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Review

The diverse biofunctions of LIM domain proteins: determined by subcellular localization and protein–protein interaction

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The LIM domain is a cysteine- and histidine-rich motif that has been proposed to direct protein–protein interactions. A diverse group of proteins containing LIM domains have been identified, which display various functions including gene regulation and cell fate determination, tumour formation and cytoskeleton organization. LIM domain proteins are distributed in both the nucleus and the cytoplasm, and they exert their functions through interactions with various protein partners.

Introduction

Protein interaction domains participate in and regulate almost all essential cellular processes, including cell growth, differentiation, apoptosis and cellular behaviour changes. One of the protein–protein interaction motifs is the LIM domain that is found throughout the eukaryotes. The term 'LIM' stems from the first letters of three homoeodomain proteins in which LIM domains were originally identified, namely Linl-1, Isl-1 and Mec-3 (Way and Chalfie, 1988; Karlsson et al., 1990). In general, the LIM domains are 50–60 amino acids in size and share two characteristic zinc finger domains, which are separated by two amino acids. The two zinc fingers that constitute a LIM domain contain eight conserved residues, mostly cysteines and histidines, which co-ordinately bond to two zinc atoms. Although diversity is evident in the sequences of LIM domains, a slightly broad consensus sequence of LIM domains has been defined as $CX_2CX_{16-23}HX_2CX_2CX_2CX_{16-21}CX_2$(C/H/D) (where X denotes any amino acid) (Figure 1). Despite the fact that zinc fingers are typical DNA binding structures, there is little evidence supporting the observation that LIM domains can bind DNA directly, even in LIM domain transcription factors. Indeed, LIM domains usually exert negative effects on the DNA binding of LHX (LIM homoeodomain) proteins (Sanchez-Garcia, et al., 1993; Bridwell et al., 2001; Yaden et al., 2005).

LIM domains can be found internally as well as near the N- or C-terminals of LIM domain proteins.

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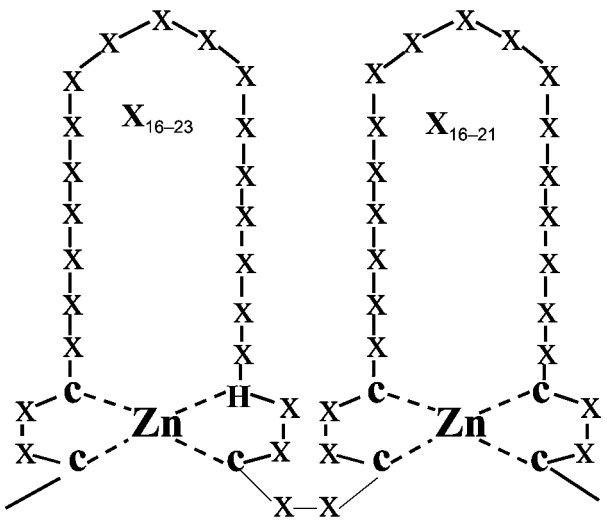
Key words: cell fate determination, cytoskeleton organization, gene regulation, LIM domain, protein–protein interaction.
Abbreviations used: ABLIM, actin-binding LIM protein; ACT, activator of CREM in testis; ALP, actinin-associated LIM protein; AR, androgen receptor; ATD, actin-target domain; bHLH, basic helix-loop-helix; Bmp, bone morphogenetic protein; BRCA1, breast-cancer susceptibility gene 1; BRCT domain, BRCA1 C-terminal domain; CH-ILKBP, calponin-homology-domain-containing integrin-linked-kinase-binding protein; ChIP, chromatin immunoprecipitation; CLIM, LIM homeobox protein cofactor; CLP-36, C-terminal LIM domain protein; CREB, cAMP-response-element-binding protein; CRP, cysteine-rich protein; CtBP2, C-terminal-binding protein; CtIP, CtBP-interacting protein; E4F1, E4 transcription factor 1; ECM, extracellular matrix; EKLF, erythroid Krüppel-like factor; EPLIN, epithelial protein lost in neoplasm; ERα, oestrogen receptor α; FHL, four and one-half LIM-domain protein; GATA1, GATA binding protein 1; GR, glucocorticoid receptor; HDAC, histone deacetylase; Hic-5, hydrogen peroxide-inducible clone-5; HNF4α, hepatic nuclear factor 4α; IGFBP-5, insulin-growth-factor-binding protein-5; ILK, integrin-linked kinase; LASP-1, LIM and SH3 protein 1; LD, leucine/aspartate repeat; LDB, LIM-domain-binding protein; LHX, LIM-homoeodomain protein; LID, LIM-interaction domain; LIMK, LIM kinase; LMO, LIM-domain-only; LPP, Lipoma preferred partner; mesDA, mesencephalic dopamine; MEF2, myocyte enhancer factor 2; MTA1, metastasis tumour antigen 1; NES, nuclear export signal; NF-κB, nuclear factor-κB; NHLH2, nescient helix loop helix 2; Nkx, NK-homoeodomain factor; NRAP, Nebulin-related actin-binding protein; PDLIM, PDZ and LIM domain; PEA3, polyoma enhancing activator 3; PINCH, particularly interesting new cysteine- and histidine-rich protein; PPAR, peroxisome-proliferator-activated receptor; PTP, protein tyrosine phosphatase; RIL, reversion-induced LIM protein; Sfrp1a, secreted frizzled-related protein; Shh, sonic hedgehog; SRF, serum response factor; TAL1, T-cell acute leukaemia 1; TGFβ, transforming growth factor β; Trip6, thyroid receptor interacting protein 6; TSHβ, thyroid stimulating hormone β; ZNF185, Zinc finger protein 185.

Figure 1 | Topology of the LIM domain

The LIM domains are generally 50–60 amino acids in size and share two characteristic zinc fingers, which are separated by two amino acids. A broad consensus sequence of LIM domains, the highlighted letters represent conserved cysteine and histidine residues that constitute the two zinc fingers.



