Atlas of Genetics and Cytogenetics
in Oncology and Haematology

OPEN ACCESS JOURNAL

INIST-CNRS

Gene Section
Review

MYLK (myosin light chain kinase)

Kui Shen, Ting Wang, Joe GN Garcia

Institute of Personalized Respiratory Medicine, Department of Medicine, University of Illinois, Chicago, IL 60612, USA (KS, TW, JGNG)

Published in Atlas Database: June 2012

Online updated version : http://AtlasGeneticsOncology.org/Genes/MYLKID43364ch3q21.html
DOI: 10.4267/2042/48362

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.
© 2012 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Identity

Other names: AAT7, KRP, MLCK, MLCK1, MLCK108, MLCK210, MSTP083, MYLK1, smMLCK

HGNC (Hugo): MYLK

Location: 3q21.1

Note

Strand: Reverse (minus, -); Genomic Size: 272007.

This gene, a member of the immunoglobulin gene superfamily, encodes myosin light chain kinase (MLCK), which is a calcium/calmodulin dependent kinase that phosphorylates myosin regulatory light chains (Potier et al., 1995) to regulate cell contractility (De Lanerolle et al., 1991; Garcia et al., 1995; Garcia et al., 1997b; Katoh et al., 2001) and cytokinesis (Dulyaninova et al., 2004; Fishkind et al., 1991; Matsumura et al., 2011; Poperechnaya et al., 2000).

Multiple transcript variants of this gene have been identified that produce both nonmuscle and smooth muscle isoforms of MLCK (Garcia et al., 1997a; Lazar and Garcia, 1999; Verin et al., 1998b).

In addition, using a separate promoter in an intron in the 3' region, it encodes telokin, a small protein identical in sequence to the C-terminus of MLCK (Gallagher and Herring, 1991; Watterson et al., 1999), which functions to stabilize unphosphorylated myosin filaments in smooth muscle (Kudryashov et al., 2002; Shirinsky et al., 1993).

A pseudogene of MYLK is located on the p arm of chromosome 3 (Brand-Arpon et al., 1999; Giorgi et al., 2001; Han et al., 2011) (modified from RefSeq, July 2008).

DNA/RNA

Description

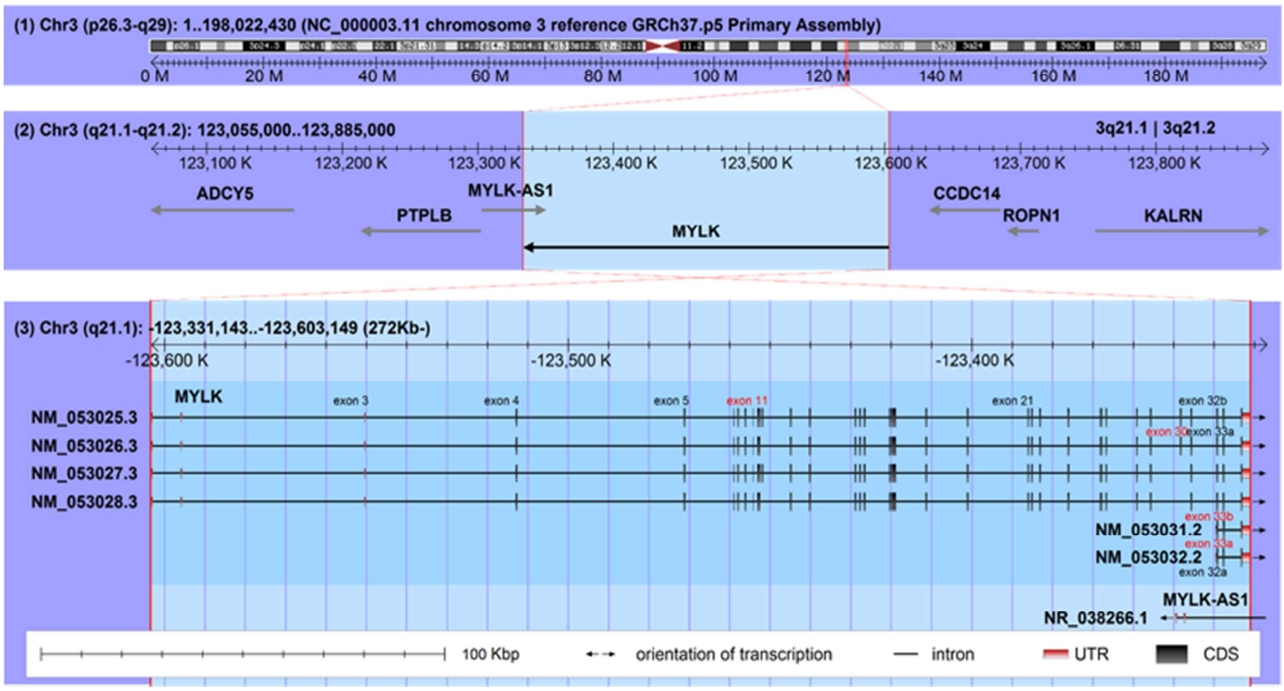
The gene is composed of 34 exons, 31 out of which are coding exons.

Transcription

Multiple MLCK isoforms are produced from the same MYLK gene by alternative splicing or alternative initiation (Lazar and Garcia, 1999; Verin et al., 1998b; Watterson et al., 1999). Six transcript variants have been identified that produce four kinase domain-encoding isoforms and two isoforms of telokin. Additional variants exist but lack full length transcripts. The longest transcript (nmMLCK1), which encodes the full length nonmuscle isoform (NM_053025), is a 7852 bp mRNA with a 5745 bp open reading frame from base pair 283 to 6027.

Pseudogene

PGOHUM00000250243, PGOHUM00000238157, and PGOHUM00000238160 (Human Pseudogenes, Build 61). Note: Partially duplicated from the original MYLK gene, the MYLKP1 pseudogene (PGOHUM00000250243) is proposed to negatively regulate MYLK gene expression (Han et al., 2011).



The MYLK gene viewed at three different levels of detail (highlighted between two red vertical boundary lines). (1) Overview within chromosome 3. (2) Partial regional view within chromosome 3q21.1-3q21.2. (3) Detailed view within chromosome 3q21.1 showing six of the transcription variants of MLCK, which include nmMLCK1 (NM_053025), 2 (NM_053026), 3A (NM_053027), 3B (NM_053028), and two telokins (NM_053031 and NM_053032). The transcripts are not drawn in exact proportion so that their introns and exons, including CDSs and UTRs, can all be seen at a limited resolution. Abbreviations: Chr, chromosome; CDS, coding sequence; UTR, untranslated region.

