Recent studies have demonstrated that a number of E3 ubiquitin ligases, including Cbl, Smurf1, Smurf2, HDM2, BCA2, SCFβTrCP and XRN1F185, play important roles in cell adhesion and migration. Cbl negatively regulates cell adhesion via α integrin and Rap1 and inhibits actin polymerization by ubiquitinating mDab1 and WAVE2. Smurf1 regulates cell migration through ubiquitination of RhoA, talin head domain and hFEM2, while Smurf2 ubiquitinates Smurf1, TGFβ type I receptor and Rap1B to modulate cell migration and adhesion. HDM2 negatively regulates cell migration by targeting NFAT (a transcription factor) for ubiquitination and degradation, while SCFβTrCP ubiquitinates Snail (a transcriptional repressor of E-cadherin) to inhibit cell migration. TRIM32 promotes cell migration through ubiquitination of Abl interactor 2 (Abi2), a tumor suppressor. RNF5 and XRN1F185 modulate cell migration by ubiquitinating paxillin. Thus, these E3 ubiquitin ligases regulate cell adhesion and (or) migration through ubiquitination of their specific substrates.

Ubiquitin is an evolutionarily conserved protein that consists of 76 amino acid residues and ubiquitination is a post-translational modification process that covalently conjugates single or multiple ubiquitins to target proteins.1,2 Most ubiquitination processes can be divided into three categories based on the length and linkage of ubiquitin chains: K48-linked and K63-linked poly-ubiquitination and mono-ubiquitination.4,5 K48-linked poly-ubiquitination, where ubiquitin is conjugated to another ubiquitin on its lysine 48 residue, is degraded by the 26S proteasome.4,6 K63-linked poly-ubiquitination fulfills a variety of signaling functions including protein kinase activation and DNA repair.5 Mono-ubiquitination usually marks membrane proteins for endocytosis and subsequent degradation in lysosomes.5

Protein ubiquitination consists of three sequential steps: activation of ubiquitin by a ubiquitin-activating enzyme (E1), transfer of ubiquitin from E1 to a ubiquitin-conjugating enzyme (E2), and conjugation of ubiquitin to target proteins by a ubiquitin ligase (E3).1,2 E3 ubiquitin ligases contain motifs for substrate recognition, are primarily responsible for recognizing specific substrate proteins, and are the key control points for protein ubiquitination.7-9 So far, approximately 500 E3 ubiquitin ligase genes have been identified in humans. The majority of these ubiquitin ligases can be divided into two categories based on specific structural motifs: (1) those possessing the HECT (homologous to the E6-AP carboxyl terminus) domain; (2) those containing the RING (really interesting new gene)-finger domain.10,11

The roles of E3 ubiquitin ligases in regulating cell proliferation, apoptosis, cancer invasion and neurodegenerative diseases have been extensively investigated and reviewed.12-16 However, their roles in cell adhesion and migration, processes that play pivotal roles in wound healing, embryonic development, cancer invasion and inflammation, are only beginning to be recognized. Indeed, more and more evidence indicates that E3 ubiquitin ligases participate in the regulation of cell adhesion and migration. Here, I summarize the roles of E3 ubiquitin ligases in cell matrix-adhesion and migration, emphasizing their mechanisms of action and highlighting future directions.

Cbl

The Cbl (Casitas B-lineage Lymphoma) family of ubiquitin ligases in mammals contains three members: c-Cbl, Cbl-b, and Cbl-c, encoded by three homologous genes (Fig. 1).17-19 C-Cbl encodes a 120 kDa cytoplasmic protein, featuring a tyrosine kinase binding (TKB) domain in the amino terminal portion, a C3HC4 Zinc-binding RING finger domain, a proline-rich region and a leucine zipper domain in the carboxyl terminal portion.20,21 The C3HC4 Zinc-binding RING finger domain mediates the E3 ubiquitin ligase activity, while all other domains function as protein-binding modules. Cbl-b and c-Cbl have similar domain structures, but their sequences between the proline-rich regions and leucine zipper domains show no significant homology.18 Cbl-c retains the TKB domain, the C3HC4 RING finger domain and very short proline-rich region, but lacks the other carboxyl terminal portion.19

Both c-Cbl and Cbl-b are ubiquitously expressed in mammalian cells. They localize in the cytoplasm and are recruited to the plasma membrane under certain circumstances.22 Cbl-b also associates with the lipid raft.23 C-Cbl is present in the thymus, spleen, testis, lung, heart and brain, as well as T- and B-cells, but is highly expressed in the thymus and testis.24 Cbl-b is ubiquitously expressed in diversified tissues, including the spleen, testis, ovary, placenta, heart, thymus, prostate, kidney, brain, lung, liver, skeletal muscle and pancreas, but the spleen has the highest...
C-Cbl interacts with a great number of proteins. This topic was extensively reviewed recently. Briefly, c-Cbl interacts with c-Met, EGFR, PDGFR, Src, Syk through its TKB domain, and binds CrkL, Fyn, Grb2, Lyn, PI3K, PLC\textsubscript{γ}, Src, Syk via its proline-rich region (Fig. 1). The phosphotyrosine residues at the C-terminal portion are associated with Abl, CrkII, CrkL, Fyn, PI3-kinase, Src and Syk, whereas Cbl-b is phosphorylated at Tyr\textsuperscript{655} and Tyr\textsuperscript{709}. Currently identified major binding partners for each domain (or region) are also listed.