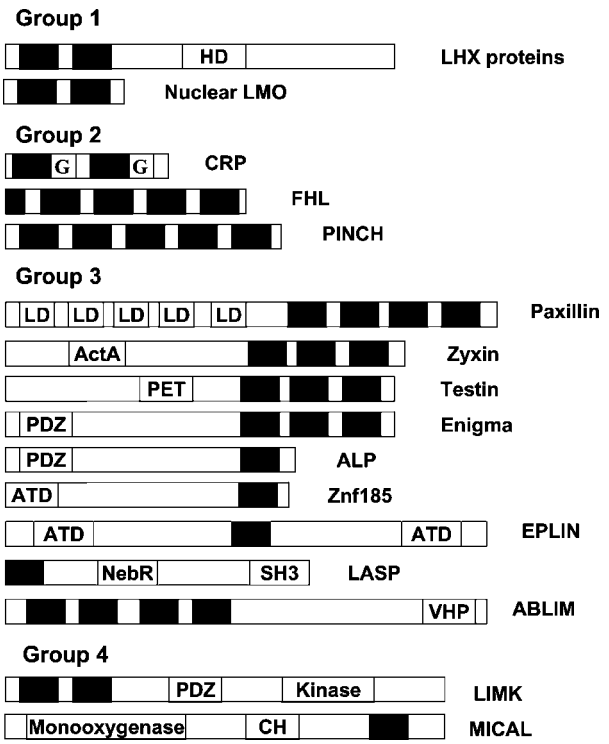
Some of them are constituted by LIM domains only, whereas others contain a variety of other functional domains, such as homeodomains, cytoskeleton-binding domains or catalytic domains. The modular nature and sequence diversity of LIM domain proteins suggests that there is functional complexity of LIM domain proteins. In the present manuscript, we will first briefly describe the classification of mammalian LIM domain proteins, and then focus on the various functions of nuclear and cytoplasmic LIM domain proteins in terms of protein–protein interactions.

Classification of LIM domain proteins

LIM domain proteins were first categorized into three groups based on the arrangement of their LIM domains and on the overall structure of the proteins. The first group includes N-terminal tandem LIM domain proteins and the third group includes C-terminal LIM domain proteins, whereas LIM domain proteins composed largely of LIM domains are classified into the second group (Dawid et al., 1998). With the increasing number and functional diversity of LIM domain proteins, they are further classified into four groups (Figure 2 and Table 1). The first group consists of

Figure 2 | Classification and the domain structures of LIM domain proteins

LIM domain proteins are roughly classified into four groups according to the arrangement and position of LIM domains. Individual LIM domains are shown as black quadrangles; other domains are shown as white quadrangles and indicated respectively on the Figure. ActA, ActA repeat region; CH, calponin homology; G, glycine rich region; HD: homeodomain; PET, prickle, espinas and testin; PEST, Pro-Glu-Ser-Thr sequence; NebR, Nebullin repeats; SH3, Src homology-3; VHP, villin head piece.



LHX proteins and nuclear LMO (LIM-domain-only) proteins, which feature two tandem N-terminal LIM domains. Proteins in this group are found in the nucleus and act as transcription factors or cofactors. The second group is made up of LMOs, which, like the nuclear LMO group, consist of two or more LIM domains clustered at their N- or C-termini; however, this group of LMOs can locate both in the nucleus and in the cytoplasm. The third and the fourth group contain various other protein–protein interaction motifs such as PDZ, LD (leucine–aspartate repeat) and ATD (actin-target domain) domains, besides the characterized LIM domain. In addition, the fourth group involves the mono-oxygenase or kinase catalytic motif,

Table 1 | Members of mammalian LIM domain proteins and their major biological functions
ACT, activator of CREM in testis; ENH, enigma homologue; MICAL, molecule interacting with CASL protein-1; OEBT, overexpressed breast tumour protein; RILP, Rab interacting lysosomal protein; WTIP, Wilms tumor 1 interacting protein.

Groups	Family	Members	Main functions
Group 1	LHX	ISL1, ISL2	Development of islet cells, pituitary cells, motor neurons, heart and limbs
		LHX2, LHX3, LHX4	Differention of various pituitary cell lineages
		LHX1, LHX5	Development of inter neurons, forebrain and urogenital systerm
		LHX6, LHX7, LHX8 LHX9 LMX1a, LMX1b	Development of head and formation of different neurons in the central nervous systerm
	Nuclear LMO	LMO1, LMO2	Involved in T-cell acute lymphoblastic leukaemia and erythropoiesis
		LMO3	Involved in neurogenesis and neuroblastoma
		LMO4	Involved in breast tumour development and pattern the thalamocortical connections
Group 2	CRP	CRP1, CRP2, CRP3	Cytoskeleton remodelling and smooth muscle differentiation
	FHL	FHL1, FHL2, FHL3, ACT	Components of adhesion complexes, transmitter of Rho signalling pathway and regulation of target genes.
	PINCH	PINCH1, PINCH2	Associated with cytoskeletal changes in response to signals from integrins and growth factor receptors. Possible nuclear function?
Group 3	Paxillin	HIC5, Leupaxin, Paxillin	Participate in the assembly of cell-ECM attachments, regulation of target genes.
	Zyxin	TRIP6, LPP, LIMD1, Ajuba, WTIP, Zyxin, Migfillin,	Participate in the assembly of cell-ECM attachments, regulation of target genes, linkers that connect cell–ECM adhesions to the actin cytoskeleton.
	Testin	Dyxin, LMO6, RILP, Testin, Prickl1, Prickl2, OEBT, Tes.	Act as linkers that connect cell–ECM adhesions to actin cytoskeleton and participate in tumour suppression
	Enigma	Enigma, ENH, Cypher, LMP4	Tropomyosin- or α-actinin-mediated actin bundling in muscle cells
	ALP	ALP, CLP-36, Mystique, RIL	α-Actinin-mediated actin bundling in both muscle and non-muscle cells
	LASP	LASP, LIM-nebulette, NRAP	Participate in the assembly of cell–ECM attachments, linkers that connect cell–ECM adhesions to the actin cytoskeleton, and cell proliferation
	EPLIN		Increases the number and size of actin stress fibres, inhibits membrane ruffling and cell transformation
	ABLIM		Binds to F-actin and plays a role in establishing or altering cell morphology
	LMO7		Connects the nectin–afadin and E-cadherin–catenin systems
	ZNF185		Interacts with F-actin and focal adhesion components
Group 4	LIMK	LIMK1, LIMK2	Cell cycle regulation and actin polymerization and depolymerization
	MICAL	MICAL, MICAL-like, MIRAB	Intermediate filament interactions

