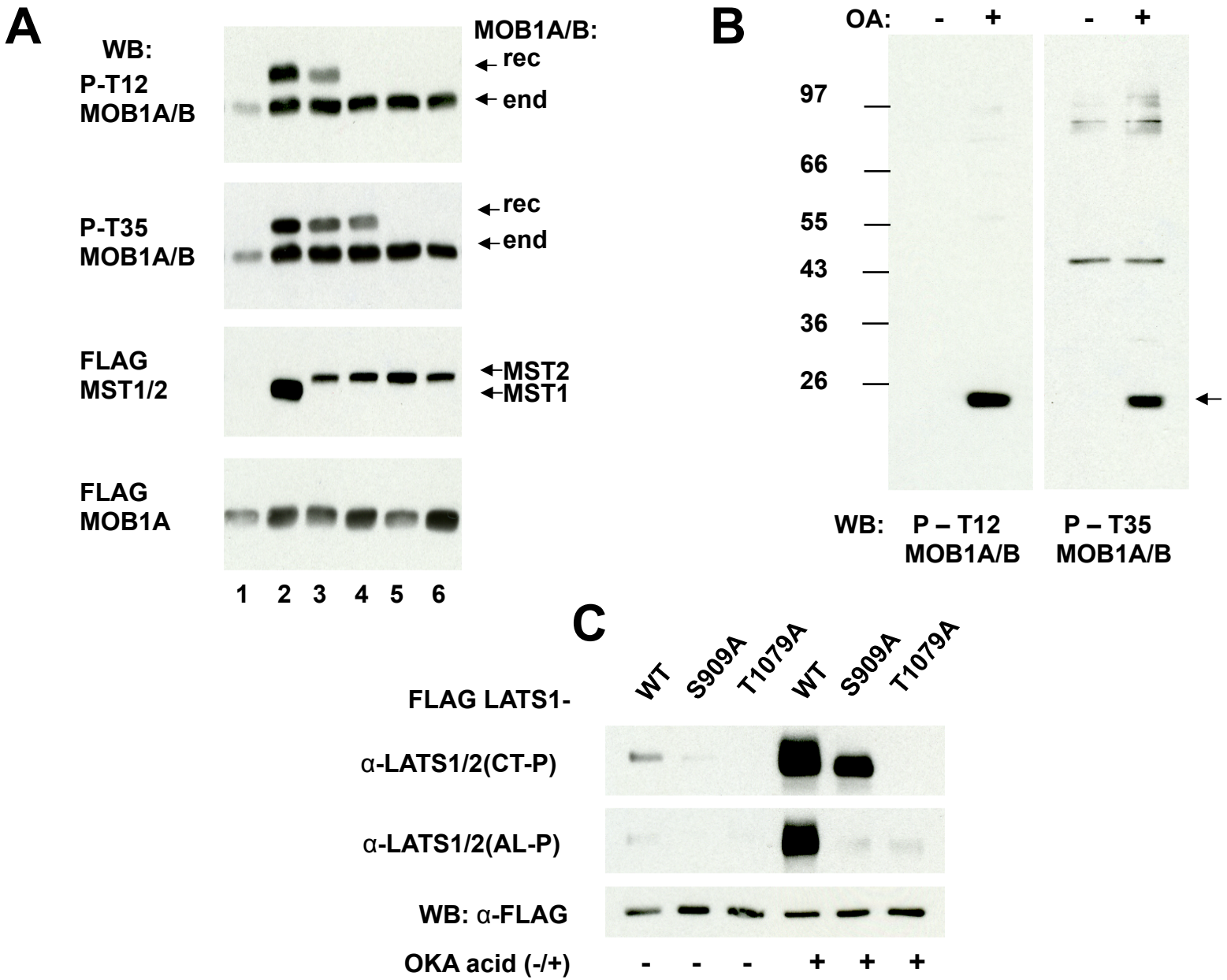
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Fig. S3

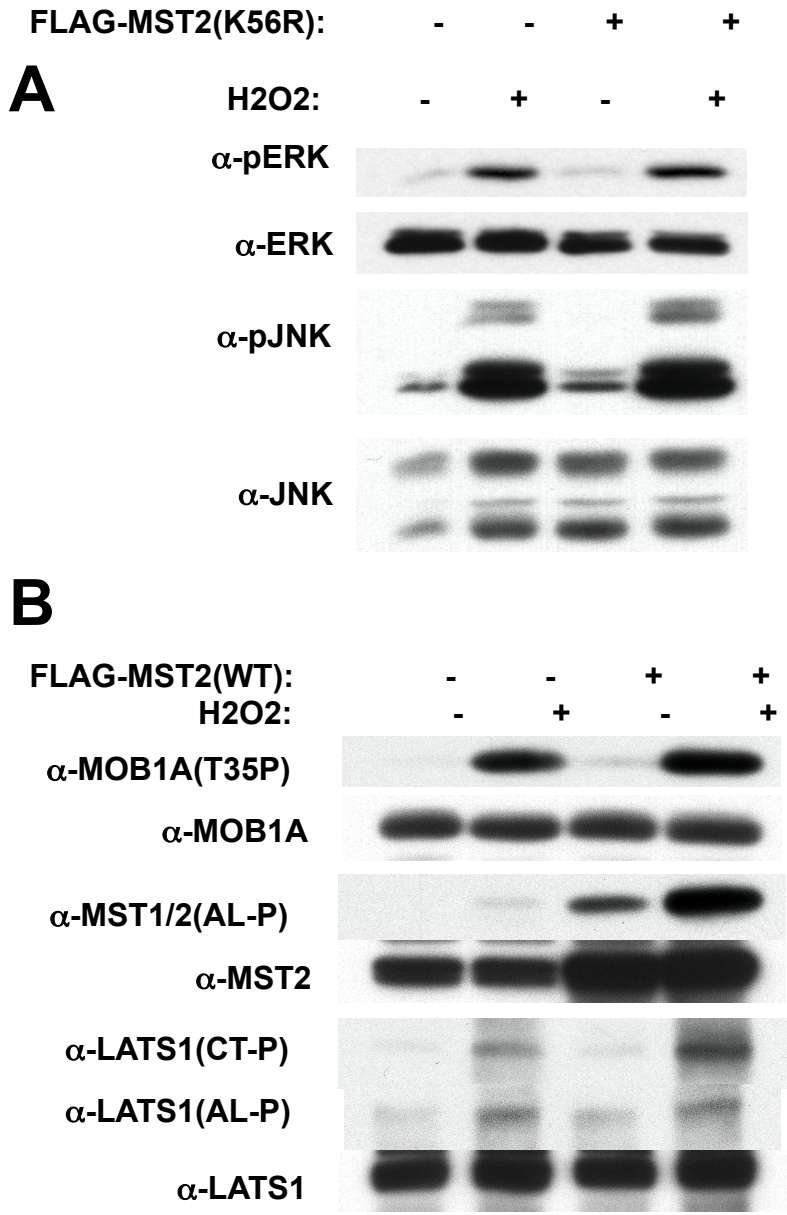