Cbl can function as a signaling adaptor by forming complexes via its various domains. In fact, many signaling processes regulated by Cbl are mediated through its signaling adaptor function. For example, the Tyr\textsuperscript{731} of c-Cbl provides a docking site for the level of expression. Cbl-c is expressed primarily in the epithelial cells of the small intestine, colon, prostate, adrenal gland, and salivary gland, but not in many tissues that express c-Cbl and Cbl-b, such as the spleen and thymus.

C-Cbl undergoes tyrosine phosphorylation upon growth factor and cytokine stimulation as well as T-cell receptor (TCR) ligation. C-Cbl is a substrate for several protein tyrosine kinases, including Src, Syk, Yes, Fyn and Abl. In vitro, Fyn predominantly phosphorylates Tyr\textsuperscript{731} and Abl phosphorylates Tyr\textsuperscript{700}, whereas Syk phosphorylates Tyr\textsuperscript{700}, Tyr\textsuperscript{731} and Tyr\textsuperscript{774}. In v-Abl-transformed cells, c-Cbl is phosphorylated at Tyr\textsuperscript{700} and Tyr\textsuperscript{774}. Overexpression of various Src family protein tyrosine kinases (PTKs) phosphorylates Tyr\textsuperscript{700}, Tyr\textsuperscript{731} and Tyr\textsuperscript{774} without apparent specificity. In T cells, c-Cbl is phosphorylated at Tyr\textsuperscript{700}, Tyr\textsuperscript{731} and Tyr\textsuperscript{774} upon TCR ligation. In adipocytes, c-Cbl is phosphorylated at Tyr\textsuperscript{700}, Tyr\textsuperscript{731} and Tyr\textsuperscript{774} in response to insulin stimulation. Thus, Tyr\textsuperscript{731}, Tyr\textsuperscript{700}, Tyr\textsuperscript{731} and Tyr\textsuperscript{774} are the major tyrosine phosphorylation sites identified in c-Cbl (Fig. 1).

Like c-Cbl, Cbl-b also becomes tyrosine phosphorylated in response to insulin stimulation and TCR engagement. In adipocytes and Jurkat cells, Cbl-b is phosphorylated at Tyr\textsuperscript{655} and Tyr\textsuperscript{709} upon TCR stimulation (Fig. 1). However, the phosphorylation of Cbl-b is much weaker as compared to that of c-Cbl upon insulin stimulation and TCR engagement.
Cbl negatively regulates cell adhesions. The involvement of Cbl in negatively regulating cell adhesions has been demonstrated in several publications. Cbl inhibits cell adhesion by ubiquitinating \( \alpha_5 \) integrin in osteoblasts, and suppresses T cell adhesion by ubiquitinating FAK or inhibiting Rap1 activation. By contrast, the macrophages from Cbl-b (-/-) mice exhibit increased recruitment in thioglycollate-induced peritonitis and mononuclear phagocytes derived from Cbl-b (-/-) bone marrow show increased adhesion to endothelial cells.

C-Cbl and \( \alpha_5 \) integrin. Alpha5 integrin co-immunoprecipitates with c-Cbl and it also co-localizes with c-Cbl at the leading edge of membrane ruffles, indicating that \( \alpha_5 \) integrin is a c-Cbl-binding protein. Binding of c-Cbl to \( \alpha_5 \) integrin results in its ubiquitination and degradation. In human calvarial osteoblasts expressing activated FGFR2, FGF stimulation causes \( \alpha_5 \) integrin ubiquitination and degradation and reduces the adhesions of osteoblasts on fibronectin. However, expressing a c-Cbl mutant lacking the RING finger domain or a c-Cbl mutant with mutation in the PTB domain restores \( \alpha_5 \) integrin levels. Also, lactacystin, a potent proteasome inhibitor, restores \( \alpha_5 \) integrin levels in FGF-stimulated osteoblasts. In addition, exogenous expression of \( \alpha_5 \) integrin rescues cell attachment. Thus, c-Cbl-mediated ubiquitination and degradation of \( \alpha_5 \) integrin reduce the adhesion of the osteoblasts to fibronectin.