which distinguishes them from the third group. Although most of these proteins are identified in the cytoplasm, and mainly interact with cytoskeleton proteins, an increasing amount of evidence shows that they can translocate into the nucleus and facilitate transcription of target genes (Kadrmas and Beckerle, 2004). Through a variety of protein–protein interactions, the functions of LIM domain proteins in the nucleus are mainly in tissue-specific gene regulation and cell fate determination, whereas cytoplasmic LIM domain proteins are mainly involved in cytoskeleton organization.

Transcriptional regulation and cell fate determination through protein–protein interactions

LHX proteins regulate gene expression and determine cell fate

LHX proteins and nuclear LMO proteins are located in the nucleus, and they play an important role in tissue-specific gene expression and thus cell fate determination. Isl-1 is one of the LHX proteins isolated originally by virtue of its ability to bind DNA sequences from the 5′-flanking region of the rat insulin gene. Mice deficient in Isl-1 fail to form the

dorsal exocrine pancreas and islet cells fail to differentiate (Ahlgren et al., 1997). On the other hand, Isl-1 takes part in the pituitary development by activating the gonadotropin-releasing hormone receptor gene together with LHX3 and steroidogenic factor 1 (Granger et al., 2006).

LHX2, LHX3 and LHX4 are members of the LHX family of transcription factors, all of which are able to stimulate pituitary-specific expression of the mouse αGSU (glycoprotein hormone α subunit) by binding specifically to the 5′-flanking region of the gene (Roberson et al., 1994; Glenn and Maurer, 1999; Bridwell et al., 2001; Mullen et al., 2007). In addition, LHX3 and LHX4 have been shown to be involved in the differentiation of various pituitary cell lineages by transcriptional activation of many other pituitary genes such as FSH-β (follicle-stimulating hormone β), POU1F1 (pit, oct and unchomeodomain transcription factor) and TSHβ (thyroid stimulating hormone β) (West et al., 2004; Machinis and Amselem, 2005). LHX3- and LHX4-deficient mice display obvious defections of pituitary development, whereas LHX2$^{-/-}$ mice do not have apparent pituitary disorders (Wandzioch et al., 2004; Machinis and Amselem, 2005; Mullen et al., 2007), indicating that LHX3 and/or LHX4 have overlapping functions with LHX2 in pituitary development.

Besides their function in the endocrine system, LHX proteins have a prominent role in gene expression in the nervous system. Both LHX1 and LHX5 are required for maintenance of the expression of paired-domain transcription factors, such as Pax2, Pax5 and Pax8, in the development of dorsal inter neurons in the spinal cord (Pillai et al., 2007), whereas LHX1 and LHX5 contribute to forebrain development by activating the transcription of secreted Wnt antagonists, Sfrp1a (secreted frizzled-related protein 1a) and Sfrp5 (Peng and Westerfield, 2006).

The LHX proteins Limx1a and Limx1b have been shown to participate in the early development of mesDA (mesencephalic dopamine) neurons in the central nervous system by targeting different downstream genes. Lmx1a induces the expression of the Msx1 (Msh homeobox homologue 1) gene, which determines the generation of dopamine neurons with a correct midbrain identity (Failli et al., 2002; Andersson et al., 2006), whereas Lmx1b stimulates specific long pentraxin 3 expression in the mesDA neurons, and also induces tyrosine hydroxylase positive neurons to differentiate into mesDA neurons (Smidt et al., 2000).

The role of LHX proteins is not restricted to the development of the neuroendocrine system. LHX1, LHX6 and LHX7 have been reported to be essential in mouse head development (Grigoriou et al., 1998; Cheah et al., 2000), and LHX1 has also been involved in orchestrating the development of the mammalian urogenital system (Kobayashi et al., 2004). In heart and limb development, several genes have been identified as Isl-1 transcriptional targets, such as MEF2 (myocyte enhancer factor), Nkx2-5 (NK-homeodomain factor 2-5), Shh (sonic hedgehog) and Bmp4 (bone morphogenetic protein 4) and Bmp7 (Dodou et al., 2004; Lin et al., 2006; Yang et al., 2006). Isl-1 binds directly to the conserved enhancer elements of the *Mef2* gene and induces its expression. However, it is not very clear whether the regulation of Shh, Bmp4 and Bmp7 expression by Isl-1 is direct or indirect.

LIM-homoeodomain proteins direct cellular differentiation by transcriptional activation of cell-specific genes, but this activation requires co-operation with other nuclear factors, including LDB [LIM-domain-binding; also known as CLIM (LIM homeobox protein cofactor) or NLI (nuclear LIM domain interactor)] cofactors and transcription factors. LDB/CLIM/NLI cofactors bind the two tandem LIM domains of diverse LHX and nuclear LMO proteins through their C-terminal LID (LIM interaction domain). Moreover, a short amino-acid sequence (residues at positions 300–327) in the LID is enough to contact with the LIM domains. LIDs can bind a single LIM domain, but bind to two tandem LIM domains with much higher affinity (Jurata and Gill, 1997; Matthews and Visvader, 2003; Deane et al., 2004). Besides a LID, LDB cofactors also contain an N-terminal dimerization domain and several other binding domains. These domains enable the formation of tetrameric or higher order complexes with LHX and/or LMO proteins, and function together to determine cell fate (Deane et al., 2004).

