Notch Signaling Suppresses p38 MAPK Activity via Induction of MKP-1 in Myogenesis*

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Cross-talks among intracellular signaling pathways are important for the regulation of cell fate decisions and cellular responses to extracellular signals. Both the Notch pathway and the MAPK pathways play important roles in many biological processes, and the Notch pathway has been shown to interact with the ERK-type MAPK pathway. However, its interaction with the other MAPK pathways is unknown. Here we show that Notch signaling activation in C2C12 cells suppresses the activity of p38 MAPK to inhibit myogenesis. Our results show that Notch specifically induces expression of MKP-1, a member of the dual-specificity MAPK phosphatase, which directly inactivates p38 to negatively regulate C2C12 myogenesis. The Notch-induced expression of MKP-1 is shown to depend on RBP-J. Moreover, inhibition of MKP-1 expression by short interfering RNA suppresses p38 inactivation and partially rescues the negative regulation of myogenesis. These results reveal a novel cross-talk between the Notch pathway and the p38 MAPK pathway that is mediated by Notch induction of MKP-1.

The mitogen-activated protein kinase (MAPK) pathways regulate a vast array of cellular responses, including cell proliferation and cell differentiation. Extracellular stimuli induce the activating phosphorylation of MAPKs, and activated MAPKs phosphorylate downstream targets, such as transcription factors, and modulate their function. To date, at least four subfamily members of the MAPK family have been identified as follows: extracellular signal-regulated kinase 1 and 2 (ERK1/2), c-Jun N-terminal kinases (JNKs), p38, and ERK5 (1–4). Phosphorylated and activated MAPKs are dephosphorylated and inactivated by serine/threonine phosphatases, tyrosine phosphatases, and/or MAPK phosphatases (MKPs), a subfamily of the MAPK family, which directly inactivate MAPKs by dephosphorylating both threonine and tyrosine residues within the activation motif of MAPKs. In mammals, 10 members of the MKPs have been reported, and they share sequence homology and are highly specific for MAPKs but differ in the substrate specificity, tissue distribution, subcellular localization, and inducibility by extracellular stimuli (5–8).

The Notch pathway also regulates a wide variety of cellular responses, including cell differentiation and cell fate decision. Notch protein, a single transmembrane receptor, is activated by ligands, such as Delta and Jagged. Once activated, Notch is cleaved, and the cleaved Notch intracellular domain translocates to the nucleus, where it binds to RBP-J (also called CBF-1), a DNA-binding protein, and mastermind (MAM), a chromatin modification protein. This complex then acts as a transcription factor and activates the transcription of many target genes, such as the Hes family (9–13).

Cross-talks among the intracellular signaling pathways play pivotal roles in the determination of the signaling specificity. However, cross-talks between the Notch pathway and the MAPK pathways have remained unclear. Skeletal muscle differentiation, termed myogenesis, is an ideal model system to examine possible cross-talks between the MAPK pathways and the Notch pathway, because it has been reported that both signaling pathways play an important role in the process. During myogenesis, muscle precursors exit from the cell cycle, differentiate, and fuse into large multinucleated myotubes. p38, a member of the MAPK family, promotes myogenesis (14–16) by phosphorylating and activating several transcription factors, including MEF2C and E47 (17, 18), and by positively regulating the SWI/SNF chromatin remodeling complex (19). Moreover, ERK5, the other member of the MAPK family, also positively regulates myogenesis (20). On the other hand, activation of the Notch pathway inhibits myogenesis (13, 21–23) by repressing the expression of MyoD (24), a myogenic regulatory factor, and inhibiting E47 (25). However, the interaction of the Notch pathway with the MAPK pathways has been unknown in myogenesis.

In this study, we have addressed the possibility of a cross-talk between the MAPK pathways and the Notch pathway, and we found that the Notch pathway suppresses p38 MAPK activity by specifically inducing MKP-1, a member of the MKP family. Our results show that MKP-1 up-regulation inhibits myogenesis and contributes to the Notch inhibition of myogenesis. These findings identify a novel cross-talk between the Notch pathway and the p38 MAPK pathway.

EXPERIMENTAL PROCEDURES

Cell Culture—C2C12 cells were cultured in Dulbecco’s modified Eagle’s medium (DMEM) containing 15% fetal bovine serum; DM, differentiation medium. 3058 JOURNAL OF BIOLOGICAL CHEMISTRY 3059
serum (FBS) (growth medium). To induce differentiation, growth medium was replaced with DMEM containing 3% horse serum (differentiation medium; DM) when cells were 90% confluent.

