Recent discoveries have unveiled the roles of a complicated network of E3 ubiquitin ligases in regulating cell migration machineries. The E3 ubiquitin ligases Smurf1 and Cul/BACURD ubiquitinate RhoA to regulate stress fiber formation and cell polarity, and ASB2α ubiquitinates filamins to modulate cytoskeletal stiffness, thus regulating cell spreading and cell migration. HACE1, XIAP, and Skp1-Cul1-F-box bind to Rac1 and cause its ubiquitination and degradation, thus suppressing lamellipodium protrusions, while PIAS3, a SUMO ligase, activates Rac1 to promote lamellipodium dynamics. Smurf1 also enhances Rac1 activation but it does not ubiquitinate Rac1. Both Smurf1 and HECTD1 regulate focal adhesion (FA) assembly and (or) disassembly through ubiquitinating the talin head domain and phosphatidylinositol 4 phosphate 5-kinase type I γ (PIPKIγ90), respectively. Thus, E3 ubiquitin ligases regulate stress fiber formation, cell polarity, lamellipodium protrusions, and FA dynamics through ubiquitinating the key proteins that control these processes.

Protein ubiquitination can be divided into three sequential steps: (1) ubiquitin activation by ubiquitin-activating enzymes (E1), (2) transfer of activated ubiquitin from E1 to ubiquitin-conjugating enzymes (E2), and (3) conjugation of ubiquitin to target proteins by ubiquitin ligases (E3). E3 ubiquitin ligases are the key control points for this process. So far, more than 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.

Besides regulating cell proliferation, apoptosis, cancer invasion, and neurodegenerative diseases, E3 ubiquitin ligases also regulate cell migration, a process that plays pivotal roles in wound healing, embryonic development, cancer metastasis, and inflammation. Cell migration is a cyclic process consisting of three steps: (1) the formation and protrusion of a leading lamellipodia; (2) subsequent adhesion to the substrate, followed by (3) the tail retraction. All these steps require extensive focal adhesion dynamics and cytoskeletal reorganization. We have reviewed the roles of E3 ubiquitin ligases in cell migration previously. In this commentary, we will highlight the new discoveries on the roles of E3 ubiquitin ligases in cell migration, focusing on how these E3 ubiquitin ligases regulate the machineries (such as focal adhesion, lamellipodia, and stress fibers) of cell migration.
E3 Ubiquitin Ligases Regulate Stress Fiber Formation, Cell Stiffness, and Cell Polarity

Ras homolog gene family, member A (RhoA), is a small GTPase protein that regulates the formation of stress fibers. Active RhoA binds to and activates Rho-kinases, ROCKII and ROKα, which in turn, either phosphorylates and inhibits myosin phosphatase or phosphorylates myosin light chain (MLC), leading to elevated MLC phosphorylation. The phosphorylated MLC then promotes the assembly of stress fibers. Stress fibers participate in FA dynamics and modulate the direction of lamellipodium spreading.19 Filamins to modulate the elasticity of the actin network and consequently cell plasticity, thus inhibiting cell migration.10,11

Filamins are large actin-binding proteins that cross-link actin into a dynamic three-dimensional structure.12 Filamins form homodimers and have multiple F-actin-binding domains, thus supporting orthogonal branching actin formation,13 whereas the hinge regions are responsible for the intrinsic flexibility of the actin networks generated by filamins.14 These properties confer filamins versatile role in regulating the elasticity and stiffness of the actin network. Filamins usually function as suppressors in cell spreading and cell migration, probably through inhibiting integrin activation or focal adhesion dynamics.15,16 It is likely that filamins-mediated increase in the stiffness of actin network also contributes to its suppression on cell migration.