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Fig.S4

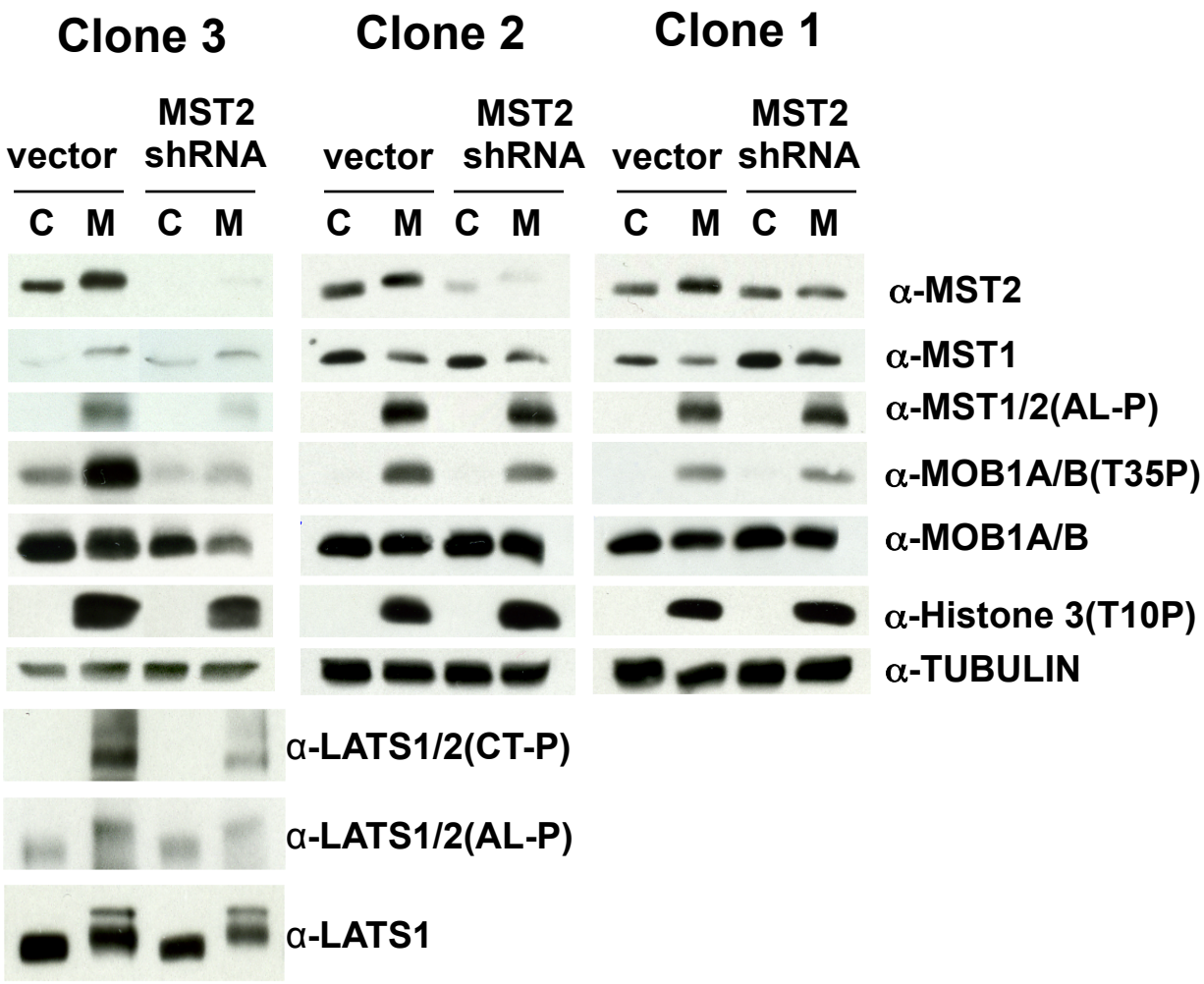
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Fig.S5