**Plasmids and Transfection**—The cDNA encoding an intracellular domain of mouse Notch was a kind gift from M. Nakafuku. The cDNA of RBP-J was isolated by PCR from C2C12 cells, and the cDNA of mouse RBP-J (R218H) was then prepared by mutagenesis. The cDNA encoding human CL100/MKP-1 was kindly provided by S. Keyse. All cDNAs were subcloned into a pcDNA3 expression vector or a pCA-MCS adenoviral construction vector (26). The cDNA for the mouse Mkp-1 promoter was isolated by PCR from the mouse brain genome library and ligated into the pGL3 luciferase reporter vector (Promega). Plasmids were transfected by using Lipofectamine Plus reagent (Invitrogen) according to the manufacturer's protocol.

**siRNA and Transfection**—RNA oligonucleotides (21 nucleotides) homologous to mouse MKP-1 were designed as follows: forward, 5'-CUA GAA ACU UCA UGC UUG ATT-3'; reverse; 5'-UCA AGC AUG AAG CUA GTT-3'. Control siRNA and RBP-J siRNA were purchased from Ambion. siRNA was transfected by using Lipofectamine 2000 reagent (Invitrogen) according to the manufacturer's protocol.

**Construction of Recombinant Adenovirus**—AdV-CA-lacZ, adenovirus expressing β-galactosidase driven by the CAG promoter, was a kind gift from S. Takada. Construction of recombinant viruses was performed according to the methods described previously (27). In brief, recombinant adenoviruses were obtained by homologous recombination in HEK 293 cells, which were maintained in a 1:1 mixture of DMEM and Ham’s F-12 containing with 10% FBS. HEK 293 cells cultured in 6-well plates were co-transfected with viral genome fragments and linearized adenoviral shuttle vector plasmids (pCA-MCS) using Effectene reagent (Qiagen). Generation of the recombinant adenovirus was screened by immunostaining and immunoblotting. The recombinant adenoviruses were amplified and purified by CsCl2 step-gradient centrifugation. Viral titer was measured by using Adeno-X rapid titer kit (Clontech). For viral infection, the purified adenoviruses (2 × 10^7 ifu/ml) were added to the medium.

**Immunoblotting and Antibodies**—Cells were lysed in lysis buffer (20 mM Tris-Cl, pH 7.5, 2 mM EGTA, 1.5 mM MgCl2, 150 mM NaCl, 10 mM NaF, 12.5 mM β-glycerophosphate, 1 mM phenylmethylsulfonyl fluoride, 2 mM dithiothreitol, 17 µg/ml aprotinin, 1 mM vanadate, and 1% Triton-X). The proteins were separated by SDS-PAGE and analyzed by immunoblotting. Antibodies specific for α-tubulin (Sigma), myogenin (Santa Cruz Biotechnology), MHC (MF20), MKP-1 (Santa Cruz Biotechnology), FLAG (Sigma), phospho-p38 (Cell Signaling), p38

**FIGURE 1.** The Notch pathway suppresses the activity of p38 in myogenesis. A, C2C12 cells were infected with adenovirus containing GFP or GFP-fused NICD (NICD-GFP). After 24 h, the cells were placed in DM and incubated for 3 days. The cells were examined by phase-contrast microscope. B, C2C12 cells were infected with GFP or NICD-GFP with FLAG tag. After 24 h, the cells were placed in DM and incubated for the indicated times. The cells were harvested with lysis buffer, and equal amounts of cell lysates were subjected to immunoblotting with the indicated antibodies. Anti-α-tubulin antibody was used to examine the amount of α-tubulin as loading controls. Anti-FLAG antibody was used to examine the expression of NICD. C, C2C12 cells were treated as in B, and the cell lysates were subjected to immunoblotting with phospho-specific p38 antibody and p38 antibody. Representative data of three independent experiments are shown at left, and the quantified amounts of phosphorylated p38 are shown at right. Values are mean ± S.D. (n = 3). Asterisk indicates p < 0.05 by unpaired t test. D, C2C12 cells were treated as in B, and the cell lysates were subjected to immunoblotting with indicated antibodies.
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(Santa Cruz Biotechnology), phospho-ERK1/2 (Cell Signaling), ERK2 (Santa Cruz Biotechnology), phospho-JNK (Promega), JNK1 (Santa Cruz Biotechnology), and ERK5 (Sigma) were used. In some cases, the intensity of the immunoblotting bands was quantified, and the amount of phosphorylated p38 was evaluated by normalizing the intensity of immunoblotting data for phospho-p38 to that for p38.

