Journal of Cellular Biochemistry 102:274–279 (2007)

Mirk/Dyrk1B in Cancer

Eileen Friedman*

Pathology Department, Upstate Medical University, State University of New York, 750 East Adams Street, Syracuse, New York

Abstract Mirk/Dyrk1B is a member of a conserved family of serine/threonine kinases which are activated by intramolecular tyrosine phosphorylation, and which mediate differentiation in different tissues—Mirk in skeletal muscle, Dyrk1A in the brain, etc. One role of Mirk in skeletal muscle differentiation is to block cycling myoblasts in the G0 quiescent state by modification of cell cycle regulators, while another role of Mirk is to limit apoptosis in fusing myoblasts. Amplification of the Mirk gene, upregulation of Mirk expression and/or constitutive activation of this kinase have been observed in several different types of cancer. If coupled with a stress condition such as serum starvation which induces a quiescent state, depletion of Mirk by RNA interference using either synthetic duplex RNAi's or pSilencer-encoded RNAi's have decreased colony formation of different cancer cell lines and enhanced apoptosis induced by chemotherapeutic drugs. Mirk is activated by phosphorylation by the stress-activated SAPK kinases MKK3 and MKK6. Our working hypothesis is that Mirk is activated by this pathway in response to various stresses, and then acts as a checkpoint kinase to arrest damaged tumor cells in a quiescent state and allow cellular repair. Pharmacological inhibition of Mirk may enhance the anti-tumor effect of chemotherapeutic drugs. J. Cell. Biochem. 102: 274–279, 2007.

Key words: Mirk/Dyrk1B; kinase; cancer

Cancer cells are in general characterized by uncontrolled proliferation and impaired apoptosis. Signaling pathways which mediate proliferation or respond to damage are not as redundant as they are in normal cells, so cancer cells rely on a few of these hyperactive pathways. Kinases in essential signaling pathways are attractive targets for therapy because of their catalytic nature and their sensitivity to inhibitors which target their ATP-binding domains. Among kinases targeted for cancer treatment are the tyrosine kinases Bcr-abl and Her2, and the serine/threonine kinases Raf, Akt, and mTOR.

Mirk/Dyrk/MINIBRAIN FAMILY OF RELATED KINASES

Mirk/Dyrk1B is a member of the Minibrain/Dyrk family of kinases [Tejedor et al., 1995; Kentrup et al., 1996; Becker et al., 1998] which mediate survival and differentiation in certain normal tissues: skeletal muscle (Mirk/Dyrk1B) [Mercer et al., 2005], neuronal cells (Dyrk1A) [Tejedor et al., 1995; Arron et al., 2006], erythropoietic cells (Dyrk3) [Geiger et al., 2001; Li et al., 2002], and sperm (Dyrk4) [Sacher et al., 2007]. Dyrk1A maps to the location of the Down Syndrome gene and is overexpressed in Down Syndrome patients, while rodents overexpressing Dyrk1A exhibit some of the symptoms of this genetic disorder [Guimera et al., 1999; Altafaj et al., 2001; Fotaki et al., 2002]. The genes DSCR1 and Dyrk1A both exhibit a 1.5-fold gene dosage pattern in Down syndrome patients. These genes work synergistically to prevent nuclear occupancy of NFATc transcription factors [Arron et al., 2006; Gwack et al., 2006], leading to reduced NFATc activity. This decrease significantly impairs the differentiation of neuronal cells and other cells in which Dyrk1A is expressed during embryogenesis leading to severe developmental alterations including mental retardation.