Protein

Description

The full length isoform nmMLCK1 is a 1914-aa protein with a molecular weight of 210715 Da.

All isoforms including telokin bind calmodulin (Davis et al., 1996; Gallagher and Herring, 1991; Geguchadze et al., 2004; Katoh et al., 2001). Various MLCK protein isoforms that result from the same MYLK gene (Lazar and Garcia, 1999) by alternative splicing or alternative initiation may be differentially regulated to achieve a tissue-specific spatiotemporal control of the binding (Davis et al., 1996; Dudek et al., 2002; Dudek et al., 2004; Hatch et al., 2001; Kishi et al., 1998) and catalytic activity of MLCK.

The full length isoform nmMLCK1 is activated by post-translational modifications (PTMs) such as phosphorylation on Tyr-464 and Tyr-471 (coded by exon 11) (Birukov et al., 2001; Dudek et al., 2010). These PTMs are catalyzed by c-Abl (Dudek et al., 2010), p60Src (Birukov et al., 2001; Garcia et al., 1999), cAMP-dependent protein kinase (PKA) (Garcia et al., 1997a; Verin et al., 1998a) and p21-activated kinases (Goeckeler et al., 2000; Sanders et al., 1999). Additional regulatory mechanisms involve acetylation (Shin et al., 2009), carboxyl-terminal deglutamylation (Rogowski et al., 2010), and kinase activation after thrombin, tumor necrosis factor (TNF), sphingosine 1-phosphate, G proteins, and during cell cycle (Garcia et al., 1995; Petrache et al., 2003; Poperechnaya et al., 2000; Somlyo and Somlyo, 2003; Ye et al., 2006; Ye and Ma, 2008).

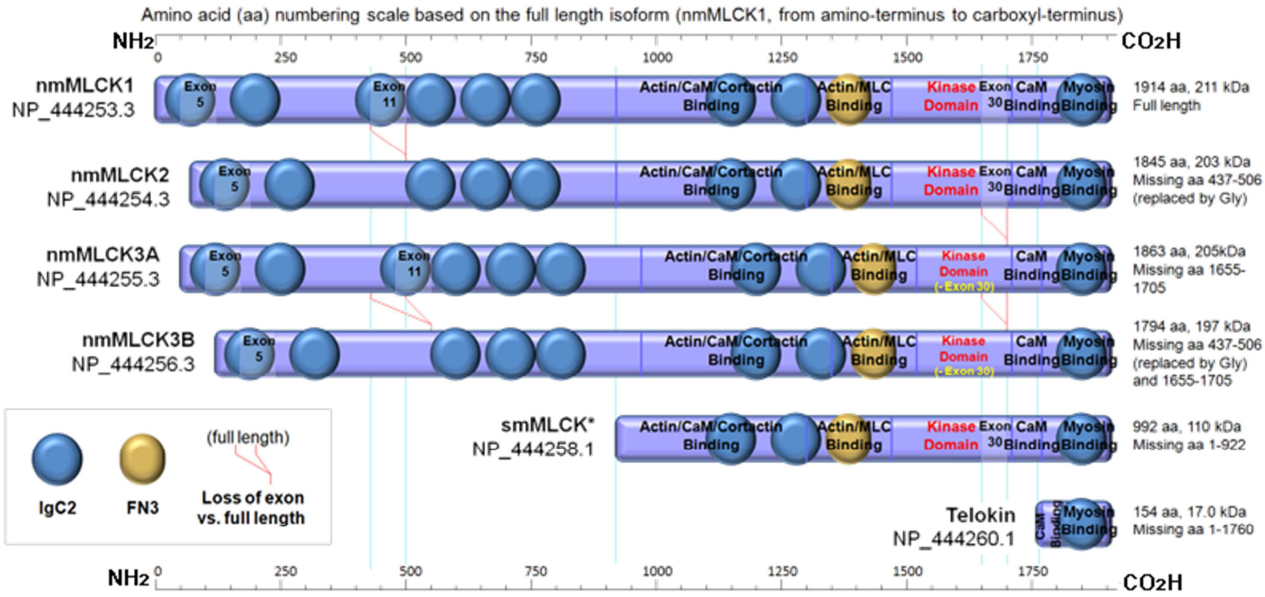
Expression

The nmMLCK or smMLCK isoforms and telokin are ubiquitously expressed in various adult and fetal tissues and in cultured endothelium with qualitative expression appearing to be neither tissue- nor development-specific (Garcia et al., 1997a; Lazar and Garcia, 1999; Potier et al., 1995; Verin et al., 1998b; Watterson et al., 1999).

The nmMLCK 1 and 2 isoforms are dominant isoforms in nonmuscle (endothelial) cells (Brown et al., 2010; Garcia et al., 1997a; Lazar and Garcia, 1999; Verin et al., 1998b).

Localisation

Lamellipodium; cytoplasm; cytoskeleton; stress fiber; cytosol; cleavage furrow.



Representative MLCK protein isoforms shown with select structural/functional information, as compared with the full length isoform (nmMLCK1). The nonmuscle MLCK isoform variants (nmMLCK 1, 2, 3A, 3B) differ in the presence or absence of exons 11 and 30. All nmMLCK variants possess unique amino termini that are absent in the smooth muscle isoform, smMLCK, and two isoforms of telokin. The longer isoform of telokin, differing by one amino acid from its shorter version (with the aa 1790 deletion), is identical to the C-termini of nmMLCK and smMLCK isoforms shown (Watterson et al., 1999). Abbreviations: aa, amino acid; CaM, calmodulin; IgC2, immunoglobulin C-2 type domain; FN3, fibronectin type 3 domain. *Note: NCBI RefSeq NM_053030.2 (NP_444258.1) was permanently suppressed because there was insufficient support for the transcript and the CDS was partial.

Function

Belongs to protein kinase superfamily, non-receptor Ser/Thr protein kinase, EC 2.7.11.18, calcium/calmodulin-dependent protein kinase (CAMK) group, MLCK family.