Cbl and Rap1. Rap1 mediates integrin activation through RIAM, while the activity of Rap1 is stimulated by C3G, a guanine nucleotide exchange factor that is activated by CrkL interaction. Shao et al. reported that Cbl promotes CrkL ubiquitination, which in turn inhibited the interaction of CrkL with C3G, thus suppressing Rap1 activation; Cbl deficiency caused an increase in the activity of C3G, Rap1 activation, and integrin-mediated cell adhesion in Cbl (-/-) thymocytes. Cbl-b deficiency also promotes cell adhesion and cell surface binding to ICAM-1 and enhanced clustering of LFA-1 in Cbl-b (-/-) T cells in response to TCR stimulation. However, the underlying molecular mechanisms remain to be elucidated.

Cbl and FAK. Cbl ubiquitates FAK in a STAP-2-dependent manner and inhibits T cell adhesion to fibronectin. STAP-2 (signal-transducing adaptor protein-2) is a signaling adaptor protein that interacts with FAK and Cbl. Sekine et al. showed that STAP-2 recruits FAK and Cbl together and mediates the ubiquitination of FAK by Cbl, thus inhibiting cell adhesion to fibronectin. Overexpression of STAP-2 causes a dramatic decrease in the levels of FAK, whereas STAP-2 (-/-) T cells have increased FAK levels. Furthermore, STAP-2 (-/-) splenocytes or T cells exhibit enhanced cell adhesion to fibronectin after PMA treatment, whereas overexpression of STAP-2 inhibits integrin-mediated T cell adhesion to fibronectin.

Cbl regulates actin polymerization. Cbl and mDab1. Cbl ubiquitinates phosphorylated mDab1 (mouse Disabled homologue 1), thus inhibiting mDab1-induced actin polymerization and filopodium formation. mDab1 binds and activates N-WASP (neuronal Wiskott–Aldrich syndrome protein) directly, inducing actin polymerization through the Arp2/3 (actin-related protein 2/3) complex and filapodium formation. Suetsugu et al. reported that mDab1 is ubiquitinated in a Cbl-dependent manner after it is phosphorylated by Fyn; Fyn activation inhibits its mDab1-induced filopodium formation. These results suggest that Cbl and Fyn negatively regulate mDab1-N-WASP-mediated actin polymerization. This pathway may regulate actin dynamics during cell migration.

Cbl and WAVE2. Cbl ubiquitinates WAVE2 to inhibit actin polymerization and lamellipodium formation. WAVE2, a member of the WASP and WAVE family proteins, has a WAVE homology/Scar homology domain (WHD/SHD), a basic region, a proline-rich region and a VCA region. Upon Rac activation, WAVE2 forms a complex with Rac and IRSp53 and then binds G-actin and Arp2/3, thus inducing actin polymerization and lamellipodium formation. On the other hand, Ceistra et al.66...
Overexpression of Cbl promotes PDGF-induced ubiquitination, this inhibition is caused by Cbl.

These results indicate that Cbl negatively regulates PDGF-induced ubiquitination and degradation, whereas a point mutation (G306E) that inactivates the tyrosine kinase binding domain of the PDGFR.

Jékely et al. showed that Cbl modulates the spatial distribution of growth factor receptors in cells through ubiquitinating the receptors, thus promoting cell polarization; cells deficient in Cbl had severe migration defects, indicating that Cbl is required for cell migration.

**Cbl and EGFR.** EGFR is a substrate for Cbl. SHIP2, an enzyme that dephosphorylates phosphatidylinositol 3,4,5-trisphosphate, interacts with Cbl and has an inhibitory effect on Cbl. SHIP2 knockdown in HeLa cells promotes Cbl-mediated EGFR ubiquitination and degradation.

**Cbl and PDGFR.** PDGFR is also a substrate for Cbl. Overexpression of Cbl promotes PDGF-induced ubiquitination and degradation of the PDGFR, whereas a point mutation (G306E) that inactivates the tyrosine kinase binding domain of Cbl abolishes Cbl’s ability to induce ubiquitination and degradation of the PDGFR.

**Cbl and Met.** Met, a receptor tyrosine kinase, is the receptor for hepatocyte growth factor/scatter factor (HGF). HGF induces c-Cbl-mediated ubiquitination of Met, while a Met mutant that is not ubiquitinated by Cbl promotes its oncogenic activation, indicating that c-Cbl is a negative regulator of HGF/Met signaling.

**Cbl and Kit.** Kit is a receptor tyrosine kinase and the receptor for stem cell factor (SCF). SCF stimulates Kit-mediated phosphorylation of Cbl, which in turn causes ubiquitination and degradation of Kit, leading to downregulation of Kit signaling.