Mirk is expressed at elevated levels in skeletal muscle compared to other normal tissues [Lee and Friedman, 1998; Lee et al., 2000]. The skeletal muscle maturation program is controlled by the basic helix-loop-helix (bHLH) transcription factor MyoD which is

*Correspondence to: Eileen Friedman, PhD, 750 East Adams Street, Syracuse, NY 13210.
E-mail: friedmae@upstate.edu

Received 21 May 2007; Accepted 22 May 2007
DOI 10.1002/jcb.21451

activated by the GTPase RhoA. RhoA also induces Mirk expression together with bHLH factors through an E-box site mapped in the Mirk promoter, enabling Mirk expression to increase about 10-fold during differentiation [Deng et al., 2003]. Mirk depletion blocks myoblast differentiation into multinucleated myotubes, while stable expression of Mirk increases their rate of fusion [Deng et al., 2003]. Mirk has transcriptional activator activity for HNF1alpha [Lim et al., 2002a] and also for the bHLH transcription factor MEF2, active in myoblast differentiation [Deng et al., 2005]. MEF2 is sequestered by class II histone deacetylases (HDACs). Mirk phosphorylates these class II HDACs at a conserved site within their nuclear localization region, reducing their nuclear accumulation in a dose-dependent and kinase-dependent manner. The reduced HDAC concentration in the nucleus frees MEF2 to transcribe myogenin [Deng et al., 2005] and enables differentiation to continue.

Myoblasts can only differentiate after arrest in G0. Mirk reinforces the G0 arrest state by destabilizing cyclin D1 and cyclin D3 by phosphorylation at Thr288, a ubiquitination site [Zou et al., 2004; Takahashi-Yanaga et al., 2006; Ewton et al., 2007]. Mirk also increases the abundance of the CDK inhibitor p27kip1 by phosphorylation at Ser10 which blocks its degradation in quiescent cells [Deng et al., 2004; Besson et al., 2006]. Myoblasts depleted of Mirk, then placed in quiescent conditions, underwent about twice as much apoptosis as controls, as shown by increased caspase 3 activation, suggesting that Mirk was essential for viability of quiescent cells [Mercer et al., 2005]. Partly differentiated myoblasts are removed from cultures of fusing myoblasts by apoptosis in a natural process which claims 20–30% of the cells [Wang and Walsh, 1996]. The CDK inhibitor p21cip1 maintains the survival of fusing myoblasts under these conditions in which many nearby cells die [Wang and Walsh, 1996]. We found that p21 moved from an exclusive nuclear location in dividing myoblasts to a cytoplasmic location in postmitotic myotubes [Mercer et al., 2005], where it presumably had an anti-apoptotic function. Mirk phosphorylates p21cip1 within its nuclear localization region at Ser153 in myoblasts. Phosphomimetic p21-S153D was found to translocate to the cytoplasm where it was more effective than wild-type p21 in blocking caspase 3 activation [Mercer et al., 2005]. In the nucleus p21cip1 has a well-characterized CDK inhibitor activity, while in the cytoplasm, p21 has an anti-apoptotic function through complexing with ASK1 (apoptosis signal regulating kinase 1) [Asada et al., 1999] and inhibiting the activation of JNK [Shim et al., 1996]. This anti-apoptotic capacity of cytoplasmic p21 allows injured neurons to recover [Tanaka et al., 2004]. Thus, Mirk has an indirect anti-apoptotic function in quiescent myotubes through its capacity to maintain p21cip1 in the cytoplasm by phosphorylating p21 within its nuclear localization signal.

Mirk's KINASE ACTIVITY

Mirk/Dyrk family kinases have been defined as arginine-directed serine/threonine kinases by use of peptide libraries [Himpel et al., 2000]. We have defined Mirk's optimal phosphorylation site using in vivo sites which our group has mapped (Fig. 1). The consensus sequence is SPSxxR with either serine phosphorylated. No arginine was seen +3 or +5 from the Mirk phosphorylation site in HNF1, but an arginine was present −3. This kind of modeling was effective in correctly identifying the site in HDAC5.

ACTIVATION OF Mirk/Dyrk KINASES

Members of the MAP kinase family are activated by dual phosphorylation of a TxY activation domain within the conserved kinase region. Mirk/Dyrk/minibrain family members exhibit a YxY site at the analogous region with