Regulates smooth muscle and nonmuscle cell contractile processes (De Lanerolle et al., 1991; Garcia et al., 1995; Katoh et al., 2001; Somlyo and Somlyo, 2003), via phosphorylation of myosin light chains (MLC), or through a non-kinase activity (Dudek et al., 2004; Herring et al., 2006; Kudryashov et al., 2002; Nakamura et al., 2008; Shirinsky et al., 1993).

Regulates cytogenesis (Dulyaninova et al., 2004; Fishkind et al., 1991; Matsumura et al., 2011; Poperechnaya et al., 2000).

Regulates other related cellular processes including cell adhesion, migration, morphology, and inflammatory responses (Garcia et al., 1998; Savkovic et al., 2001), e.g., apoptosis (Mills et al., 1998; Petrache et al., 2003; Wright et al., 1993), and vascular permeability (Dudek et al., 2004; Garcia et al., 1995; Garcia et al., 1998; Shen et al., 2010; Vandenbroucke et al., 2008; Yuan et al., 2002), all via the regulation of cytoskeletal rearrangements. Genetic variants in MYLK are implicated in inflammatory disorders such as asthma and acute lung injury (Flores et al., 2007; Gao et al., 2006; Gao et al., 2007).

Implicated in tumor formation and metastasis (see below).

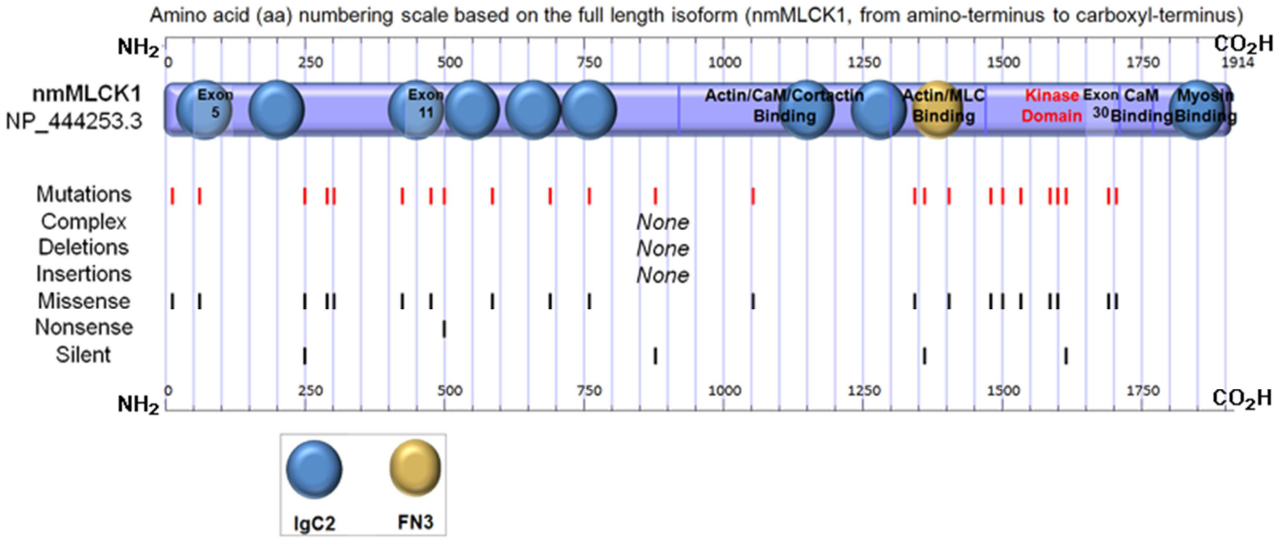
Homology

The human MYLK gene is conserved in Euteleostomi, with a high percentage of identity in the pairwise alignment of protein/DNA vs. chimpanzee (99,1% / 99,4%), monkey (97,3% / 97,0%), dog (89,1% / 89,0%), mouse (85,9% / 85,6%), rat (85,4% / 86,0%), chicken (71,4% / 68,8%), and zebrafish (63,0% / 65,5%) (Homologene). The paralogs of human MYLK gene include MYLK2-4, DAPK1-3, STK17A and STK17B, and SPEG (Ensembl) (Manning et al., 2002).

Mutations

Note

Some protein-coding somatic mutations in MYLK are associated with cancers (Catalogue of Somatic Mutations in Cancer–COSMIC) (Greenman et al., 2007). Several variants of MYLK are associated with familial aortic dissections (Wang et al., 2010). A few race-specific single nucleotide polymorphism (SNP) variants of MYLK, both in coding and noncoding regions, are associated with the susceptibility to acute lung injury, sepsis and severe asthma (Flores et al., 2007; Gao et al., 2006; Gao et al., 2007).



Cancer-associated somatic mutations in MYLK in the protein coding region (Catalogue of Somatic Mutations in Cancer–COSMIC). Abbreviations: CaM, calmodulin; IgC2, immunoglobulin C-2 type domain; FN3, fibronectin type 3 domain; Complex, complex substitutions; Missense, missense substitutions; Nonsense, nonsense substitutions; Silent, silent substitutions.

Implicated in

Cancers

Note

Myosin light chain kinase (MLCK) plays a crucial role in the cell migration and tumor metastasis. Some somatic mutations in MYLK are associated with cancers (Greenman et al., 2007). MLCK is critical for adhesion turnover at the cell front, a process central to migration (Webb et al., 2004) and it is involved in membrane blebbing (Godin and Ferguson, 2010). Deficiency in MLC phosphorylation causes cytokinesis failure and multipolarity (hence genomic instability) in cancer cells (Wu et al., 2010).

Breast cancer

Note

MLCK activity correlates the recruitment of nonmuscle myosin IIA and myosin IIB into the spreading margin of MDA-MB-231 breast cancer cells, with both myosin isoforms required for cell migration but only myosin IIB critical to lamellar protrusion (Betapudi et al., 2006).

MLC phosphorylation by MLCK through β1-integrin is required for actin stress fiber formation and the dormancy-to-proliferation metastatic switch for latent breast cancer cells (Barkan et al., 2008; Barkan et al., 2011). MLCK functions downstream of Ras, MAP kinase kinase (MEK) and extracellular signal regulated kinase (ERK) to promote invasive migration of breast cancer cells in an integrin-selective manner, i.e., mediated by a β1-integrin (probably α5β1) and α5β5, but not by α5β3 (Mierke, 2011; Mierke et al., 2011b; Nguyen et al., 1999; Zhou et al., 2008).