**Cbl downregulates non-receptor protein tyrosine kinases (PTKs).** Cbl ubiquitinates a great number of non-receptor PTKs, including Syk, Fyn, Src and Abl. Although these PTKs are regulators of cell migration, currently there are no direct links between the ubiquitination of these PTKs and cell migration.

**Smurfs**

Smurf (Smad ubiquitin regulatory factor) 1 and 2 are members of the Nedd4 family ubiquitin ligases. These enzymes feature an amino terminal C2 domain and 2–3 WW domains that are responsible for cellular localization and substrate recognition, and a catalytic carboxyl terminal HECT domain (Fig. 3). Smurf1 is localized in both the nucleus and the cytoplasm. A nuclear export signal sequence in the carboxyl terminus of Smurf1 is responsible for its cytoplasmic distribution. Smurf2 is predominantly a nuclear protein, but it can form a complex with Smad7, resulting in its export and recruitment to the activated TGFβ receptor.

Smurfs were originally identified as regulators of TGFβ family signaling, but recent studies show that they regulate a wide range of signaling networks including the Wnt signaling pathway. TGFβ family signaling regulates a wide range of biological processes including cell growth, differentiation and development. Signaling is initiated with the activation of Type I and II serine/threonine receptor kinases through dimerization of TGFβ receptors, which phosphorylate the receptor-regulated Smads (R-Smads) 1, 2, 3, 5 and 8. The phosphorylated Smads then interact with the common Smad, Smad4, resulting in translocation to the nucleus and transcription initiation. Smurf1 negatively regulates bone morphogenetic protein signaling by ubiquitinating R-Smad 1 and 5.

Smurf1 also regulates transcription by ubiquitinating Runx2, a bone-specific transcription factor. On the other hand, Smurf2 inhibits TGFβ signaling mainly through binding and ubiquitinating R-Smad 2 and TGFβ receptor.

Besides the canonical roles in cell growth and differentiation, accumulating evidence indicates that Smurfs play key roles in regulating cell adhesion and migration (Fig. 4). First, Smurf1 is localized to lamellipodia and filopodia and a fraction of Smurf1 is also localized to focal adhesions. Second, Smurfs ubiquitinate a number of molecules that regulate cell adhesion and migration, such as RhoA, Rap1, talin head and hPEM-2.

Exogenous expression of Smurf1 promotes proliferative activity; overexpression of Smurf2 promotes the migration of a human trophoblast cell line. Fourth, inhibition of Smurf1 by Smurf1C699A, a ligase-dead mutant or siRNA abrogates proliferative activity and cell migration; also, inhibition of Smurf2 by Smurf2C716G, a ligase-dead mutant or siRNA induces cell rounding and inhibits cell migration and metastasis in cancer cell lines. These results collectively implicate Smurfs in the regulation of cell adhesion and migration.

**Smurf1 and RhoA.** The discovery of Smurf1-mediated RhoA ubiquitination represents the first direct evidence for the role of Smurf in cell migration. RhoA plays a pivotal role in cell migration by regulating stress fiber and focal adhesion formation. In migratory cells, RhoA activity is low at the leading edge and higher at the rear and sides. Wang et al. reported that Smurf1 is localized to lamellipodia and targets RhoA there for ubiquitination and degradation, thus inhibiting stress fiber formation and facilitating proliferative activity and cell migration. However,
excess Smurf-mediated RhoA degradation impairs cell migration. For example, gene silencing of synaptopodin, an actin-associated protein that competitively inhibits Smurf1-mediated ubiquitination of RhoA, induces the loss of stress fibers and non-polarized filopodium formation and inhibits cell migration. Thus, Smurf1-mediated ubiquitination of RhoA is responsible for precise temporal and spatial regulation of RhoA, which is required for optimal cell migration.

Smurf1 and talin head domain. Talin is an acrin and β-integrin tail-binding protein that regulates integrin activation and focal adhesion turnover. Talin is cleaved into a ~47-kDa head domain and a ~190-kDa rod domain by calpain. The talin head (TH) domain localizes to focal adhesions and stimulates integrin activation. Smurf1 binds to TH and mediates TH ubiquitination and degradation, thus leading to focal adhesion disassembly. This action of Smurf1 is inhibited by Cdk5, a regulator of cell migration and cancer metastasis. Cdk5 phosphorylates TH at Ser25 and abrogates its binding to Smurf1, thus inhibiting TH ubiquitination and focal adhesion disassembly. Thus, precise coordination of the roles of Smurf1 and Cdk5 is required for optimal cell migration.

Smurf1 and hEMP-2. hPEM-2, a guanine nucleotide exchange factor for Cdc42, is also a substrate of Smurf1. Smurf1 binds the PH domain of hPEM-2 via its C2 domain and induces hPEM-2 ubiquitination and degradation in cells. Thus, Smurf1-mediated ubiquitination of hPEM-2 may play a role in the spatiotemporal regulation of Cdc42 during cell migration.