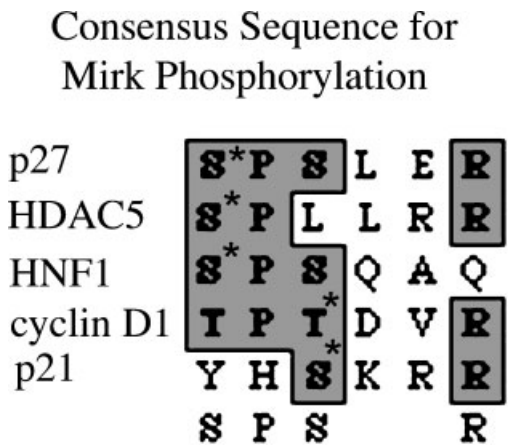

Fig. 1. The regions around the phosphorylation sites our group has mapped in p27kip [Deng et al., 2004], HDAC5 [Deng et al., 2005], HNF1 [Lim et al., 2002a], cyclin D1 [Zou et al., 2004], and p21cip1 [Mercer et al., 2005] are shown with the phosphorylated serine or threonine marked with an asterisk. The consensus sequence of SPSxxR is shown below.

only the second tyrosine residue phosphorylated [Himpel et al., 2001]. This "activation" domain was shown to be intramolecularly phosphorylated only during translation, so that mature members of the Mirk/Dyrk family have only serine/threonine kinase activity [Lochhead et al., 2005]. Activation of Mirk/Dyrk/minibrain kinases in response to extracellular signals must then be mediated by other mechanisms. Dyrk1A activity was increased by binding to 14-3-3 proteins [Kim et al., 2004], and is mediated by autophosphorylation at a C-terminal serine [Alvarez et al., 2007], which is not conserved in Mirk.

Recently, it was found that, in the absence of functional p53, DNA damage activates two survival pathways, the p38 SAPK/MK2 pathway as well as the ATR-Chk1 pathway [Reinhardt et al., 2007]. A characteristic of the newly discovered p38 SAPK/MK2 checkpoint kinase signaling cascade is its expected ability to be activated by a stress-activated MAP kinase kinase. Mirk is directly activated by phosphorylation by such a kinase, MKK3 [Lim et al., 2002a; Mercer et al., 2005]. MKK3 and MKK6 are MAP kinase kinases which activate p38 in response to stress. Mirk and p38 compete for access to activated MKK3 and p38 can complex with Mirk as part of this competition [Lim et al., 2002b]. Mirk can be activated through a Rac/MKK3 signaling pathway [Jin et al., 2005], and in some cancer cells through an oncogenic K-ras to rac to MKK3 or MKK6 pathway [Jin et al., 2007a]. Other upstream activators of MKK3/Mirk signaling are unknown, but could include TOA kinases. TOA kinases are known to mediate activation of p38 in response to DNA damage through an ATM/TOA/MKK3 (MEK3) signaling pathway [Raman et al., 2007].

Mirk is active as a kinase in rhabdomyosarcoma cells and in pancreatic cancer cells, the latter through the oncogenic K-ras/rac/MKK3 pathway [Deng et al., 2006; Mercer et al., 2006; Jin et al., 2007a]. The capacity of Mirk to be activated by stress signals initiated by DNA damaging agents or spindle poisons is under investigation [Jin et al., 2007b; Hu et al., 2007]. A model of Mirk activation by cellular stresses is given in Figure 2.

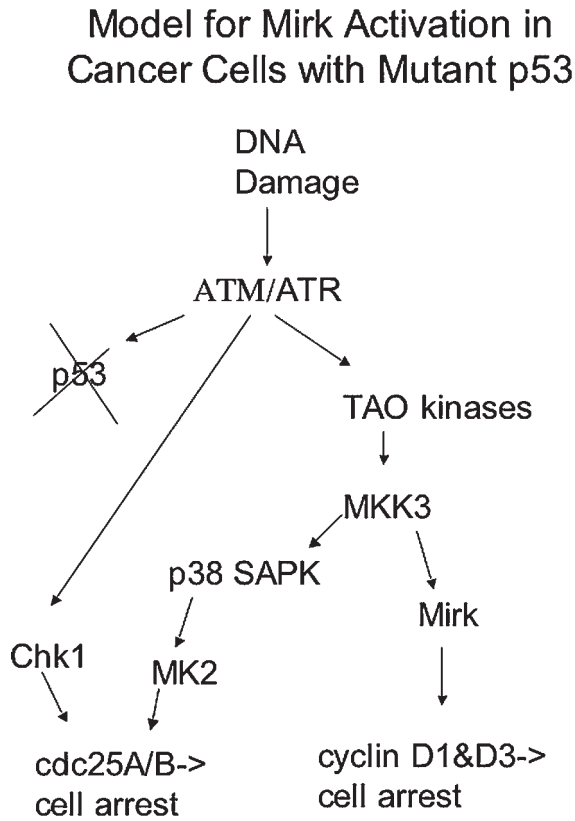

Fig. 2. Model for activation of Mirk by DNA damage.