Endothelial nmMLCK is activated by invasive breast cancer cells at the invasion site, leading to regional MLC diphosphorylation and myosin contraction.

Blocking endothelial MLC diphosphorylation blunts tumor transcellular (i.e., through individual endothelial cells), but not paracellular (i.e., through cell-cell junctions) invasion (Khuon et al., 2010). Human mammary tumor cells exhibit at least two modes of invasive migration, including the extracellular proteolysis-dependent mesenchymal mode (invadopodia-associated extracellular matrix degradation) (Alexander et al., 2008) and the proteolysis-independent amoeboid mode, with both modes mediated by MLCK and Rho kinase ROCK (Alexander et al., 2008; Torka et al., 2006).

TNF induction of apoptosis and DNA fragmentation requires MLCK activation in mammary carcinoma and other cancer cell lines (Wright et al., 1993).

MLCK is responsible for high proliferative ability of breast cancer cells via anti-apoptosis (Cui et al., 2010). The increase in MLC phosphorylation correlates with apoptotic blebbing (Mills et al., 1998).

Subsequent MLC dephosphorylation that results from a proapoptotic agent or MLCK inhibition (inhibitor or antibody) precedes caspase activation (Fazal et al., 2005), which further induces apoptosis in vitro and in vivo, and retards the growth of mammary cancer cells in mice (Fazal et al., 2005; Gu et al., 2006).

Lung cancer

Note

The invasiveness of tumor cells depends in part on their motility, which in turn depends on cytoskeletal function (Minamiya et al., 2005). The expression level

of MLCK, the cytoskeletal regulator, correlates with disease recurrence and distant metastasis in non-small cell lung cancer (NSCLC) (Minamiya et al., 2005). E1AF, an Ets family transcription factor frequently overexpressed in NSCLCs, induces motility and invasion as well as tumorigenesis and metastasis in NSCLC cells in a MLCK-dependent pathway (Hakuma et al., 2005). A few anti-cancer drug candidates, including glabridin, 7-chloro-6-piperidin-1-yl-quinoline-5,8-dione (PT-262), and all-trans-retinoic acid (ATRA), inhibit cell metastasis by decreasing cancer cell migration and invasion of human lung adenocarcinoma A549 cells via modulation of expression (Gui et al., 2011) or activity (Tsai et al., 2011a; Tsai et al., 2011b) of MLCK. Glycosylphosphatidylinositol-anchored receptor CD24 is found to enhance invasion of A125 human lung cancer cells through increased generation or transmission of contractile forces which is dependent on MLCK activity (Mierke et al., 2011a).

Colon cancer

Note

MLCK is differentially expressed in microsatellite stable (MSS) sporadic colon cancer and hereditary nonpolyposis colorectal cancer (HNPCC) (Lee et al., 2008). It is suggested to be a potential colon tumor marker. MLCK regulates transendothelial migration of colon cancer cells in E-selectin-mediated activation of p38 MAPK (Tremblay et al., 2006), and possibly via changing cellular contractility by regulation of adhesion sites and stress fibers (Krndija et al., 2010). Inhibition of MLCK suppresses peripheral accumulation of phospho-MLC and Src-induced formation of integrin-dependent adhesions in KM12C colon cancer cells, whereas at the same time restoring E-cadherin redistribution to regions of cell-cell contact (Avizienyte et al., 2004; Avizienyte et al., 2005; Nguyen et al., 2002).

Prostate cancer

Note

Inhibitors of MLCK markedly reduce the invasiveness of prostate cancer cells due to impaired cellular motility (Tohtong et al., 2003). These inhibitors also retard the growth of established prostate tumor in vivo (Gu et al., 2006). MLCK is considered as a central mediator of migration, proliferation and invasion of prostatic adenocarcinoma cell line (Tohtong et al., 2003) downstream of PKC delta (Kharait et al., 2007), boric acid, and phenylboronic acid (McAuley et al., 2011) in DU145 cell line (metastatic prostate cancer cell line). The MYLK gene is one of the top seven most informative genes that discriminate between normal and tumoral prostate conditions by
analyzing cDNA microarrays of approximately 25000 genes (Fujita et al., 2008). MLCK is down-regulated by androgens in human prostate cancer cells (Leveille et al., 2009).

Other cancers

Note

MLC phosphorylation or MLCK activation is directly involved in the activation of membrane-associated actomyosin required for the collection of surface proteins into a cap structure in mouse T-lymphoma cells (analogous to muscle cell sliding filament contraction) (Bourguignon et al., 1981; Kerrick and Bourguignon., 1984). Inhibitors of MLCK (ML-7 and ML-9) induce differentiation of human monoblastic leukemia U937 cells (Makishima et al., 1991; Makishima et al., 1993; Yamamoto-Yamaguchi et al., 1996). Apoptotic membrane blebbing is accompanied by increased MLC phosphorylation and regulated by MLCK in PC12, a neuroendocrine tumor cell line (Mills et al, 1998). MLCK regulates the activation of volume-sensitive organic osmolyte/anion channels (VSOAC) by mediating hypotonicity-induced Ca^{2+} entry (not correlating with MLC phosphorylation) in cervical cancer cells (Shen et al., 2002).

References

Bourguignon LY, Nagpal ML, Hsing YC. Phosphorylation of myosin light chain during capping of mouse T-lymphoma cells. J Cell Biol. 1981 Dec;91(3 Pt 1):889-94

Kerrick WG, Bourguignon LY. Regulation of receptor capping in mouse lymphoma T cells by Ca2+-activated myosin light chain kinase. Proc Natl Acad Sci U S A. 1984 Jan;81(1):165-9

De Lanerolle P, Strauss JD, Felsen R, Doerman GE, Paul RJ. Effects of antibodies to myosin light chain kinase on contractility and myosin phosphorylation in chemically permeabilized smooth muscle. Circ Res. 1991 Feb;68(2):457-65

Fishkind DJ, Cao LG, Wang YL. Microinjection of the catalytic fragment of myosin light chain kinase into dividing cells: effects on mitosis and cytokinesis. J Cell Biol. 1991 Sep;114(5):967-75

Gallagher PJ, Herring BP. The carboxyl terminus of the smooth muscle myosin light chain kinase is expressed as an independent protein, telokin. J Biol Chem. 1991 Dec 15;266(35):23945-52