In mouse head development, dimerization of LDB is necessary to bridge two LHX1 proteins to its C-terminal LID and two single-stranded DNA-binding proteins to its middle region. LHX1, LDB and single-stranded DNA-binding proteins form the transcription complex, which is important in the head-organizing activity during early mouse development.

Depletion of each individual protein alone causes a headless phenotype (van Meyel et al., 2003; Enkhmandakh et al., 2006). In the central nervous system, LDB/NL1 is involved in the identity of motor neurons and interneurons by binding to different LHX proteins: binding to LHX3 triggers interneuron differentiation, whereas binding to Isl-1 promotes motor neuron differentiation (Thaler et al., 2002).

Besides LDB cofactors, LHX proteins direct cellular differentiation through binding with tissue-specific transcription factors. Pit-1 is a pituitary POU domain factor, which interacts specifically with the LIM domain of P-Lim/LHX3 through its POU domain, and the interaction between Pit1 and P-LIM remarkably enhances the *TSH*β promoter activity (Bach et al., 1995; Bach, 2000). T-box transcription factor Tbx20 is expressed most notably in the heart, and plays an important role in the development of specific cardiac structures. Tbx20 can interact with Isl-1, which is crucial for anterior heart field formation by activating the enhancers of both *Mef2* and *Nkx2-5* gene (Ahn et al., 2000; Cai et al., 2003).

More recently, it has been reported that Isl-1 and the orphan nuclear receptor HNF4α (hepatic nuclear factor 4α) are co-expressed in pancreatic β-cells, and are required for the differentiation and function of these endocrine cells (Eeckhoute et al., 2006). Moreover, HNF4α interacted directly with Isl-1 through its ligand-binding domain and its C-terminal F domain. The interaction between HNF4α and Isl-1 activates several genes associated with islet development, such as the HNF1α, PPARα (peroxisome-proliferator-activated receptor α) and insulin. In addition, bHLH (basic helix-loop-helix) transcription factors, such as Olig2 and Neurogenin2, have also been implicated to collaborate with LHX proteins to generate motor neurons in the ventral neural tube. However, there is a lack of direct evidences for protein–protein interaction between these proteins at present (Mizuguchi et al., 2001; Allan and Thor, 2003).

Nuclear LMO proteins regulate gene expression and are frequently involved in tumour formation

Nuclear LMO proteins including LMO1, LMO2, LMO3 and LMO4 consist of two LIM domains and few, if any, other motifs (Sanchez-Garcia and Rabbitts, 1994). As shown for LHX proteins, the LMO proteins occupy important roles in transcriptional regulation and development. Additionally, this class of LIM proteins has also been shown to be involved in oncogenesis. Accumulating evidence shows that LMO1 and LMO2 act as oncogenic proteins, and that they are activated by distinct chromosomal translocations in T-cell acute lymphoblastic leukaemia (Rabbitts, 1998; Chervinsky et al., 1999; Ferrando et al., 2004). However, LMO2 is actually involved in erythropoiesis, an observation that was first demonstrated using a gene deletion approach. Lmo2 knockout mice die during embryogenesis due to a failure to develop mature erythrocytes. Subsequently, it was shown that LMO2 is required for the haematopoiesis in the adult animals as well (Warren et al., 1994; Yamada et al., 1998).

As LIM domains lack intrinsic DNA-binding activity, nuclear LMOs have been considered to be involved in transcriptional regulation by forming complexes with other transcription factors. For example, a bHLH transcription factor, TAL1 (T-cell acute leukaemia 1)/SCL (stem cell leukaemia), is physically associated with LMO1 or LMO2 with its bHLH domain. Enforced expression of LMO1 or LMO2 inhibits the expression of TAL1/SCL target genes in the primitive thymocytes, and finally causes the deregulation of the transition checkpoint from the $CD4^{-}CD8^{-}$ to $CD4^{+}CD8^{+}$ stages (Herblot et al., 2000). On the other hand, LMO3 has been demonstrated to interact with a neuronal specific bHLH transcription factor, NHLH2 (nescient helix loop helix 2), to regulate neurogenesis. However, the increased expression of LMO3 and NHLH2 was significantly associated with poor prognosis in primary neuroblastoma (Aoyama et al., 2005).

Studies of nuclear LMO proteins have been focused on LMO4 because of its various functions in tumorigenesis and cellular differentiation. In breast tissue, multiple proteins, including the cofactor CtIP [CtBP (C-terminal binding protein)-interacting protein], the breast and ovarian tumour suppressor BRCA1 (breast-cancer susceptibility gene 1) and the LIM-domain-binding protein LDB1, have been identified to interact with LMO4. The interaction of CtIP with LMO4 appears to be mediated by two regions within the CtIP: a small domain at the N-terminus and a C-terminal region, whereas the interaction of BRCA1 with LMO4 is medicated by the two tandem

C-terminal BRCT domains (BRCA1 C-terminal domains) of BRCA1. In functional assays, LMO4 is shown to repress BRCA1-mediated transcription activation, thus invoking a potential role for LMO4 as a negative regulator of BRCA1 in sporadic breast cancer (Sum et al., 2002). Further studies have shown that LMO4 also exhibits binding to both ERα (oestrogen receptor α) and MTA1 (metastasis tumour antigen 1), and exists as a complex with ERα, MTA1, and HDACs (histone deacetylases), implying that LMO4 is also a component of the MTA1 corepressor complex. Consistent with this notion, LMO4 overexpression represses ERα transactivation functions in an HDAC-dependent manner, and contributes to the process of breast cancer progression by allowing the development of ERα-negative phenotypes (Singh et al., 2005).