Mirk IN CANCER

Genetic alterations including mutations, translocations, and amplifications can lead to cancer. Such amplicons are maintained in cancers when the amplified genes provide a selective growth or survival advantage. The 19q13 amplicon was first detected as a double minute, and has since been identified in 10–20% of pancreatic cancers, about 30% of ovarian cancers, as well as cases of follicular lymphoma, mantle cell lymphoma, Burkitt's lymphoma, and both small-cell and non small cell lung cancer. Several different studies have localized this amplicon in pancreatic cancers to a region around 19q13.1-13.2 (reviewed in [Karhu et al., 2006; Moniaux et al., 2006]). Mirk/Dyrk1B is localized at 19q13.1 [Lee et al., 2000]. A recent study found the Mirk gene within the consistently amplified 660 kb subregion of the 19q13 amplicon in pancreatic cancers [Kuuselo et al., 2007]. Our group has shown that Mirk is amplified within pancreatic cancer and ovarian cancer cell lines known to exhibit the 19q13 amplicon: ovarian cancer lines OVBCAR3, OVCAR4 and OV90 and pancreatic cancer cell lines Panc1 and SU86.86 [Hu et al., 2007].

Mirk is expressed in several different types of cancers, and when stably overexpressed in colon

cancer cells with low endogenous Mirk expression, mediates survival when cells are placed in serum-free medium to induce quiescence, compared with kinase-inactive control transfectants [Lee et al., 2000]. These stable transfectants may, in some senses, be analogous to cancers with amplification of the Mirk gene. Interestingly, analysis of several Mirk stable transfectant colon cancer cell lines showed that the overexpressed Mirk mediated rapid turnover of cyclin D1, but was unable to stabilize p27kip1 [Ewton et al., 2003]. More recently analysis of pancreatic cancer cell lines using RNAi to deplete Mirk demonstrated that Mirk, whether amplified or not, retained the capacity to destabilize cyclin D1 and cyclin D3 by phosphorylation [Ewton et al., 2007]. When Mirk was depleted in each of five pancreatic cancer cell lines, the cells lost the ability to remain in quiescence. The increased levels of cyclin D1 and cyclin D3 activated CDKs so that p130/Rb2 was highly phosphorylated and could no longer sequester the transcription factor E2F4 which controls the maintenance of quiescence [Ewton et al., 2007].

Depletion of Mirk in two rhabdomyosarcoma cell lines (a skeletal muscle tumor of children), and in two pancreatic cancer cell lines, decreased the clonogenicity of these tumor cell lines about threefold to fourfold [Deng et al., 2006; Mercer et al., 2006]. Clonogenic assays provide a stress condition because cells are plated at very low cell density. In support of the importance of stress conditions to reveal Mirk's biological role, depletion of Mirk in two pancreatic cancer cell lines by synthetic duplex RNAi's followed by 2 days in serum-free medium reduced their clonogenicity about 10-fold, instead of the threefold to fourfold seen when a serum-free period was not employed [Jin et al., 2007a]. Moreover, depletion of Mirk in three pancreatic tumor cell lines in log phase culture in growth medium, an unstressed condition, only marginally increased apoptosis in the general population [Deng et al., 2006].

FUTURE DIRECTIONS

We hope to define whether or not Mirk is a type of checkpoint kinase which arrests cell cycle progression in response to chemotherapeutic drugs, irradiation or serum starvation. Specific questions will be asked. Do DNA damaging agents and spindle fiber poisons activate Mirk, and if so, do they activate Mirk through the Rac/MKK3 pathway like oncogenic K-ras? Another question to be answered is where cells arrest as a result of Mirk activation, G0 or G2. Mirk levels vary widely through the cell cycle with the highest levels and activity in G0 [Deng et al., 2004]. Elevated levels of Mirk have also been seen in myoblasts in mitosis [Mercer et al., 2005]. Cyclin D3 levels have been reported to be elevated in G2 so Mirk activation could potentially signal a block in G2 as well as in G0.