Makishima M, Honma Y, Hozumi M, Sampi K, Hattori M, Motoyoshi K. Induction of differentiation of human leukemia cells by inhibitors of myosin light chain kinase. FEBS Lett. 1991 Aug 5;287(1-2):175-7

Makishima M, Honma Y, Hozumi M, Nagata N, Motoyoshi K. Differentiation of human monoblastic leukemia U937 cells induced by inhibitors of myosin light chain kinase and prevention of differentiation by granulocyte-macrophage colony-stimulating factor. Biochim Biophys Acta. 1993 Apr 16;1176(3):245-9

Shirinsky VP, Vorotnikov AV, Birukov KG, Nanaev AK, Collinge M, Lukas TJ, Sellers JR, Watterson DM. A kinase-related protein stabilizes unphosphorylated smooth muscle myosin minifilaments in the presence of ATP. J Biol Chem. 1993 Aug 5;268(22):16578-83

Wright SC, Zheng H, Zhong J, Torti FM, Larrick JW. Role of protein phosphorylation in TNF-induced apoptosis: phosphatase inhibitors synergize with TNF to activate DNA fragmentation in normal as well as TNF-resistant U937 variants. J Cell Biochem. 1993 Nov;53(3):222-33

Garcia JG, Davis HW, Patterson CE. Regulation of endothelial cell gap formation and barrier dysfunction: role of myosin light chain phosphorylation. J Cell Physiol. 1995 Jun;163(3):510-22

Potier MC, Chelot E, Pekarsky Y, Gardiner K, Rossier J, Turnell WG. The human myosin light chain kinase (MLCK) from hippocampus: cloning, sequencing, expression, and localization to 3qcen-q21. Genomics. 1995 Oct 10;29(3):562-70

Davis HW, Crimmins DL, Thoma RS, Garcia JG. Phosphorylation of calmodulin in the first calcium-binding pocket by myosin light chain kinase. Arch Biochem Biophys. 1996 Aug 1;332(1):101-9

Yamamoto-Yamaguchi Y, Makishima M, Kanatani Y, Kasukabe T, Honma Y. Reversible differentiation of human monoblastic leukemia U937 cells by ML-9, an inhibitor of myosin light chain kinase. Exp Hematol. 1996 May;24(6):682-9

Garcia JG, Lazar V, Gilbert-McClain LI, Gallagher PJ, Verin AD. Myosin light chain kinase in endothelium: molecular cloning and regulation. Am J Respir Cell Mol Biol. 1997a May;16(5):489-94

Garcia JG, Schaphorst KL, Shi S, Verin AD, Hart CM, Callahan KS, Patterson CE. Mechanisms of ionomycin-induced endothelial cell barrier dysfunction. Am J Physiol. 1997b Jul;273(1 Pt 1):L172-84

Garcia JG, Verin AD, Herenyiova M, English D. Adherent neutrophils activate endothelial myosin light chain kinase: role in transendothelial migration. J Appl Physiol. 1998 May;84(5):1817-21

Kishi H, Ye LH, Nakamura A, Okagaki T, Iwata A, Tanaka T, Kohama K. Structure and function of smooth muscle myosin light chain kinase. Adv Exp Med Biol. 1998;453:229-34

Mills JC, Stone NL, Erhardt J, Pittman RN. Apoptotic membrane blebbing is regulated by myosin light chain phosphorylation. J Cell Biol. 1998 Feb 9;140(3):627-36

Verin AD, Gilbert-McClain LI, Patterson CE, Garcia JG. Biochemical regulation of the nonmuscle myosin light chain kinase isoform in bovine endothelium. Am J Respir Cell Mol Biol. 1998a Nov;19(5):767-76

Verin AD, Lazar V, Torry RJ, Labarrere CA, Patterson CE, Garcia JG. Expression of a novel high molecular-weight myosin light chain kinase in endothelium. Am J Respir Cell Mol Biol. 1998b Nov;19(5):758-66

Brand-Arpon V, Rouquier S, Massa H, de Jong PJ, Ferraz C, Ioannou PA, Demaille JG, Trask BJ, Giorgi D. A genomic region encompassing a cluster of olfactory receptor genes and a myosin light chain kinase (MYLK) gene is duplicated on human chromosome regions 3q13-q21 and 3p13. Genomics. 1999 Feb 15;56(1):98-110

Garcia JG, Verin AD, Schaphorst K, Siddiqui R, Patterson CE, Csortos C, Natarajan V. Regulation of endothelial cell myosin light chain kinase by Rho, cortactin, and p60(src). Am J Physiol. 1999 Jun;276(6 Pt 1):L989-98

Lazar V, Garcia JG. A single human myosin light chain kinase gene (MLCK; MYLK). Genomics. 1999 Apr 15;57(2):256-67

Nguyen DH, Catling AD, Webb DJ, Sankovic M, Walker LA, Somlyo AV, Weber MJ, Gonias SL. Myosin light chain kinase functions downstream of Ras/ERK to promote migration of urokinase-type plasminogen activator-stimulated cells in an integrin-selective manner. J Cell Biol. 1999 Jul 12;146(1):149-64

Sanders LC, Matsumura F, Bokoch GM, de Lanerolle P. Inhibition of myosin light chain kinase by p21-activated kinase. Science. 1999 Mar 26;283(5410):2083-5

Watterson DM, Schavocky JP, Guo L, Weiss C, Chlenski A, Shirinsky VP, Van Eldik LJ, Haiech J. Analysis of the kinase-related protein gene found at human chromosome 3q21 in a multi-gene cluster: organization, expression, alternative splicing, and polymorphic marker. J Cell Biochem. 1999 Dec 1;75(3):481-91

Goeckeler ZM, Masaracchia RA, Zeng Q, Chew TL, Gallagher P, Wysolmerski RB. Phosphorylation of myosin light chain kinase by p21-activated kinase PAK2. J Biol Chem. 2000 Jun 16;275(24):18366-74

Poperechnaya A, Varlamova O, Lin PJ, Stull JT, Bresnick AR. Localization and activity of myosin light chain kinase isoforms during the cell cycle. J Cell Biol. 2000 Oct 30;151(3):697-708

Birukov KG, Csortos C, Marzilli L, Dudek S, Ma SF, Bresnick AR, Verin AD, Cotter RJ, Garcia JG. Differential regulation of alternatively spliced endothelial cell myosin light chain kinase isoforms by p60(Src). J Biol Chem. 2001 Mar 16;276(11):8567-73