More recent studies have demonstrated that LMO4 can interact with Smad proteins, and associate with the promoter of the *PAI-1* (plasminogen activator inhibitor-1) gene in a TGFβ (transforming growth factor β)-dependent manner, suggesting that such interactions may mediate the effects of LMO4 on TGFβ signalling (Lu et al., 2006). Furthermore, co-immunoprecipitation experiments indicate that LMO4 can also form a complex with CREB (cAMP response element-binding protein) and interact with CLIM1 and CLIM2 to pattern the thalamocortical connections during mouse development (Kashani et al., 2006). Collectively, nuclear LMO proteins regulate gene expression by interacting with multiple transcription factors and cofactors to form large transcription complexes. However, a specific protein motif that binds to the LIM domain remains elusive.

Cytoplasmic LIM domain proteins shuttle into the nucleus and regulate gene expression

Recent studies of LIM domain proteins reveal that many previously identified cytoplasmic LIM domain proteins are able to localize in the nucleus, which indicates that they can shuttle between cytoplasm and nucleus to regulate gene expression. FHL2 (four and one-half LIM domain protein 2) and FHL3 are components of adhesion complexes that bind to the cytoplasmic domain of several α- and β-integrin chains (Li et al., 2001; Samson et al., 2004). Nevertheless several extracellular stimulations and some physiological contexts induce translocation of FHL2 and FHL3 into the nucleus, which results in the subsequent transcription regulation of target genes. For example, when NIH 3T3 cells were stimulated with bioactive lipids, namely LPA (lysophosphatidic acid) or SPP (sphingosine-1-phosphate), which are activators of the Rho signalling pathway, FHL2 is observed to translocate into the nucleus resulting in the subsequent activation of FHL2- and AR (androgen receptor)-dependent genes (Muller et al., 2002). Therefore FHL2 acts as a molecular transmitter of the Rho signalling pathway, by integrating extracellular cues into altered gene expression. Stimulation of NIH 3T3 cells with 20% serum or UV light can also induce a significant translocation of FHL2 into the nucleus. Moreover, nuclear accumulation of FHL2 is co-ordinated with increased expression of the oncoproteins Fos and Jun, and powerfully stimulates Fos- and Jun-dependent transcription (Morlon and Sassone-Corsi, 2003). In addition, upon UV light stimulation, FHL2 interacts directly with the E1A-targeted transcription factor E4F1 (E4 transcription factor 1) in the nucleus. The E4F1–FHL2 complex inhibits the repressive effects of E4F1 on transcription, and thereby stimulates cell proliferation (Paul et al., 2006).

Under physiological conditions, FHL2, CBP (CREB-binding protein)/p300 and β-catenin form a ternary complex and synergistically enhance β-catenin-mediated transcription. In murine *Fhl2*$^{-/-}$ embryo fibroblasts, the transactivation activity of β-catenin is markedly reduced, and this defect can be restored by exogenous expression of Fhl2 (Labalette et al., 2004). In another experiment, Yan et al. (2003) observed that FHL2 and BRCA1 can physically interact both in yeast and in human cells. Moreover, this interaction is mediated through the second BRCT domain of BRCA1 and the last three LIM domains of FHL2. BRCA1 enhances FHL2-mediated transcription activation in transient transfections, whereas a lack of BRCA1 binding sites in FHL2 completely abolishes its transactivation function.

More importantly, FHL2 is involved in the proliferation and differentiation of osteoblast cells by two opposite regulation pathways: FHL2 interacts with TRAF6 [TNF (tumour necrosis factor) receptor-associated factor 6] and subsequently inhibits TRAF6-induced NF-κB (nuclear factor-κB) transcriptional activity. On the other hand, IGFBP-5 (insulin-growth-factor-binding protein-5), an important bone formation regulator can interact with

FHL2, and stimulates transcription of putative IGFBP-5 target genes (Amaar et al., 2002; Bai et al., 2005). Fhl2-deficient mice exhibit a dramatic decrease of bone mass in both genders. The osteopenia is caused by a reduced bone formation rate that is solely due to the diminished activity of Fhl2 (Gunther et al., 2005; Lai et al., 2006).

Like FHL2, FHL3 has been shown to behave both as a transcription co-activator and as a co-repressor. In Cos cells, FHL3 interacts specifically with CREB and enhances the transcription of reporter genes driven by the c-*fos* and cyclin A promoters (Fimia et al., 2000). Although in a human mast cell line HMC-1 cultured with GM-CSF (granulocyte/macrophage colony-stimulating factor), FHL3, NFY (nuclear factor Y) and MZF1 (myeloid zinc finger protein) constitute a ternary complex in the nucleus. This complex is recruited to the β-chain gene of the high-affinity receptor for IgE, and represses its transcription in an HDAC-dependent manner (Takahashi et al., 2005; 2006). Furthermore, FHL3 recruits EKLF (erythroid Krüppel-like factor)/KLF and the co-repressor CtBP2 through distinct amino acid regions. Co-expression of EKLF and CtBP2 leads to the nuclear enrichment of FHL3, and they co-operatively repress GATA1 (GATA-binding protein 1)-mediated transcription activation (Turner et al., 2003). On the other hand, FHL3 strongly activates a GAL (galactosidase)-driven luciferase reporter in response to Rho-GTPase activation. As Rho activation regulates actin cytoskeleton dynamics, the localization of FHL3 to the nucleus and focal adhesions is consistent with a role for FHL3 in transcription downstream of Rho signalling (Chrzanowska-Wodnicka and Burridge, 1996; Muller et al., 2002).