Also to be identified are the substrates of Mirk in tumors which signal its biological effects. Although Mirk had indirect anti-apoptotic functions in myoblasts through localization of p21cip1 in the cytoplasm [Mercer et al., 2005], Mirk may not have this anti-apoptotic function in tumor cells because the level of p21 in most cancers is low because they are mutant in p53. Mirk does phosphorylate class II histone deacetylases at a serine site conserved in HDAC5 (serine 279), HDAC9, MITR, and HDAC4 [Deng et al., 2005]. Class II histone deaceylases have many biological targets which they sequester. Freeing one or more nuclear targets by reducing the nuclear concentration of class II HDACs may cause some of the biological functions of Mirk.

REFERENCES

Altafaj X, Dierssen M, Baamonde C, Marti E, Visa J, Guimera J, Oset M, Gonzalez J, Florez J, Fillat C, Estivill X. 2001. Neurodevelopmental delay, motor abnormalities and cognitive deficits in transgenic mice overexpressing Dyrk1A (minibrain), a murine model of Down's syndrome. Hum Mol Genet 10:1915–1923.

Alvarez M, Altafaj X, Aranda S, de la Luna S. 2007. DYRK1A Autophosphorylation on Serine Residue 520 Modulates Its Kinase Activity via 14-3-3 Binding. Mol Biol Cell 18:1167–1178.

Arron JR, Winslow MM, Polleri A, Chang C-P, Wu H, Gao X, Neilson JR, Chen L, Heit JJ, Kim SK, 2006. NFAT dysregulation by increased dosage of DSCR1 and DYRK1A on chromosome 21. Nature 441(7093):595.

Asada M, Yamada T, Ichijo H, Delia D, Miyazono K, Fukumuro K, Mitzutani S. 1999. Apoptosis inhibitory activity of cytoplasmic p21cip1/waf1 in monocytic differentiation. EMBO J 18:1223–1234.

Becker W, Weber Y, Wetzel K, Eirmbter K, Tejedor F, Joost H-G. 1998. Sequence characteristics, subcellular localization and substrate specificity of Dyrk-related kinases, a novel family of dual specificity protein kinases. J Biol Chem 273:25893–25902.

Besson A, Gurian-West M, Chen X, Kelly-Spratt KS, Kemp CJ, Roberts JM. 2006. A pathway in quiescent cells that controls p27Kip1 stability, subcellular localization, and tumor suppression. Genes Dev 20(1):47–64.

Deng X, Ewton DZ, Pawlikowski B, Maimone M, Friedman E. 2003. Mirk/dyrk1B Is a Rho-induced Kinase Active in Skeletal Muscle Differentiation. J Biol Chem 278(42): 41347–41354.

Deng X, Mercer SE, Shah S, Ewton DZ, Friedman E. 2004. The Cyclin-dependent Kinase Inhibitor p27Kip1 Is Stabilized in G0 by Mirk/dyrk1B Kinase. J Biol Chem 279(21):22498–22504.

Deng X, Ewton DZ, Mercer SE, Friedman E. 2005. Mirk/dyrk1B Decreases the Nuclear Accumulation of Class II Histone Deacetylases during Skeletal Muscle Differentiation. J Biol Chem 280(6):4894–4905.

Deng X, Ewton DZ, Li S, Naqvi A, Mercer SE, Landas S, Friedman E. 2006. The Kinase Mirk/Dyrk1B Mediates Cell Survival in Pancreatic Ductal Adenocarcinoma. Cancer Res 66(8):4149–4158.

Ewton D, Lee K, Deng X, Lim S, Friedman E. 2003. Rapid turnover of cell-cycle regulators found in Mirk/dyrk1B transfectants. Int J Cancer 103(1):21–28.