RT-PCR Analysis—Whole-cell RNA was extracted by using an RNasey mini kit according to the manufacturer’s instructions (Qiagen). Total RNA was then reverse-transcribed into cDNA by using Moloney murine leukemia virus reverse transcriptase (Invitrogen) with oligonucleotide random hexamers. Prepared cDNA was purified and subjected to quantitative PCR analysis by using Light Cycler (Roche Diagnostics) with the SYBR Green PCR kit (Qiagen). The data were normalized to glyceraldehyde-3-phosphate dehydrogenase mRNA. The primers for the PCR analysis were as follows: for MKP-1, 5′-CTCCAGGAGATGAAAGG-3′ and 5′-CTCCAGCTCATATTGTCG-3′; for MKP-2, 5′-GTGGGTTATCCCACTTCTTCTATAC-3′; for MKP-3, 5′-GCCCAATGCTGTTTGTATGGGATTG-3′; for MKP-4, 5′-CATGGACTGCTGCTTCTCT-3′ and 5′-CTGGAGATGAGGACCTGTGAT-3′; for MKP-5, 5′-CTGCCATCTTATCATCAGTAC-3′ and 5′-CTGGATGAGGTCCATCAGTCTG-3′; for MKP-6, 5′-CTGGTATCCATCTTCTTCTAC-3′ and 5′-CTCAGCCATTGGAGGCGTTT-3′; for MKP-7, 5′-GGTGGCTTTGCTGG-3′; for MKP-8, 5′-GCTTCCTCGATGAAC-3′; and for MKP-9, 5′-ATGCGG-3′.

Luciferase Assay—Cells split onto 12-well dishes were harvested for assay 24 h after transfection. The luciferase activity in cell lysates was measured by using the luciferase assay system (Promega). To determine the transfection efficiency, the co-transfection efficiency was measured by using the luciferase assay system (Promega). To determine the transfection efficiency, the co-transfection efficiency was measured by using the luciferase assay system (Promega). To determine the transfection efficiency, the co-transfection efficiency was measured by using the luciferase assay system (Promega). To determine the transfection efficiency, the co-transfection efficiency was measured by using the luciferase assay system (Promega).

mRNA Stability Assay—Cells were treated with actinomycin D (5 μg/ml) and harvested 10, 20, 30, 45, 60, and 120 min after treatment. The rate of the decrease of MKP-1 mRNA was examined by RT-PCR.

RESULTS AND DISCUSSION

To investigate the possible crosstalk between the Notch pathway and the MAPK pathways during myogenesis, we used the C2C12 myogenic cell line. When C2C12 cells are cultured in differentiation medium (DM) for 2–3 days, they differentiate to multinucleated myotubes (Fig. 1A) and express muscle lineage-specific genes such as myogenin and myosin heavy chain (MHC) (Fig. 1B). Expression of the Notch intracellular domain (NICD), which activates the Notch signaling pathway, in C2C12 cells inhibited the formation of myotubes (Fig. 1A) and abolished the expression of myogenin and MHC completely (Fig. 1B), indicating that Notch signaling activation inhibits C2C12 myogenesis, as reported previously (13, 22). Thus, we first examined whether activation of the Notch pathway affects the activities of MAPKs during myogenesis. We expressed NICD with adenovirus in C2C12 cells and cultured the cells in DM for several days, and we examined the phosphorylation states of MAPKs by immunoblotting. Among the four MAPK family members, the amount of phosphorylated p38 was decreased when NICD was expressed (Fig. 1C), suggesting that p38 activity is suppressed by NICD expression. The phosphorylation states of ERK1/2, JNK, and ERK5 were not affected (Fig. 1D). These data suggest that the Notch pathway specifically inhibits the p38 pathway in myogenesis. As p38 plays an impor-
tant role in myogenesis, the inhibition of p38 activity is likely to be an important factor for Notch inhibition of myogenesis.