In addition, other LIM-only proteins such as CRPs (cysteine-rich proteins) and PINCH (particularly interesting new cysteine- and histidine-rich proteins) exhibit dual subcellular localizations and transcriptional regulation functions. CRP1 and CRP2 are characterized by the presence of two LIM domains linked to short glycine-rich repeats. In the cytoplasm, these proteins interact with zyxin and α-actinin and participate in cytoskeleton remodelling (Weiskirchen and Gunther, 2003). In the nucleus, CRP1 and CRP2 act as bridging molecules that associate with SRF (serum response factor) and GATA proteins. SRF–CRP–GATA complexes strongly activate smooth muscle gene targets and facilitate smooth muscle differentiation. A dominant-negative CRP2 mutant blocked pro-epicardial cells from differentiating into smooth muscle cells (Chang et al., 2003). However, it still remains to be determined which types of physiological processes regulate the nucleus–cytoplasm shuttling of CRP proteins.

PINCH, including PINCH1 and PINCH2, is an adaptor protein found in focal adhesions. However, sequence analyses reveal that PINCH contains a putative leucine-rich NES (nuclear export signal) and a basic nuclear localization signal. Furthermore, endogenous PINCH has been characterized as a shuttling protein (Campana et al., 2003). Recently, Mori et al. (2006) found that PINCH1 is capable of hetero-oligomerization with Hic-5 (hydrogen peroxide-inducible clone-5), another focal adhesion LIM protein. The complex directs shuttling of PINCH1 between the cytoplasmic and nuclear compartments in the presence of ILK (integrin-linked kinase). Disrupting the interaction between PINCH1 and Hic-5 inhibits nuclear targeting of PINCH1 and impairs cellular growth. However, PINCH1 target genes have not been identified. PINCH1-deficient mice die at the peri-implantation stage, whereas PINCH2-null mice are viable, and show no overt abnormal phenotype. Histological analysis of tissues that express high levels of PINCH2 show a significant up-regulation of PINCH1 in PINCH2-null mice (Li et al., 2005; Stanchi et al., 2005), suggesting that PINCH1 has overlapping functions with PINCH2 and also has its own particular functions that cannot be compensated for by PINCH2 *in vivo*.

Besides LMO proteins, the majority of paxillin and zyxin focal adhesion LIM-domain proteins have been reported to shuttle into the nucleus and regulate gene expression (Wang and Gilmore, 2003). Among them, Hic-5, TRIP6 (thyroid receptor interacting protein 6) and LPP (lipoma preferred partner) have been extensively studied in recent years. Hic-5 belongs to the paxillin family which is featured by four or five N-terminal LD (leucine–aspartate repeat) motifs and four C-terminal LIM domains. Both LD motifs and LIM domains can serve as protein–protein interaction interfaces. Using the yeast two-hybrid system, Hic-5 has been identified as co-activator of various nuclear receptors such as AR, GR (glucocorticoid receptor) and PPARγ (Guerrero-Santoro et al., 2004; Drori et al., 2005; Heitzer and DeFranco, 2006). Further studies using ChIP (chromatin

immunoprecipitation) assays show that Hic-5 and other nuclear co-activators recruit to the promoter of AR or GR responsive genes in hormone-treated cells. Ablation of Hic-5 expression results in reduction of both the co-activators recruitment and the transactivation of nuclear receptors (Guerrero-Santoro et al., 2004; Heitzer and DeFranco, 2006). In addition, Hic-5 interacts with transcription factors such as SP-1 and Smad3, up-regulating or inhibiting their transcriptional activation respectively (Shibanuma et al., 2004; Wang et al., 2005). Recent studies have shown that oxidants, such as H_2O_2, may be the main cause for the nuclear accumulation of Hic-5. Shuttling mechanisms that control the movement of Hic-5 between the cytoplasm and nucleus have been explained (Shibanuma et al., 2003; 2005).

TRIP6 and LPP belong to the zyxin protein family. Proteins in this group contain a divergent N-terminal domain rich in proline residues and a C-terminal region with three LIM domains (Wang and Gilmore, 2003). Although TRIP6 localizes primarily to focal adhesion plaques, it has a conserved NES, nuclear targeting sequences and multiple transactivation domains, suggesting that TRIP6 has a potential function in transcriptional regulation. Consistent with this finding, TRIP6 has been found to interact with transcription factors, such as AP-1 and NF-κB, through different C-terminal LIM domains. Moreover, ChIP analyses show that TRIP6 is recruited to the promoters of target genes together with AP-1 or NF-κB and activates their expression (Kassel et al., 2004; Solaz-Fuster et al., 2006). However, in the presence of glucocorticoids, GR joins the TRIP6 complex and mediates transrepression of the transcription factors AP-1 and NF-κB. Reducing the level of TRIP6 by RNA interference or abolishing its interaction with GR by dominant-negative mutation eliminates this transrepression (Kassel et al., 2004). Therefore TRIP6 exerts its nuclear functions by acting as a molecular platform, enabling target promoters to integrate activating or repressing signals. Similarly, LPP possess a Crm1-dependent NES and has been shown to interact directly with the ETS-domain transcription factor PEA3 (polyoma enhancing activator 3). Overexpression of LPP enhances the expression of the PEA3 target gene, matrix metalloproteinase-1, whereas LPP elimination by RNA interference reduces its transcription activity (Petit et al., 2005; Guo et al., 2006). As the expression of matrix metalloproteinase-1 contributes to the metastatic spreading of tumour cells by degrading the ECM (extracellular matrix), LPP may represent a potential candidate gene for the pathogenesis and diagnosis of cancers.