Giorgi D, Brand-Arpon V, Rouquier S. The functional myosin light chain kinase (MYLK) gene localizes with marker D3S3552 on human chromosome 3q21 in a >5-Mb yeast artificial chromosome region and is not linked to olfactory receptor genes. Cytogenet Cell Genet. 2001;92(1-2):85-8

Hatch V, Zhi G, Smith L, Stull JT, Craig R, Lehman W. Myosin light chain kinase binding to a unique site on F-actin revealed by three-dimensional image reconstruction. J Cell Biol. 2001 Aug 6;154(3):611-7

Katoh K, Kano Y, Amano M, Onishi H, Kaibuchi K, Fujiwara K. Rho-kinase--mediated contraction of isolated stress fibers. J Cell Biol. 2001 Apr 30;153(3):569-84

Savkovic SD, Ramaswamy A, Koutsouris A, Hecht G. EPEC-activated ERK1/2 participate in inflammatory response but not tight junction barrier disruption. Am J Physiol Gastrointest Liver Physiol. 2001 Oct;281(4):G890-8

Dudek SM, Birukov KG, Zhan X, Garcia JG. Novel interaction of cortactin with endothelial cell myosin light chain kinase. Biochem Biophys Res Commun. 2002 Nov 8;298(4):511-9

Kudryashov DS, Vorotnikov AV, Dudnakova TV, Stepanova OV, Lukas TJ, Sellers JR, Watterson DM, Shirinsky VP. Smooth muscle myosin filament assembly under control of a kinase-related protein (KRP) and caldesmon. J Muscle Res Cell Motil. 2002;23(4):341-51

Manning G, Whyte DB, Martinez R, Hunter T, Sudarsanam S. The protein kinase complement of the human genome. Science. 2002 Dec 6;298(5600):1912-34

Nguyen QD, Faivre S, Bruyneel E, Rivat C, Seto M, Endo T, Mareel M, Emami S, Gespach C. RhoA- and RhoD-dependent regulatory switch of Galpha subunit signaling by PAR-1 receptors in cellular invasion. FASEB J. 2002 Apr;16(6):565-76

Shen MR, Furla P, Chou CY, Ellory JC. Myosin light chain kinase modulates hypotonicity-induced Ca2+ entry and Cl- channel activity in human cervical cancer cells. Pflugers Arch. 2002 May;444(1-2):276-85

Yuan SY, Wu MH, Ustinova EE, Guo M, Tinsley JH, De Lanerolle P, Xu W. Myosin light chain phosphorylation in neutrophil-stimulated coronary microvascular leakage. Circ Res. 2002 Jun 14;90(11):1214-21

Petrache I, Birukov K, Zaiman AL, Crow MT, Deng H, Wadgaonkar R, Romer LH, Garcia JG. Caspase-dependent cleavage of myosin light chain kinase (MLCK) is involved in TNF-alpha-mediated bovine pulmonary endothelial cell apoptosis. FASEB J. 2003 Mar;17(3):407-16

Somlyo AP, Somlyo AV. Ca2+ sensitivity of smooth muscle and nonmuscle myosin II: modulated by G proteins, kinases,

and myosin phosphatase. Physiol Rev. 2003 Oct;83(4):1325-58

Tohtong R, Phattarasakul K, Jiraviriyakul A, Sutthiphongchai T. Dependence of metastatic cancer cell invasion on MLCK-catalyzed phosphorylation of myosin regulatory light chain. Prostate Cancer Prostatic Dis. 2003;6(3):212-6

Avizienyte E, Fincham VJ, Brunton VG, Frame MC. Src SH3/2 domain-mediated peripheral accumulation of Src and phospho-myosin is linked to deregulation of E-cadherin and the epithelial-mesenchymal transition. Mol Biol Cell. 2004 Jun;15(6):2794-803

Dudek SM, Jacobson JR, Chiang ET, Birukov KG, Wang P, Zhan X, Garcia JG. Pulmonary endothelial cell barrier enhancement by sphingosine 1-phosphate: roles for cortactin and myosin light chain kinase. J Biol Chem. 2004 Jun 4;279(23):24692-700

Dulyaninova NG, Patskovsky YV, Bresnick AR. The N-terminus of the long MLCK induces a disruption in normal spindle morphology and metaphase arrest. J Cell Sci. 2004 Mar 15;117(Pt 8):1481-93

Geguchadze R, Zhi G, Lau KS, Isotani E, Persechini A, Kamm KE, Stull JT. Quantitative measurements of Ca(2+)/calmodulin binding and activation of myosin light chain kinase in cells. FEBS Lett. 2004 Jan 16;557(1-3):121-4

Webb DJ, Donais K, Whitmore LA, Thomas SM, Turner CE, Parsons JT, Horwitz AF. FAK-Src signalling through paxillin, ERK and MLCK regulates adhesion disassembly. Nat Cell Biol. 2004 Feb;6(2):154-61

Avizienyte E, Brunton VG, Fincham VJ, Frame MC. The SRC-induced mesenchymal state in late-stage colon cancer cells. Cells Tissues Organs. 2005;179(1-2):73-80

Fazal F, Gu L, Ihnatovych I, Han Y, Hu W, Antic N, Carreira F, Blomquist JF, Hope TJ, Ucker DS, de Lanerolle P. Inhibiting myosin light chain kinase induces apoptosis in vitro and in vivo. Mol Cell Biol. 2005 Jul;25(14):6259-66

Hakuma N, Kinoshita I, Shimizu Y, Yamazaki K, Yoshida K, Nishimura M, Dosaka-Akita H. E1AF/PEA3 activates the Rho/Rho-associated kinase pathway to increase the malignancy potential of non-small-cell lung cancer cells. Cancer Res. 2005 Dec 1;65(23):10776-82

Minamiya Y, Nakagawa T, Saito H, Matsuzaki I, Taguchi K, Ito M, Ogawa J. Increased expression of myosin light chain kinase mRNA is related to metastasis in non-small cell lung cancer. Tumour Biol. 2005 May-Jun;26(3):153-7

Betapudi V, Licate LS, Egelhoff TT. Distinct roles of nonmuscle myosin II isoforms in the regulation of MDA-MB-231 breast cancer cell spreading and migration. Cancer Res. 2006 May 1;66(9):4725-33