We hypothesized that a member of the MKP family is responsible for p38 inactivation induced by the Notch pathway. To test this possibility, we examined the effect of NICD expression on the mRNA level of each MKP in C2C12 cells. Among the MKP members, an expression level of MKP-1 mRNA was elevated markedly by NICD expression (Fig. 2A). The amount of MKP-1 mRNA started to increase within 5 h after infection of adenovirus containing NICD and almost attained the plateau level within 24 h (Fig. 2A, inset). Accordingly, the amount of MKP-1 protein was also increased by NICD expression (Fig. 2B). These results clearly indicate that Notch signaling induces up-regulation of MKP-1 expression in C2C12 cells. As MKP-1 mRNA was not induced by NICD in NIH3T3 cells (data not shown), this induction of MKP-1 may be cell type-specific.

Because it has been reported that MKP-1 preferentially dephosphorylates p38 and JNK (28), it is likely that induction of MKP-1 expression mediates, at least in part, Notch-induced inactivation of p38 (see below). Recently, it has been reported that during Caenorhabditis elegans vulval development, lin-12 (C. elegans Notch) up-regulates lip-1, a C. elegans ortholog of mammalian MKP-3, and negatively regulates mpk-1 (C. elegans ERK1/2) (29). Thus, because MKP-3, unlike MKP-1, acts preferentially on ERK1/2, the Notch pathway interacts with the ERK1/2 MAPK pathway in this C. elegans system. Therefore, it is attractive to hypothesize that Notch induction of MKP is an evolutionarily conserved mechanism, and the difference in the target MAPK pathway with which the Notch pathway interacts may be caused by the difference in the induced MKP.

We then investigated the molecular mechanisms by which the Notch pathway induces up-regulation of MKP-1 mRNA in C2C12 cells. The stability of MKP-1 mRNA was not significantly affected by expression of NICD (data not shown), suggesting that the Notch pathway increases the MKP-1 mRNA transcription. To determine whether Notch could enhance the transcription from the Mkp-1 promoter, we generated four luciferase reporter constructs containing parts of the Mkp-1 promoter region. MKP1A-Luc, MKP1B-Luc, MKP1C-Luc, and MKP-1D Luc contain the Mkp-1 promoter region from /H11002 to /H11001, from /H11002 to /H11001, from /H11002 to /H11001, and from /H11002 to /H11001, respectively (Fig. 3A).

**FIGURE 3.** The Notch pathway induces MKP-1 expression via an RBP-J-dependent pathway. A, schematic representation of the promoter region of MKP-1 and reporter constructs used in these experiments (upper panel). The reporter constructs (50 ng) were transfected with or without NICD (500 ng) in C2C12 cells. After 24 h, the cells were harvested, and the lysates were subjected to a luciferase (Luc) assay (lower panel). B, various amounts of RBP-J(R218H) (125, 250, and 375 ng) were transfected with NICD (125 ng) and MKP1C-Luc (50 ng) in C2C12 cells. After 24 h, the cells were harvested, and the lysates were subjected to a luciferase assay. Inset, the lysates were subjected to a /H9252-galactosidase assay. C, C2C12 cells were transfected with RBP-J siRNA or control siRNA. After 24 h, some of the cells were infected with NICD. The cells were harvested 48 h after siRNA transfection. The amounts of RBP-J and MKP-1 mRNA were evaluated by RT-PCR analysis. D, C2C12 cells were infected with adenovirus containing GFP or NICD-GFP. After 16 h, the cells were serum-starved for 12 h and then treated with 20% FBS for 8 h. The cells were collected, and the relative levels of MKP-1 mRNA were determined by RT-PCR analysis. Values are mean ± S.D. (n = 4). Asterisk indicates p < 0.01 by unpaired t test.
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FIGURE 4. Expression of MKP-1 suppresses myogenesis. A, C2C12 cells were infected with GFP or MKP-1. After 24 h, the cells were placed in DM and then incubated for 3 days. The cells were examined with a phase-contrast microscope. B–D, C2C12 cells were infected with GFP or MKP-1. After 24 h, the cells were placed in DM and incubated for the indicated times. The cells were harvested with lysis buffer, and equal amounts of cell lysates were subjected to immunoblotting with the indicated antibodies. E, C2C12 cells were treated with 10 μM SB203580. After 24 h, the cells were placed in DM and then incubated for 3 days with or without SB203580. The cells were harvested with lysis buffer, and equal amounts of cell lysates were subjected to immunoblotting with the indicated antibodies.