LIMK1 (LIM-kinase 1) and LIMK2 are serine/threonine kinases that were first identified by their ability to phosphorylate the actin disassembly factor cofilin. Via Rho\ROCK (Rho-associated kinase)\LIMK\cofilin or Rac\Cdc42\Pak1 (p21/Cdc42/Rac1-activated kinase 1)\LIMK\cofilin signal pathway, LIMKs play an important role in regulating actin cytoskeleton organization in response to various extracellular stimuli (Edwards et al., 1999; Maekawa et al., 1999). On the other hand, various studies show that LIMKs may have a function in the nucleus (Amano et al., 2002; Sumi et al., 2002). Both LIMK1 and LIMK2 can act in the nucleus to suppress Rac/Cdc42-dependent cyclin D1 expression. Surprisingly, inhibition of cyclin D1 expression by LIMKs is independent of both cofilin phosphorylation and actin polymerization (Roovers et al., 2006). Moreover, LIMK1 up-regulates the promoter activity of urokinase type plasminogen activator and induces its mRNA and protein expression in breast cancer cells (Bagheri-Yarmand et al., 2006). Further studies show that nucleus–cytoplasm shuttling of LIMK2 is controlled by a unique basic-amino-acid-rich motif (residues 491–503) in LIMK2 that is not present in LIMK1. Phosphorylation of Thr^{494} within this motif reduces the nuclear import of LIMK2, and phosphorylation of both Ser^{283} and Thr^{494} inhibits the nuclear import of LIMK2 completely (Goyal et al., 2006). LIMK1 knockout mice exhibit cofilin and actin cytoskeleton associated dysfunctions, such as abnormalities in spine morphology and brain function. The phenotype of Limk2 knockout mice shows a defect in spermatogenesis (Meng et al., 2002; Takahashi et al., 2002). However, the relationships between the phenotype defects and the nuclear functions of Limk2 require further investigation.

Cytoskeleton organization through protein–protein interactions

In the cytoplasm, LIM-domain proteins are distributed extensively in cytoskeleton-associated structures, such as actin filaments, focal adhesions, growth cones, intercalated discs and Z-lines of muscle cells.

Through interaction with the cytoskeleton or ECM adhesion components, cytoplastic LIM-domain proteins are involved in many cellular physiological activities, such as cell shape modulation, cell motility and integrin-dependent adhesion and signalling.

Interaction with F-actin and actin-based cytoskeletons

The majority of the cytoplasmic LIM-domain proteins identified have been found to interact with F-actin and actin-based cytoskeletons alone or with other binding partners. ABLIM (actin-binding LIM protein), which can mediate such interactions between actin filaments and cytoplasmic targets, consists of a C-terminal cytoskeletal domain and four N-terminal LIM motifs. The cytoskeletal domain is approx. 50% identical to erythrocyte dematin, an actin-bundling protein of the red cell membrane skeleton. Both *in vivo* and *in vitro* studies demonstrate that ABLIM can bind to F-actin through the dematin-like domain and play a role in establishing or altering cell morphology (Roof et al., 1997; Barrientos et al., 2007).

Apart from ABLIM, EPLIN (epithelial protein lost in neoplasm) is another cytoskeleton-associated protein; it has at least two actin-binding sites that flank a centrally located LIM domain. EPLIN is co-localized with the actin cytoskeleton, and functions in increasing the number and size of actin stress fibres, and inhibits membrane ruffling induced by Rac (Maul and Chang, 1999; Maul et al., 2001; 2003). The function of EPLIN *in vivo* is not known. However, in many cancer-derived or transformed cell lines, the expression of EPLIN is significantly down-regulated, In addition, enforced EPLIN expression inhibits anchorage-independent growth of transformed NIH 3T3 cells, suggesting that the loss of EPLIN may contribute to the transformed phenotype (Song et al., 2002).

In addition, PDLIM (PDZ and LIM domain) proteins have been shown to directly regulate actin polymerization and depolymerization reactions. For example, ALP (actinin-associated LIM protein) contains a C-terminal LIM domain and an N-terminal PDZ domain through which ALP interacts with the spectrin-like motifs of α-actinin-2 (Xia et al., 1997; Pomies et al., 1999). The interaction of ALP and α-actinin-2 occurs at sites of actin anchorage, such as the intercalated discs of cardiac muscle cells to enhance the ability of α-actinin-2 to bundle actin filaments. Mice that lack ALP lead to right ventricular dysplasia and a mild right ventricular cardiomyopathy (Pashmforoush et al., 2001; Lorenzen-Schmidt et al., 2005).

Interaction of PDLIM proteins with the actin cytoskeleton has also been shown in non-muscle cells. By contrast, CLP-36 (C-terminal LIM domain protein 36) is predominantly expressed in activated human platelets, endothelial cells and epithelial cells, where it localizes with actin stress fibres. Moreover, MS analysis indicates that both non-muscle α-actinin-1 and α-actinin-4 form complexes with CLP-36 (Bauer et al., 2000; Vallenius et al., 2000). Similarly, RIL (reversion-induced LIM protein) is mostly expressed in epithelial cells and is found to localize with actin stress fibres. RIL interacts with α-actinin via its PDZ domain. However, RIL overexpression leads to abnormal actin filaments showing thick irregular stress fibres not seen with CLP-3, indicating the association of RIL with α-actinin enhances the ability of α-actinin to co-sediment with actin filament (Vallenius et al., 2004).

Interaction with cell–ECM adhesion components and signal transduction

Cell–ECM adhesion is crucial for the control of cell behaviour. It connects the ECM to the intracellular cytoskeleton and transduces bidirectional signals between the extracellular and intracellular compartments. The subcellular machinery that mediates cell–ECM adhesion and signalling is complex. Several cytoplasmic LIM-domain proteins have been demonstrated to be assembled into signalling networks by interaction with membrane proximal proteins. ILK is a focal adhesion serine/threonine protein kinase which has emerged as a key signalling protein functioning at one of the early convergence points of integrin- and growth-factor-signalling pathways. ILK binds to PINCH through its N-terminal ankyrin repeat domain, and binding to PINCH is crucial for the focal adhesion localization of ILK (Wu and Dedhar, 2001).