Smurf2 and Smurf1. Fukunaga et al. reported that Smurf2 binds Smurf1 and induces its ubiquitination and degradation, but Smurf1 fails to induce degradation of Smurf2. They also showed that knockdown of Smurf2 in human breast cancer MDA-MB-231 cells causes an increase in the Smurf1 protein level, and promotes cell migration in vitro and bone metastasis in vivo. However, this result is inconsistent with studies showing that Smurf2 knockdown inhibits the migration and metastasis of MDA-MB-231 cells, and indicates that further investigation is required to clarify the role of Smurf2 in cell migration.

Smurf2 and TGFβ type I receptor. Trophoblast cell migration and invasion are key steps during embryo implantation. These are regulated by Smurf2-mediated degradation of TGFβ type I receptor (TGFβR I). Overexpression of Smurf2 in a human trophoblast cell line leads to TGFβR I degradation, and enhances cell migration and invasion. In contrast, Smurf2 knockdown using siRNA causes a significant increase in TGFβR I levels and inhibits the migration of trophoblast cells.

Smurf2 and Rap1B. Rap1 is a small GTPase that regulates integrin activation, cell migration, cell polarity and differentiation. Rap1B is a substrate for Smurf2. Smurf2 ubiquitinates inactive Rap1B and mediates its degradation in proteasomes. Smurf2-mediated degradation of Rap1B is essential for neuronal polarity. Because of the role of Rap1 in cell migration, Smurf2-mediated Rap1B ubiquitination may regulate cell migration.

HDM2

HDM2 is the human counterpart of Mdm2 (murine double minute 2), which encodes a 90-kDa protein. Hdm2 is overexpressed in a wide range of human cancers, including breast cancers, esophageal cancers, lung cancers, and malignant melanomas. HDM2 is a RING finger ubiquitin ligase that mediates the ubiquitination of p53, a classic tumor suppressor. It has been reported that HDM2 also targets NFAT (nuclear factor of activated T cells) for ubiquitination and degradation. NFAT is a transcription factor that is emerging as a novel positive regulator of cell migration and cancer invasion. It is downstream of the PI 3-kinase-Akt-HDM2 pathway. Stimulation of the PI 3-kinase pathway results in sequential activation of Akt and then HDM2, which in turn mediates NFAT ubiquitination and degradation, thus inhibiting the migration of cancer cells.
BCA2

The BCA2 protein is a RING finger E3 ubiquitin ligase and is overexpressed in human breast tumors. Wild-type BCA2 significantly promotes the migration of MCF-7 cells in wound healing assays, whereas mutants that are deficient in autoubiquitination (RING mutation or NH2-terminal lysine mutations) significantly inhibit migration.117

SCFβ-TRCP

SCFβ-TRCP is a ubiquitin ligase complex that consists of Skp1, Cul1 and the E-box protein β-TRCP and it is responsible for mediating phosphorylation-dependent ubiquitination of a number of protein substrates, including IkBα, WEE1, catenin and Snail.118 Snail is a key transcription repressor of E-cadherin and is essential for epithelial-mesenchymal transition (EMT), which is critical for epithelial cell migration and cancer metastasis.119,120 Snail is phosphorylated by GSK-3 and subsequently is targeted for ubiquitination and degradation by SCFβ-TRCP, whereas the small C-terminal domain phosphatase (SCP), a specific phosphatase for Snail, induces Snail dephosphorylation and inhibits Snail ubiquitination and degradation, thus suppressing E-cadherin expression and promoting cell migration.121,122 The NFκB pathway also abrogates Snail ubiquitination and degradation through COP9 signalosome 2-mediated inhibition of SCFβ-TRCP, thus promoting cell migration.123

TRIM32

Tripartite motif protein 32 (TRIM32) is a RING domain E3 ubiquitin ligase that is highly expressed in human head and neck squamous cell carcinoma.124 It features a RING and a B-box finger domain, a coiled-coil domain at the N-terminus and multiple NHL domains at the C-terminus.125 TRIM32 binds to and ubiquinates Abl interactor 2 (Abi2), a tumor suppressor and a cell migration inhibitor.126 Overexpression of TRIM32 causes Abi2 degradation and enhances cell growth and cell migration, whereas a dominant-negative mutant of TRIM32 without the RING domain inhibits Abi2 degradation.