This result shows that the Notch pathway increases the transcription of MKP-1 and suggests that the region responsible for induction by Notch is mapped between −5015 and −2006 bp upstream from the transcription start site of the MKP-1. There are RBP-J-dependent and -independent pathways in Notch signaling (30), and both pathways are suggested to contribute to Notch inhibition of myogenesis (25, 31, 32). Therefore, we next examined whether Notch induction of MKP-1 was dependent on RBP-J. We used RBP-J(R218H), which is unable to bind to DNA and acts as a dominant negative form (13). The reporter assay has shown that RBP-J(R218H) suppresses the NICD-induced increase of the luciferase activity in a dose-dependent manner (Fig. 3B). The transcription of control plasmid was not affected by RBP-J(R218H) (Fig. 3B, inset). We then examined whether down-regulation of RBP-J expression by siRNA affects the Notch-induced MKP-1 expression. Our RBP-J siRNA treatment suppressed the RBP-J expression by about 40% at the mRNA level (Fig. 3C, left) and also suppressed NICD-induced MKP-1 expression by about 40% (Fig. 3C, right), suggesting that RBP-J is necessary for the NICD-induced MKP-1 expression. Therefore, it is likely that Notch induction of MKP-1 is dependent on RBP-J. Interestingly, overexpression of Hes1, a direct target of the RBP-J-dependent Notch pathway, did not affect the NICD-induced luciferase activity in this assay (data not shown), suggesting that Notch induction of MKP-1 is Hes1-independent. Because it has been reported that MKP-1 expression is also induced after serum stimulation (33), we then examined whether NICD expression and serum treatment use different mechanisms to induce MKP-1. The amount of MKP-1 mRNA induced by serum stimulation was nearly equal to that induced by NICD expression (Fig. 3D). Interestingly, serum treatment and NICD expression synergistically increased MKP-1 mRNA (Fig. 3D), suggesting that these stimuli use different pathways to induce MKP-1 expression.

We then examined whether MKP-1 expression alone suppresses p38 activity and myogenesis. In agreement with a previous report showing that stable MKP-1 expression inhibits myotube formation (34), transient expression of MKP-1 markedly reduced the number of myotubes, although a few myotubes were detected at day 3 (Fig. 4A). The expression level of MHC was decreased, and the expression of myogenin was almost completely suppressed in cells expressing MKP-1 (Fig. 4B). This observation is apparently inconsistent with the previous study showing that MKP-1 expression does not affect the expression of myogenin and MHC (34). The difference may result from a higher expression level of MKP-1 in our transient expression protocol. MKP-1 expression under our conditions almost completely abolished p38 activity (Fig. 4C) and markedly suppressed the activities of ERK1/2 and JNK (Fig. 4D). It should be noted that inhibition of p38 activity by the pharmacological p38 inhibitor, SB203580, decreased the expression of myogenin and MHC, as reported previously (14–16), and that the inhibitory effect of SB203580 treatment on myogenesis was similar to the effect of MKP-1 expression. Therefore, our results suggest that MKP-1 expression suppresses p38 activity and myogenesis. However, when compared with NICD expression (see Fig. 1), the ability of MKP-1 expression to inhibit myogenesis is rather weak.