Ewton DZ, Deng X, Jin K, Park S, Nakhla H, Friedman E. 2007. Mirk/dyrk1B acts as a downstream effector of Foxo3 in mediating quiescence in pancreatic cancer cells. J Biol Chem (submitted for publication).

Fotaki V, Dierssen M, Alcantara S, Martinez S, Marti E, Casas C, Visa J, Soriano E, Estivill X, Arbones ML. 2002. Dyrk1A Haploinsufficiency Affects Viability and Causes Developmental Delay and Abnormal Brain Morphology in Mice. Mol Cell Biol 22(18):6636–6647.

Geiger JN, Knudsen GT, Panek L. Pandit AK, Yoder MD, Lord KA, Creasy CL, Burns BM, Gaines P, Dillon SB, Wojchowski DM. 2001. mDYRK3 kinase is expressed selectively in late erythroid progenitor cells and attenuates colony-forming unit-erythroid development. Blood 97(4):901–910.

Guimera J, Casas C, Estivill X, Pritchard M. 1999. Human minibrain homologue (MNBH/DYRK1): Characterization, alternative splicing, differential tissue expression and overexpression in Down syndrome. Genomics 57:407–418.

Gwack Y, Sharma S, Nardone J. Tanasa B, Iuga A, Srikanth S, Okamura H, Bolton D, Feske S, Hogan PG, Rao A. 2006. A genome-wide Drosophila RNAi screen identifies DYRK-family kinases as regulators of NFAT. Nature 441:646.

Himpel S, Tegge W, Frank R, Leder S, Joost H, Becker W. 2000. Specificity determinants of substrate recognition by the protein kinase DYRK1A. J Biol Chem 275:2431–2438.

Himpel S, Panzer P, Eirmbter K, Czajkowska H, Sayed M, Packman L, Blundell T, Kentrup H, Grotzinger J, Joost H, Becker W. 2001. Identification of the autophosphorylation sites and characterization of their effects in the protein kinase DYRK1A. Biochem J 359: 497–505.

Hu J, Nakhla H, Wormer D, Mercer S, Friedman E. 2007. Mirk is Amplified in Ovarian Carcinomas and Mediates Survival Response to Cisplatin (submitted for publication).

Jin K, Lim S, Mercer SE, Friedman E. 2005. The Survival Kinase Mirk/dyrk1B Is Activated through Rac1-MKK3 Signaling. J Biol Chem 280(51):42097–42105.

Jin K, Park S-J, Ewton D, Friedman E. 2007a. The survival kinase Mirk/dyrk1B is a downstream effector of oncogenic K-ras. Cancer Res (in press).

Jin K, Park SJ, Friedman E. 2007b. Activation of Mirk by Nocodazole by a Rac1/MKK3 Stress-signaling pathway (in preparation).

Karhu R, Mahlamaki E, Kallioniemi A. 2006. Pancreatic adenocarcinoma- genetic portrait from chromosomes to microarrays. Genes Chromosomes Cancer 45:721–730.

Kentrup H, Becker W, Heukelbach J. Wilmes A, Schurman A, Huppertz C, Kainulainen H, Joost H-G. 1996. Dyrk, a dual specificity protein kinase with unique structural features whose activity is dependent on tyrosine residues between subdomains VII and VIII. J Biol Chem 271: 3488–3495.

Kim D, Won J, Shin DW, Kang J, Kim YJ, Choi SY, Hwang M-K, Jeong B-W, Kim GS, Joe CO. 2004. Regulation of Dyrk1A kinase activity by 14- 3-3. Biochem Biophys Res Commun 323(2):499–504.

Kuuselo R, Savinainen K, Azorsa DO, Basu GD, Karhu R, Tuzmen S, Mousses S, Kallioniemi A. 2007. Intersex-like (IXL) Is a Cell Survival Regulator in Pancreatic Cancer with 19q13 Amplification. Cancer Res 67(5):1943–1949.

Lee K-M, Friedman E. 1998. Novel dual-specific tyr-thr/ser kinase cloned from colon carcinoma cells. Proc AACR 39:273.