XRN1F85 and RNF5

XRN1F85 is a Xenopus RING finger domain ubiquitin ligase. It shares 91% homology with human RNF185. XRN1F85 binds and ubiquinates paxillin,127 a signaling adaptor and a focal adhesion-associated protein implicated in regulating focal adhesion dynamics and cell migration.128,129 It enhances the turnover of paxillin at focal adhesions and promotes mesodermal cell migration during gastrulation.127

RNF5, a RING finger domain ubiquitin ligase, was originally identified as a regulator of growth and development of Caenorhabditis elegans.130 The human homologue of RNF5 interacts with the NH2-terminus of paxillin and mediates its ubiquitination.131 RNF5 requires intact RING and C-terminal domains to mediate paxillin ubiquitination. However, instead of inducing paxillin degradation, RNF5-mediated ubiquitination causes a translocation of paxillin from focal adhesions to the cytoplasm. Overexpression of RNF5 inhibits cell migration in wound healing assays.131

Conclusions and Future Prospects

E3 ubiquitin ligases are emerging as important regulators of cell adhesion and migration. They regulate cell adhesion and migration through ubiquitinating specific substrates, such as adhesion molecules, actin polymerization regulators, small GTPases, protein kinases, growth factor receptors and transcription factors. These ubiquitin ligases may temporally and spatially regulate their substrates, thus promoting cell polarization, such as Smurf1-mediated ubiquitination of RhoA. They may also regulate the levels of cell migration promoters, thus modulating the migration of cells, such as SCFβ-TRCP-mediated Snail ubiquitination. These ligases also target many molecules that regulate cell adhesion and migration for ubiquitination and degradation, but direct links between the ubiquitination of these molecules and cell migration remain to be elucidated. Future studies will focus on the roles and the underlying mechanisms of different E3 ubiquitin ligases in cell adhesion and migration. It is of great importance to identify other E3 ubiquitin ligases and novel substrates that regulate cell adhesion and migration. How ubiquitin ligases temporally and spatially regulate their substrates and whether this kind of regulation participates in cycling processes such as focal adhesion assembly/disassembly during cell migration is another key issue. Eventually, we would like to understand how E3 ubiquitin ligases coordinate other signaling pathways that may regulate both inhibition and acceleration of cell migration.

Acknowledgements

I thank Drs. Ken Jacobson, Mark Ginsberg, Zenon Rajfur and Ms. Michelle Itano for their critical reading of this manuscript. Supported by a Cell Migration Consortium grant (NIH GM64346) to M.G. and K.J. and a Ruth L. Kirschstein National Research Service Award (F32 HL08321) to C.H.

References

1. Finley D, Chau V. Ubiquitination. Annu Rev Cell Biol 1991; 7:25-69.
2. Weissman AM. Regulating protein degradation by ubiquitination. Immunol Today 1997; 18:189-98.
3. Pickart CM. Mechanisms underlying ubiquitination. Annu Rev Biochem 2001; 70:503-33.
4. Pickart CM. Ubiquitin in chains. Trends Biochem Sci 2000; 25:544-8.
5. Sun L, Chen ZJ. The novel functions of ubiquitination in signaling. Curr Opin Cell Biol 2004; 16:119-26.
6. Thrower JS, Hoffman L, Rechsteiner M, Pickart CM. Recognition of the polyubiquitin proteolytic signal. EMBO J 2000; 19:94-102.
7. Jackson PK, Eldridge AG, Freed E, Funstenhall L, Hsu JY, Kaiser BK, et al. The loric of the rings: Substrate recognition and catalysis by ubiquitin ligases. Trends Cell Biol 2000; 10:429-39.
8. Crews CM. Feeding the machine: Mechanisms of proteasome-catalyzed degradation of ubiquitinated proteins. Curr Opin Chem Biol 2003; 7:334-9.
9. Deshaies RJ, Joazeiro CAP. Ring domain e3 ubiquitin ligases. Annu Rev Biochem 2009; 78:399-434.
10. Pickart CM. Mechanisms underlying ubiquitination. Annu Rev Biochem 2001; 70:503-33.
11. Andrély HCRP. E3 ubiquitin ligases. Essays Biochem 2005; 41:15-30.
30. Barber DL, Mason JM, Fukazawa T, Reedquist KA, Meisner H, Czech MP. Coupling of the proto-oncogene product c-cbl to the epidermal growth factor receptor. J Biol Chem 1995; 270:25332-5.

28. Meisner H, Czech MP. Negative regulation of fc{epsilon}ri-mediated mast cell activation by ubiquitin-protein ligase cbl-2. Blood 2003; 102:1779-86.

27. Ribon V, Salier AR. Insulin stimulates tyrosine phosphorylation of the proto-oncogene product of c-cbl in 3T3-L1 adipocytes. Biochem J 1997; 324:839-45.

26. Meinzer H, Czech M. The c-cbl protein product of the proto-oncogene c-cbl forms a complex with phosphatidylinositol 3-kinase p85 and cd19 in anti-igm-stimulated human b-lymphoma cells. Blood 1998; 91:46-53.

25. Winiarczuk D, Strife A, Clarkson B. C-kit ligand stimulates tyrosine phosphorylation of the c-cbl protein product in human hematopoietic cells. Leukemia 1996; 10:1436-42.