We then inhibited endogenous MKP-1 expression by siRNA. Our MKP-1 siRNA treatment suppressed the MKP-1 expression by about 70% at the mRNA level in both the presence and absence of NICD protein induced in the presence of NICD by about 70% (Fig. 5A, left). We then examined the effect of MKP-1 siRNA on C2C12 differentiation. Down-regulation of MKP-1 by siRNA enhanced the activity of p38 throughout differentiation (Fig. 5B), suggesting that MKP-1 negatively regulates p38 during differentiation. Moreover, down-regulation of MKP-1 by siRNA enhanced the expression of myogenin at both the protein and the mRNA levels (Fig. 5, C and D), suggesting that endogenous MKP-1 negatively regulates myogenesis. It should be noted that MKP-1 siRNA treatment did not robustly
enhance the expression of MHC (Fig. 5D). This result was consistent with the result that the overexpression of MKP-1 did not completely abolish MHC expression (Fig. 4B), and suggests that myogenin expression and MHC expression may have different modes of regulatory mechanisms during myogenesis, and MKP-1 may be more directly involved in the regulation of myogenin expression. Interestingly, the enhancement of myogenin and MHC expression by MKP-1 siRNA was inhibited by the
treatment with SB203580, suggesting that MKP-1 acts on p38 during myogenesis (Fig. 5D). Finally, we down-regulated MKP-1 by siRNA during Notch inhibition of C2C12 myogenesis to examine whether the Notch pathway requires MKP-1 induction to inhibit myogenesis. MKP-1 siRNA treatment enhanced the p38 activity in the presence of NICD (Fig. 5E), and the p38 activity in MKP-1 siRNA-treated cells expressing NICD was roughly equal to that in control siRNA-treated cells expressing GFP in all time points (Fig. 5E), indicating that down-regulation of p38 activity by NICD is mediated by MKP-1 expression. When NICD was expressed in C2C12 cells, myotubes were not apparent even in the presence of MKP-1 siRNA (data not shown), and the expression of myogenin or MHC was not detected in immunoblotting (data not shown). We then examined whether myogenin mRNA levels in the presence of NICD are affected by the down-regulation of MKP-1. Although the amount of myogenin mRNA was increased even in the presence of NICD (Fig. 5F), the protein level was very low because we could not detect myogenin protein by immunoblotting. The expression level of myogenin mRNA in C2C12 cells in the presence of NICD was increased by MKP-1 siRNA treatment after 3 days (Fig. 5F), indicating that the differentiation is enhanced by MKP-1 siRNA treatment even in the presence of NICD. Furthermore, the increase in myogenin expression by MKP-1 siRNA was inhibited by SB203580 treatment (Fig. 5F), suggesting that the effect of MKP-1 siRNA on myogenesis is through p38 activation. Thus, it is likely that MKP-1 mainly acts on p38 during Notch inhibition of myogenesis. Although p38 activity is affected at day 1, myogenin expression was not affected until day 3. This may imply that the long term activation of p38 seems to be required to overcome the Notch inhibition of myogenesis. Therefore, these results also suggest that the increase of p38 activity could partially cancel the inhibitory effect of the Notch pathway on myogenesis. This partial effect of down-regulation of MKP-1 on myogenesis is consistent with the recent finding that the p38 pathway seems to modulate the activity of MyoD at a restricted subset of promoters rather than to act globally on all MyoD-regulated genes (35). Thus, we can conclude that Notch induction of MKP-1 plays an important role in Notch regulation of myogenesis. It also should be noted that SB203580 treatment with NICD expression inhibited myogenesis. It also should be noted that Notch induction of MKP-1 depends on an RBP-J-dependent mechanism. However, it remains to be determined whether the Notch-RBP-J complex induces MKP-1 mRNA directly or indirectly. It is still unclear whether the p38 pathway and the Notch pathway are important for muscle development in vivo. However, it has been shown that the p38 pathway and the Notch pathway play an opposite role in adult muscle regeneration processes, and although p38 promotes activation and differentiation of muscle satellite cells (36), Notch keeps these cells in an undifferentiated state (37). Therefore, there might be a cross-talk between the p38 pathway and the Notch pathway via induction of MKP-1 during satellite cell activation. Moreover, future studies would reveal the role of the identified interaction of the Notch pathway with the p38 MAPK pathway in other biological processes.