Gao L, Grant A, Halder I, Brower R, Sevransky J, Maloney JP, Moss M, Shanholtz C, Yates CR, Meduri GU, Shriver MD, Ingersoll R, Scott AF, Beaty TH, Moitra J, Ma SF, Ye SQ, Barnes KC, Garcia JG. Novel polymorphisms in the myosin light chain kinase gene confer risk for acute lung injury. Am J Respir Cell Mol Biol. 2006 Apr;34(4):487-95

Gu LZ, Hu WY, Antic N, Mehta R, Turner JR, de Lanerolle P. Inhibiting myosin light chain kinase retards the growth of mammary and prostate cancer cells. Eur J Cancer. 2006 May;42(7):948-57

Herring BP, El-Mounayri O, Gallagher PJ, Yin F, Zhou J. Regulation of myosin light chain kinase and telokin expression in smooth muscle tissues. Am J Physiol Cell Physiol. 2006 Nov;291(5):C817-27

Torka R, Thuma F, Herzog V, Kirfel G. ROCK signaling mediates the adoption of different modes of migration and invasion in human mammary epithelial tumor cells. Exp Cell Res. 2006 Nov 15;312(19):3857-71

Tremblay PL, Auger FA, Huot J. Regulation of transendothelial migration of colon cancer cells by E-selectin-mediated activation of p38 and ERK MAP kinases. Oncogene. 2006 Oct 26;25(50):6563-73

Ye D, Ma I, Ma TY. Molecular mechanism of tumor necrosis factor-alpha modulation of intestinal epithelial tight junction barrier. Am J Physiol Gastrointest Liver Physiol. 2006 Mar;290(3):G496-504

Flores C, Ma SF, Maresso K, Ober C, Garcia JG. A variant of the myosin light chain kinase gene is associated with severe asthma in African Americans. Genet Epidemiol. 2007 May;31(4):296-305

Gao L, Grant AV, Rafaels N, Stockton-Porter M, Watkins T, Gao P, Chi P, Muñoz M, Watson H, Dunston G, Togias A, Hansel N, Sevransky J, Maloney JP, Moss M, Shanholtz C, Brower R, Garcia JG, Grigoryev DN, Cheadle C, Beaty TH, Mathias RA, Barnes KC. Polymorphisms in the myosin light chain kinase gene that confer risk of severe sepsis are associated with a lower risk of asthma. J Allergy Clin Immunol. 2007 May;119(5):1111-8

Greenman C, Stephens P, Smith R, Dalgliesh GL, Hunter C, Bignell G, Davies H, Teague J, Butler A, Stevens C, Edkins S, O'Meara S, Vastrik I, Schmidt EE, Avis T, Barthorpe S, Bhamra G, Buck G, Choudhury B, Clements J, Cole J, Dicks E, Forbes S, Gray K, Halliday K, Harrison R, Hills K, Hinton J, Jenkinson A, Jones D, Menzies A, Mironenko T, Perry J, Raine K, Richardson D, Shepherd R, Small A, Tofts C, Varian J, Webb T, West S, Widaa S, Yates A, Cahill DP, Louis DN, Goldstraw P, Nicholson AG, Brasseur F, Looijenga L, Weber BL, Chiew YE, DeFazio A, Greaves MF, Green AR, Campbell P, Birney E, Easton DF, Chenevix-Trench G, Tan MH, Khoo SK, Teh BT, Yuen ST, Leung SY, Wooster R, Futreal PA, Stratton MR. Patterns of somatic mutation in human cancer genomes. Nature. 2007 Mar 8;446(7132):153-8

Kharait S, Hautaniemi S, Wu S, Iwabu A, Lauffenburger DA, Wells A. Decision tree modeling predicts effects of inhibiting contractility signaling on cell motility. BMC Syst Biol. 2007 Jan 29;1:9

Alexander NR, Branch KM, Parekh A, Clark ES, Iwueke IC, Guelcher SA, Weaver AM. Extracellular matrix rigidity promotes invadopodia activity. Curr Biol. 2008 Sep 9;18(17):1295-9

Barkan D, Kleinman H, Simmons JL, Asmussen H, Kamaraju AK, Hoenorhoff MJ, Liu ZY, Costes SV, Cho EH, Lockett S, Khanna C, Chambers AF, Green JE. Inhibition of metastatic outgrowth from single dormant tumor cells by targeting the cytoskeleton. Cancer Res. 2008 Aug 1;68(15):6241-50

Fujita A, Gomes LR, Sato JR, Yamaguchi R, Thomaz CE, Sogayar MC, Miyano S. Multivariate gene expression analysis reveals functional connectivity changes between normal/tumoral prostates. BMC Syst Biol. 2008 Dec 5;2:106

Lee WS, Seo G, Shin HJ, Yun SH, Yun H, Choi N, Lee J, Son D, Cho J, Kim J, Cho YB, Chun HK, Lee WY. Identification of differentially expressed genes in microsatellite stable HNPCC and sporadic colon cancer. J Surg Res. 2008 Jan;144(1):29-35

Nakamura A, Xie C, Zhang Y, Gao Y, Wang HH, Ye LH, Kishi H, Okagaki T, Yoshiyama S, Hayakawa K, Ishikawa R, Kohama K. Role of non-kinase activity of myosin light-chain kinase in regulating smooth muscle contraction, a review dedicated to Dr. Setsuro Ebashi. Biochem Biophys Res Commun. 2008 Apr 25;369(1):135-43

Vandenbroucke E, Mehta D, Minshall R, Malik AB. Regulation of endothelial junctional permeability. Ann N Y Acad Sci. 2008 Mar;1123:134-45

Ye D, Ma TY. Cellular and molecular mechanisms that mediate basal and tumour necrosis factor-alpha-induced regulation of myosin light chain kinase gene activity. J Cell Mol Med. 2008 Aug;12(4):1331-46

Zhou X, Liu Y, You J, Zhang H, Zhang X, Ye L. Myosin light-chain kinase contributes to the proliferation and migration of breast cancer cells through cross-talk with activated ERK1/2. Cancer Lett. 2008 Nov 8;270(2):312-27

Léveillé N, Fournier A, Labrie C. Androgens down-regulate myosin light chain kinase in human prostate cancer cells. J Steroid Biochem Mol Biol. 2009 Apr;114(3-5):174-9