24. Galisteo ML, Dikic I, Batzer AG, Langdon WY. The c-cbl proto-oncogene is preferentially expressed in thymus and testis tissue and encodes a nuclear-protein. J Biol Chem 1989; 63:5420-4.

23. Qu X, Sada K, Kyo S, Maeno K, Miah SMS, Yamamura JP. Tyrosine phosphorylation induces tyrosine phosphorylation of p120-cbl and cd97 and formation of multiple signaling complexes in t lymphocytes and natural killer cells. J Biol Chem 1998; 273:3856-62.

22. Liu J, DeYoung SM, Hwang JB, O'Leary EE, Saltiel AR. Aps facilitates c-cbl tyrosine phosphorylation and glut4 translocation in response to insulin in 3T3-L1 adipocytes. Mol Cell Biol 2002; 22:3599-609.

21. Lupher ML Jr, Andoniou CE, Bonita D, Miyake S, Joazeiro CANP, Wing SS, Huang H-k, Leverson JD, Keane MM, Ettenberg SA, Nau MM, Banerjee P, Keane MM, Riverolezcano OM, Mitchell JA, Robbins AL, Bernassola F, Karin M, Ciechanover A, Melino G. The target of rap1 activation induces c-cbl tyrosine phosphorylation and glut4 translocation. J Biol Chem 1996; 271:15354-7.

20. Doncian C, Wang E, Langdon W, Samelson L. The protein product of the c-cbl proto-oncogene is the 120-kda tyrosine-phosphorylated protein in jarkut cells activated via the t cell antigen receptor. J Biol Chem 1994; 269:22921-4.

19. Vanzka S, Aming M, Neff L, Peyman A, Uhlmann E, Levy JB, et al. C-cbl is downstream of c-src in a signaling pathway necessary for bone resorption. Nature 1996; 383:528-31.

18. Kondo T, Shary J, Shinjyo M, Hillaire J, Fromm HA, Simons K, Melchers F. Domains of c-cbl and cbl-b3kb inactivation of phospholipase c-gamma2 in b cells. J Exp Med 2002; 196:51-63.

17. Zhang H-G, Wang J, Yang X, Hsu H-C, Mounts JD. Regulation of apoptosis proteins in cancer cells by c-cbl. Oncogene 2004; 23:2009-15.

16. Bernassola F, Alves-Rodrigues A, Gregori L, Figueiredo-Pereira ME, Schlessinger J. Tyrosine phosphorylation of the c-cbl proto-oncogene product c-cbl is induced by interleukin-4 and enhances mitogenic and survival signals of interleukin-4 receptor by linking with the phosphatidylinositol 3-kinase pathway. Blood 1998; 91:86-93.

15. Yuasa T, Tenuka T, Maeda A, Inazu T, Yamanashi Y, Gu H, et al. Cbl-b positively regulates btk-mediated activation of phospholipase c-gamma2 in b cells. J Exp Med 2002; 196:51-63.

14. Kreb M, Jorgensen G, Longo D. The protein product of the proto-oncogene c-cbl forms a complex with phosphatidylinositol 3-kinase p85 and cd19 in anti-igm-stimulated human b-lymphoma cells. Blood 1996; 88:3502-7.

13. Krek W. Proteolysis and the g1-s transition: The scf receptor. Curr Opin Genet Dev 1998; 8:36-42.

12. Alves-Rodrigues A, Gregori L, Figueiredo-Pereira ME, Komiya S, et al. The proto-oncogene product c-cbl associates with cbl and phosphorylates tyrosine 731 in cbl. Oncogene 2004; 23:7104-9.

11. Krek W. The c-cbl oncoprotein. Nat Rev Cancer 2001; 1:425-31.

10. Liu J, Kimura A, Baumann CA, Saltiel AR. Aps facilitates c-cbl tyrosine phosphorylation and glut4 translocation in response to insulin in 3T3-L1 adipocytes. Mol Cell Biol 2002; 22:3599-609.

9. Liu J, DeYoung SM, Hwang JB, O'Leary EE, Saltiel AR. The role of c-cbl and cbl-b3kb in insulin-stimulated glucose transport. J Biol Chem 2003; 278:36754-62.