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REFERENCES
1. Chang, L., and Karin, M. (2001) Nature 410, 37–40
2. Chen, Z., Gibson, T. B., Robinson, F., Silvestro, L., Pearson, G., Xu, B., Wright, A., Vanderbilt, C., and Cobb, M. H. (2001) Chem. Rev. 101, 2449–2476
3. Nishida, E., and Gotoh, Y. (1993) Trends Biochem. Sci. 18, 128–131
4. Sturgill, T. W., and Wu, J. (1991) Biochim. Biophys. Acta 1092, 350–357
5. Camps, M., Nichols, A., and Arkinstall, S. (2000) FASEB J. 14, 6–16
6. Farooq, A., and Zhou, M. M. (2004) Cell. Signal. 16, 769–779
7. Keyse, S. M. (2000)Curr. Opin. Cell Biol. 12, 186–192
8. Tanoue, T., Yamamoto, T., and Nishida, E. (2002) J. Biol. Chem. 277, 22942–22949
9. Artavanis-Tsakonas, S., Rand, M. D., and Lake, R. J. (1999) Science 284, 770–776
10. Fryer, C. J., Lamar, E., Turbachova, I., Kintner, C., and Jones, K. A. (2002) Genes Dev. 16, 1397–1411
11. Greenwald, I. (1998) Genes Dev. 12, 1751–1762
12. Jarriault, S., Brou, C., Logeat, F., Schroeter, E. H., Kopan, R., and Israel, A. (1995) Nature 377, 355–358
13. Kato, H., Taniguchi, Y., Kurooka, H., Minoguchi, S., Sakai, T., Nomura-Ozakazi, S., Tamura, K., and Honjo, T. (1997) Development (Camb.) 124, 4133–4141
14. Cuenda, A., and Cohen, P. (1999) J. Biol. Chem. 274, 4341–4346
15. Wu, Z., Woodring, P. J., Bhakta, K. S., Tamura, K., Wen, F., Feramisco, J. R., Karin, M., Wang, J. Y., and Puri, P. L. (2000) Mol. Cell. Biol. 20, 3951–3964
16. Zetser, A., Gredinger, E., and Bengal, E. (1999) J. Biol. Chem. 274, 5193–5200
17. Lluis, F., Ballestar, E., Suelves, M., Esteller, M., and Munoz-Canoves, P. (2005) EMBO J. 24, 974–984
18. Penn, B. H., Bergstrom, D. A., Dilworth, F. J., Bengal, E., and Tapscott, S. J. (2004) Genes Dev. 18, 2348–2353
19. Simon, C., Forcales, S. V., Hill, D. A., Imbalzano, A. N., Latella, L., and Puri, P. L. (2004) Nat. Genet. 36, 738–743
20. Dinev, D., Jordan, B. W., Neufeld, B., Lee, J. D., Lindemann, D., Rapp, U. R., and Ludwig, S. (2001) EMBO Rep. 2, 829–834
21. Hsieh, J. J., Nofziger, D. E., Weinmaster, G., and Hayward, S. D. (1997) J. Virol. 71, 1938–1945
22. Kopan, R., Nye, J. S., and Weintraub, H. (1994) Development (Camb.) 120, 2385–2396
23. Lindell, C. E., Shawber, C. J., Boulter, J., and Weinmaster, G. (1995) Cell 80, 909–917
24. Kuroda, K., Tani, S., Tamura, K., Minoguchi, S., Kurooka, H., and Honjo, T. (1999) J. Biol. Chem. 274, 7238–7244
25. Ordentlich, P., Lin, A., Shen, C. P., Blaumueller, C., Matsuno, K., Artavanis-Tsakonas, S., and Kadesch, T. (1998) Mol. Cell. Biol. 18, 2230–2239
26. Nakagawa, S., and Takeichi, M. (1998) Neuron 25, 2963–2971
27. Moriyoishi, K., Richards, L. J., Akazawa, C., O’Leary, D. D., and Nakashima, S. (1996) Neuron 16, 255–260
28. Franklin, C. C., and Kraft, A. S. (1997) J. Biol. Chem. 272, 16917–16923
29. Berset, T., Hoier, E. F., Battu, G., Canevascini, S., and Hajnal, A. (2001) Science 291, 1055–1058
30. Martínez Arias, A., Zecchini, V., and Brenner, K. (2002) Curr. Opin. Genet. Dev. 12, 524–533
31. Nofziger, D., Miyamoto, A., Lyons, K. M., and Weinmaster, G. (1999) Development (Camb.) 126, 1689–1702
32. Shawber, C., Nofziger, D., Hsieh, J. J., Lindsell, C., Bogler, O., Hayward, D., and Weinmaster, G. (1996) Development (Camb.) 122, 3765–3773
33. Charles, C. H., Abler, A. S., and Lau, L. F. (1992) Oncogene 7, 187–190
34. Bennett, A. M., and Tonks, N. K. (1997) Science 278, 1288–1291
35. Bergstrom, D. A., Penn, B. H., Strand, A., Perry, R. L., Rudnicki, M. A., and Tapscott, S. J. (2002) Mol. Cell 9, 587–600
36. Jones, N. C., Tyner, K. J., Nibarger, L., Stanley, H. M., Cornelison, D. D., Fedorov, Y. V., and Olwin, B. B. (2005) J. Cell Biol. 169, 105–116
37. Conboy, I. M., and Rando, T. A. (2002) Dev. Cell 3, 397–409