Soon after, Tu et al. (2001) found that CH-ILKBP (calponin-homology-domain-containing ILK-binding protein) links PINCH as well. ILK, PINCH and CH-ILKBP form a ternary complex, which localizes to focal adhesions and associates with the cytoskeleton. Further analyses of binding-defective point

mutants revealed that the assembly of the PINCH–ILK–CH-ILKBP complex is essential for their localization to cell–ECM adhesion sites, and the formation of the PINCH–ILK–CH-ILKBP complex precedes integrin-mediated cell adhesion and cell spreading. Furthermore, inhibition of protein kinase C, but not that of actin polymerization, inhibited the PINCH–ILK–CH-ILKBP complex formation, suggesting that the PINCH–ILK–CH-ILKBP complex probably serves as a downstream effector of protein kinase C in the cellular control of focal adhesion assembly (Zhang et al., 2002).

Besides PINCH, paxillin and zyxin are well-defined LIM-domain proteins that participate in the assembly of cell–ECM attachments. Through its LD motifs, paxillin binds to actopaxin, ILK, FAK (focal adhesion kinase), PKL (paxillin kinase linker) and vinculin. Although the LIM domains of paxillin mediate interactions with tubulin and the PTP (protein tyrosine phosphatase), PTP-PEST (PTP-Pro-Glu-Ser-Thr sequence), which is involved in the regulation of cell spreading and migration (Schaller, 2001). Utilizing *PTP-PEST*$^{-/-}$ and *paxillin*$^{-/-}$ fibroblasts, Jamieson et al. (2005) observed that paxillin is essential for PTP-PEST mediated inhibition of cell spreading and membrane protrusion as well as inhibition of adhesion-induced Rac activation. Furthermore, paxillin binding is necessary for PTP-PEST stimulation of cell migration (Brown and Turner, 2002).

Zyxin co-localizes with integrins at sites of cell-substratum adhesion and is postulated to serve as a docking site for the assembly of multimeric protein complexes involved in regulating cell motility. LASP-1 (LIM and SH3 protein 1) is one of the zyxin interacting proteins, and the interaction of zyxin with LASP-1 is necessary and sufficient to recruit zyxin to focal contacts. In addition, another focal adhesion protein, WASP (vasodilator-stimulated phosphoprotein), binds to the ActA repeat region of zyxin, linking zyxin to cadherin-mediated cell–cell adhesions (Grunewald et al., 2007). Furthermore, the zyxin /Ajuba/TRIP6 family of LIM proteins associates with the focal adhesion-targeting domain of p130^{Cas}, and localizes p130^{Cas} to nascent adhesion sites in migrating cells, thereby leading to the activation of Rac pathway (Yi et al., 2002; Pratt et al., 2005). On the other hand, like other zyxin/paxillin family members mentioned above, paxillin and zyxin have been found to shuttle between the nucleus and the cytoplasm (Wang and Gilmore, 2003; Moon et al., 2006). However, their target genes and nuclear functions have not been reported.

In addition to participation in the organization of focal adhesions, members of the LIM-domain protein family acts as linkers that connect cell–ECM adhesions to the actin cytoskeleton. For instance, Migfilin is a recently identified component of cell–ECM adhesions, it contains three C-terminal LIM domains, through which it binds to Mig-2 [also known as RFTN1 (raftlin, lipid raft linker 1)], an integrin effector that is required for cell spreading. Although the N-terminus of migfilin binds the actin-crosslinking protein filamin. Mig-2 recruits migfilin to cell–ECM adhesions, and the interaction with filamin mediates the association of migfilin with actin filaments. SiRNA (small interfering RNA)-mediated depletion of migfilin compromises the organization of adherens junctions and impairs cell shape modulation (Tu et al., 2003; Gkretsi et al., 2005). NRAP (nebulin-related actin-binding protein) is a LASP family LIM-domain protein that is concentrated in the myotendinous junctions in skeletal muscle and in intercalated discs in cardiac muscle. The single N-terminal LIM-domain of NRAP binds talin, a focal-adhesion protein that regulates integrin activation, whereas the C-terminal nebulin super-repeats bind to actin. Therefore NRAP functions as a protein that anchors the terminal actin filaments of myofibrils to the sarcolemma to transmit tension (Luo et al., 1999).

Recently, Zhang et al. (2007), cloned the complete *ZNF185* (Zinc finger protein 185) cDNA from normal human prostate tissue. Analysis of the putative translated sequence confirmed that ZNF185 contains two zinc-finger motifs in the C-terminus that fit the consensus pattern of a LIM domain. Expression and localization of ZNF185 in PCa cells and fibroblasts have shown that, in addition to F-actin stress fibres, ZNF185 localizes to several other cytoskeleton-related areas, including focal adhesions and filopodia/lamellipodias. Moreover, their data suggested it is the N-terminal ATD and not the LIM domain that is necessary for the targeting of ZNF185 to the actin cytoskeleton. Further studies to identify proteins interacting with other domains of ZNF185 will help to clarify the mechanism of its diverse subcellular localization and function.

Conclusion

The LIM domain has been well established as a protein–protein interaction motif. Moreover, other domains such as PDZ, LD and actin-binding domains in LIM-domain proteins interact with partner proteins effectively, so LIM domain proteins act as the core of multiple protein complexes and function in various cellular processes. Nuclear LIM-domain proteins mainly exert tissue-specific gene regulation and cell fate determination functions through interaction with other transcription factors or cofactors, whereas LIM-domain proteins in the cytoplasm take part in cytoskeletal organization and signal transduction through interaction with cytoskeleton and cell–ECM proteins. However, recent studies have revealed that a large member of LIM domain proteins associated with focal adhesion or related structures shuttle between the cytoplasm and the nucleus. Despite the fact that the mechanism of shuttling for some LIM-domain proteins has been explained, they are largely unknown, especially under the physiological conditions. Moreover, the nuclear function of these shuttling LIM-domain proteins and the relationship between nuclear function and extracellular stimulations still need further study.

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