Lee K, Deng X, Friedman EMirk. 2000. Protein Kinase Is a Mitogen-activated Protein Kinase Substrate That Mediates Survival of Colon Cancer Cells. Cancer Res 60(13): 3631–3637.

Li K, Zhao S, Karur V, Wojchowski DM. 2002. DYRK3 Activation, Engagement of Protein Kinase A/cAMP Response Element-binding Protein, and Modulation of Progenitor Cell Survival. J Biol Chem 277(49):47052–47060.

Lim S, Jin K, Friedman E. 2002a. Mirk Protein Kinase Is Activated by MKK3 and Functions as a Transcriptional Activator of HNF1alpha. J Biol Chem 277(28):25040–25046.

Lim S, Zou Y, Friedman E. 2002b. The Transcriptional Activator Mirk/Dyrk1B Is Sequestered by p38alpha /beta MAP Kinase. J Biol Chem 277(51):49438–49445.

Lochhead P, Sibbet G, Morrice N, Cleghon V. 2005. Activation-Loop Autophosphorylation Is Mediated by a Novel Transitional Intermediate Form of DYRKs. Cell 121:925–936.

Mercer SE, Ewton DZ, Deng X, Lim S, Mazur TR, Friedman E. 2005. Mirk/Dyrk1B Mediates Survival during the Differentiation of C2C12 Myoblasts. J Biol Chem 280(27): 25788–25801.

Mercer SE, Ewton DZ, Shah S, Naqvi A, Friedman E. 2006. Mirk/Dyrk1b Mediates Cell Survival in Rhabdomyosarcomas. Cancer Res 66(10):5143–5150.

Moniaux N, Nemos C, Schmied BM. Chauhan SC, Deb S, Morikane K, Choudhury A, VanLith M, Sutherlin M, Sikela JM, 2006. The human homologue of the RNA polymerase II-associated factor 1 (hPaf1), localized on the 19q13 amplicon, is associated with tumorigenesis. Oncogene 25(23):3247.

Raman M, Earnest S, Zhang K, Zhao Y, Cobb M. 2007. TAO kinases mediate activation of p38 in response to DNA damage. EMBO J 26:2005–2014.

Reinhardt HC, Aslanian AS, Lees JA, Yaffe MB. 2007. p53-Deficient Cells Rely on ATM- and ATR-Mediated Checkpoint Signaling through the p38MAPK/MK2 Pathway for Survival after DNA Damage. Cancer Cell 11(2): 175.

Sacher F, Moller C, Bone W, Gottwald U, Fritsch M. 2007. The expression of the testis-specific Dyrk4 kinase is highly restricted to step 8 spermatids but is not required for male fertility in mice. Mol Cell Endocrinol 267(1–2): 80.

Shim J, Lee H, Park J, Kim H, Choi E. 1996. A non-enzymatic p21 protein inhibitor of stress-activated protein kinases. Nature 381:804–806.

Takahashi-Yanaga F, Mori J, Matsuzaki E, Watanabe Y, Hirata M, Miwa Y, Morimoto S, Sasaguri T. 2006. Involvement of GSK-3beta and DYRK1B in Differentiation-inducing Factor-3-induced Phosphorylation of Cyclin D1 in HeLa Cells. J Biol Chem 281(50): 38489–38497.

Tanaka H, Yamashita T, Yachi K, Fujiwara T, Yoshikawa H, Tohyama M. 2004. Cytoplasmic p21Cip1/WAF1 enhances axonal regeneration and functional recovery after spinal cord injury in rats. Neuroscience 127:155–164.

Tejedor F, Zhu X, Kaltenbach E, Ackermann A, Baumann A, Canal I, Heisenberg M, Fischbach K, Pongs O. 1995. Minibrain:a new protein kinase family involved in postembryonic neurogenesis in Drosophila. Neuron 14: 287–301.

Wang J, Walsh K. 1996. Resistance to apoptosis conferred by Cdk inhibitors during myocyte differentiation. Science 273:369–371.

Zou Y, Ewton D, Deng D, Mercer S, Friedman E. 2004. Mirk/dyrk1B Kinase Destabilizes Cyclin D1 by Phosphorylation at Threonine 288. J Biol Chem 279:27790–27798.