8. Zeng S, Xu Z, Lipkowitz S, Longley JB. Regulation of ras activation induces tyrosine phosphorylation of p120-cbl and cd97 and formation of multiple signaling complexes in t lymphocytes and natural killer cells. J Biol Chem 1998; 273:3856-62.
80. Zhu HT, Kavsak P, Abdollah S, Wrana JL, Thomsen AM. Direct regulation of c-abl. Biochem J 2006; 399:59-67.
81. Umebayashi K, Stenmark H, Yoshimori T. Ubc4/5 deficient for cell transformation. Mol Cell 2001; 7:355-67.
82. Masson K, Heiss E, Band H, Ronnstrand L. Direct tyrosine kinase regulator cbl enhances the ubiquitination and degradation of the p53 E3 ubiquitin ligase for itself and p53. J Biol Chem 2000; 275:8945-51.
83. Huang C, Rajfur Z, Yousefi N, Chen ZZ, Jacobson K, O'Keefe RJ, et al. Smad6 interacts with runx2 and mediates smad ubiquitin regulatory factor 1-induced runx2 degradation. J Biol Chem 2006; 281:3569-75.
84. Lin X, Liang M, Feng X-H. Smurf2 is a ubiquitin c3 ligase mediating proteasome-dependent degradation of smad2 in transforming growth factor-beta signaling. J Biol Chem 2000; 275:36018-22.
85. Yang Q, Chen S-P, Zhang X-P, Wang H, Zhu C, Lin H-Y. Smurf2 participates in human trophoblast invasion by inhibiting tgf[beta] type 1 receptor. J Histochem Cytochem 2009; 57:605-12.
86. Wang HR, Zhang Y, Ozdamar B, Ogunjimi AA, Albor A, Liu YG, El-Hizawi S, Vanderbeek GE, Babcock M, et al. Ring protein trim32 associated with skin carcinogenesis has anti-apoptotic and pro-metastatic functions. J Cell Sci 2009; 122:3421-30.
87. Fukunaga E, Inoue Y, Komiya S, Horiguchi K, Goto K, Sano M, et al. Smurf2 induces ubiquitin-dependent degradation of smurf1 to prevent migration of breast cancer cells. J Biol Chem 2008; 283:35660-7.
88. Bos JL, de Rooij J, Reeedquist KA. Rap1 GTPase: Adhering to new models. Nat Rev Mol Cell Biol 2001; 2:269-77.
89. Harner M, Ninari N. Rap1 gspase: Functions, regulation, and malignancy. J Biochem 2003; 134:479-84.
90. Momand J, Jung D, Wizikynski S, Niland J. The mdm2 gene amplification database. Nucl Acids Res 1998; 26:3453-9.
91. Tao W, Levine AJ. Nucleocytoplasmic shuttling of oncoprotein mdm2 is required for mdm2-mediated degradation of p53. Proc Natl Acad Sci USA 1999; 96:5077-80.
92. Fung S, Jensen JP, Ludwig RL, Vouwen KH, Weissman AM. Mdm2 is a ring finger-dependent ubiquitin protein ligase for itself and p53. J Biol Chem 2000; 275:8945-51.
93. Hastrup H, Møller B, Sorensen S, Gustafsson E, Babcock M, et al. Mdm2 is a ring finger-dependent ubiquitin protein ligase for itself and p53. J Biol Chem 2000; 275:8945-51.
94. Wang HR, Zhang Y, Ozdamar B, Ogunjimi AA, Albor A, Liu YG, El-Hizawi S, Vanderbeek GE, Babcock M, et al. Ring protein trim32 associated with skin carcinogenesis has anti-apoptotic and pro-metastatic functions. J Cell Sci 2009; 122:3421-30.
95. Yang Q, Chen S-P, Zhang X-P, Wang H, Zhu C, Lin H-Y. Smurf2 participates in human trophoblast cell invasion by inhibiting tgf[beta] type 1 receptor. J Histochem Cytochem 2009; 57:605-12.
96. Wang HR, Zhang Y, Ozdamar B, Ogunjimi AA, Albor A, Liu YG, El-Hizawi S, Vanderbeek GE, Babcock M, et al. Ring protein trim32 associated with skin carcinogenesis has anti-apoptotic and pro-metastatic functions. J Cell Sci 2009; 122:3421-30.
127. Iioka H, Iemura S-i, Natsume T, Kinoshita N. Wnt signalling regulates paxillin ubiquitination essential for mesodermal cell motility. Nat Cell Biol 2007; 9:813-21.
128. Huang C, Rajfur Z, Borchers C, Schaller MD, Jacobson K. Jnk phosphorylates paxillin and regulates cell migration. Nature 2003; 424:219-23.
129. Huang C, Jacobson K, Schaller MD. Map kinases and cell migration. J Cell Sci 2004; 117:4619-28.
130. Kyushiki H, Kuga Y, Suzuki M, Takahashi E, Horie M. Cloning, expression and mapping of a novel ring-finger gene (rnf5), a human homologue of a putative zinc-finger gene from Caenorhabditis elegans. Cytogenet Cell Genet 1997; 79:114-7.
131. Didier C, Broday L, Bhoumik A, Israeli S, Takahashi S, Nakayama K, et al. Rnf5, a ring finger protein that regulates cell motility by targeting paxillin ubiquitination and altered localization. Mol Cell Biol 2003; 23:5331-45.