Shin DH, Chun YS, Lee KH, Shin HW, Park JW. Arrest defective-1 controls tumor cell behavior by acetylating myosin light chain kinase. PLoS One. 2009 Oct 14;4(10):e7451

Barkan D, El Touny LH, Michalowski AM, Smith JA, Chu I, Davis AS, Webster JD, Hoover S, Simpson RM, Gauldie J, Green JE. Metastatic growth from dormant cells induced by a col-I-enriched fibrotic environment. Cancer Res. 2010 Jul 15;70(14):5706-16

Brown M, Adyshev D, Bindokas V, Moitra J, Garcia JG, Dudek SM. Quantitative distribution and colocalization of non-muscle myosin light chain kinase isoforms and cortactin in human lung endothelium. Microvasc Res. 2010 Jul;80(1):75-88

Cui WJ, Liu Y, Zhou XL, Wang FZ, Zhang XD, Ye LH. Myosin light chain kinase is responsible for high proliferative ability of breast cancer cells via anti-apoptosis involving p38 pathway. Acta Pharmacol Sin. 2010 Jun;31(6):725-32

Dudek SM, Chiang ET, Camp SM, Guo Y, Zhao J, Brown ME, Singleton PA, Wang L, Desai A, Arce FT, Lal R, Van Eyk JE, Imam SZ, Garcia JG. Abl tyrosine kinase phosphorylates nonmuscle Myosin light chain kinase to regulate endothelial barrier function. Mol Biol Cell. 2010 Nov 15;21(22):4042-56

Godin CM, Ferguson SS. The angiotensin II type 1 receptor induces membrane blebbing by coupling to Rho A, Rho kinase, and myosin light chain kinase. Mol Pharmacol. 2010 Jun;77(6):903-11

Khuon S, Liang L, Dettman RW, Sporn PH, Wysolmerski RB, Chew TL. Myosin light chain kinase mediates transcellular intravasation of breast cancer cells through the underlying endothelial cells: a three-dimensional FRET study. J Cell Sci. 2010 Feb 1;123(Pt 3):431-40

Krndija D, Schmid H, Eismann JL, Lother U, Adler G, Oswald F, Seufferlein T, von Wichert G. Substrate stiffness and the receptor-type tyrosine-protein phosphatase alpha regulate spreading of colon cancer cells through cytoskeletal contractility. Oncogene. 2010 May 6;29(18):2724-38

Rogowski K, van Dijk J, Magiera MM, Bosc C, Deloulme JC, Bosson A, Peris L, Gold ND, Lacroix B, Grau MB, Bec N, Larroque C, Desagher S, Holzer M, Andrieux A, Moutin MJ, Janke C. A family of protein-deglutamylating enzymes associated with neurodegeneration. Cell. 2010 Nov 12;143(4):564-78

Shen Q, Rigor RR, Pivetti CD, Wu MH, Yuan SY. Myosin light chain kinase in microvascular endothelial barrier function. Cardiovasc Res. 2010 Jul 15;87(2):272-80

Wang L, Guo DC, Cao J, Gong L, Kamm KE, Regalado E, Li L, Shete S, He WQ, Zhu MS, Offermanns S, Gilchrist D, Elefteriades J, Stull JT, Milewicz DM. Mutations in myosin light chain kinase cause familial aortic dissections. Am J Hum Genet. 2010 Nov 12;87(5):701-7

Wu Q, Sahasrabudhe RM, Luo LZ, Lewis DW, Gollin SM, Saunders WS. Deficiency in myosin light-chain phosphorylation causes cytokinesis failure and multipolarity in cancer cells. Oncogene. 2010 Jul 22;29(29):4183-93

Gui S, Wang Y, Cheng Y, Zhou Q, Chen F and Wang Y.. Mechanism of all-trans-retinoic acid in inhibiting the migration of human lung adenocarcinoma A549 cells. Chin Pharm Bull. 2011 Jan;21(1):33-6.

Han YJ, Ma SF, Yourek G, Park YD, Garcia JG.. A transcribed pseudogene of MYLK promotes cell proliferation. FASEB J. 2011 Jul;25(7):2305-12. Epub 2011 Mar 25.

Matsumura F, Yamakita Y, Yamashiro S.. Myosin light chain kinases and phosphatase in mitosis and cytokinesis. Arch Biochem Biophys. 2011 Jun 15;510(2):76-82. Epub 2011 Mar 21. (REVIEW)

McAuley EM, Bradke TA, Plopper GE.. Phenylboronic acid is a more potent inhibitor than boric acid of key signaling networks involved in cancer cell migration. Cell Adh Migr. 2011 Sep-Oct;5(5):382-6.

Mierke CT.. Cancer cells regulate biomechanical properties of human microvascular endothelial cells. J Biol Chem. 2011 Nov 18;286(46):40025-37. Epub 2011 Sep 22.

Mierke CT, Bretz N, Altevogt P.. Contractile forces contribute to increased glycosylphosphatidylinositol-anchored receptor CD24-facilitated cancer cell invasion. J Biol Chem. 2011a Oct 7;286(40):34858-71. Epub 2011 Aug 2.

Mierke CT, Frey B, Fellner M, Herrmann M, Fabry B.. Integrin alpha5beta1 facilitates cancer cell invasion through enhanced contractile forces. J Cell Sci. 2011b Feb 1;124(Pt 3):369-83. Epub 2011 Jan 11.

Tsai CC, Liu HF, Hsu KC, Yang JM, Chen C, Liu KK, Hsu TS, Chao JI.. 7-Chloro-6-piperidin-1-yl-quinoline-5,8-dione (PT-262), a novel ROCK inhibitor blocks cytoskeleton function and cell migration. Biochem Pharmacol. 2011a Apr 1;81(7):856-65. Epub 2011 Jan 26.

Tsai YM, Yang CJ, Hsu YL, Wu LY, Tsai YC, Hung JY, Lien CT, Huang MS, Kuo PL.. Glabridin inhibits migration, invasion, and angiogenesis of human non-small cell lung cancer A549 cells by inhibiting the FAK/rho signaling pathway. Integr Cancer Ther. 2011b Dec;10(4):341-9. Epub 2010 Nov 8.

This article should be referenced as such:

Shen K, Wang T, Garcia JGN. MYLK (myosin light chain kinase). Atlas Genet Cytogenet Oncol Haematol. 2012; 16(12):901-908.