As illustrated in Figure 1, both Smurf1 and Cul3/BACURD ubiquitinate RhoA to regulate stress fiber formation and cell polarity,17,18 whereas ASB2α ubiquitinates Filamins to modulate the elasticity of the actin network and consequently cell spreading.19

RhoA ubiquitination

**SMURF1**

RhoA ubiquitination by Smurf1 has been reviewed previously.5 However, because this discovery has inspired many new studies (see the following paragraphs), it deserves to be mentioned again. It is well known that migratory cells are polarized with low RhoA activity at the leading edge and higher at the rear and sides.20 The underlying molecular mechanism was unknown before Wang’s discovery. Wang et al.7 reported that Smurf1 (Smad ubiquitin regulatory factor 1), a Nedd4 family ubiquitin ligase, was localized to lamellipodia, where it targeted RhoA for ubiquitination and degradation, thus inhibiting stress fiber formation to facilitate protrusive activity and polarity.17 Thus, Smurf1-mediated ubiquitination of RhoA is responsible for precise temporal and spatial regulation of RhoA, which is required for optimal cell migration.17

Smurf1 features an N-terminal C2 domain and two WW domains that are responsible for cellular localization and substrate recognition, and a catalytic carboxyl terminal HECT domain.21 SMURF1 amplification was detected in forty of nine patients (4.2%) in primary human pancreatic cancers.22 The protein levels of Smurf1 are downregulated by SCF/FBXL15 ubiquitin ligase complex,23 whereas it is upregulated by deubiquitinase FAM/USP9X.24

Many proteins, including RhoA, talin head, hPEM-2, Smad1, Smad5, Runx2, and Axin, were identified as Smurf1 substrates.17,25-30 It is likely that the roles of Smurf1 in regulating different pathways are controlled by its binding proteins. CCM2 (Cerebral Cavernous Malformations 2) binds Smurf1 through its phosphotyrosine binding (PTB) domain, and promotes Smurf1-mediated degradation of RhoA.31 APC/Cdh1 E3 and CKIP-1 promote the activity of Smurf1, thus downregulating multiple downstream targets that control osteoblast differentiation.32,33 The estrogen receptor α (ERα) forms a protein complex with Smurf and Smad, and enhances Smad ubiquitination and degradation in an estrogen-dependent manner.14 The roles of Smurf1 in regulating different pathways are also changed by protein kinases. For instance, protein kinase A-mediated phosphorylation of Smurf1 at T306 reduces ubiquitination of polarity protein Par6 while increases RhoA ubiquitination, thus elevating the Par6/RhoA ratio and consequently promoting axon growth in hippocampal neurons.35

**Cul3/BACURD**

BACURDs are a family of RhoA-binding BTB domain (for BR-C, ttk and bab, a domain present near the N terminus of zinc finger proteins) adaptors conserved from insects to mammals.36 BACURDs and Cul3, a Cullin family scaffold protein, assemble to SCF (Skp1-Cullin1-F-box protein)-like ubiquitin ligase complexes through BTB domain. Chen et al. reported that Cul3/BACURD complex specifically ubiquitinated RhoA, and that dysfunction of the Cul3/BACURD complex caused profound stress fiber accumulation, thus inhibiting cell migration and impairing RhoA-mediated convergent extension movements during Xenopus gastrulation.37

**Filamin ubiquitination**

ASB2α (Ankyrin repeat-containing protein with a Suppressor of cytokine signaling Box 2α) is a subunit of an active Cullin 5-RING E3 ubiquitin ligase complex. The ASB2α Cullin 5-ring E3 ubiquitin ligase is highly expressed in immature dendritic cells (DCs) and is downregulated after DC maturation. It was reported that ASB2α ubiquitin ligase mediated the ubiquitination and degradation of filamins, a suppressor of cell motility, and regulated cell spreading and migration in immature DCs but not in mature DCs.19 Moreover, ASB2α−/− immature DCs showed defects in cell spreading, podosome rosette formation, and cell migration. Furthermore, ASB2α−/− immature DCs exhibited reduced matrix-degrading function leading to defective migration, indicating that ASB2 ubiquitinates filamins to modulate cytoskeletal dynamics, thus regulating cell spreading and cell migration.

E3 Ubiquitin Ligases Regulate Lamellipodium Protrusions

Rac1 is a member of the Rac subfamily of the Rho family of GTPases. Although Rac1 regulates a variety of signaling events, the main function of Rac1 is to control lamellipodium protrusions.36 As a central regulator of cell migration, Rac1 activates the WAVE protein complex, which in turn activates Arp2/3 complex to stimulate the assembly of branching actin filament network. The new polymerized actin network then generates pushing force to promote lamellipodium protrusions.

Rac1 is ubiquitinated by a number of E3 ubiquitin ligases, including HACE1,
XIAP, and Skp1-Cullin-F-box, resulting in Rac1 degradation and reduction in lamellipodium extension (Fig. 1). On the other hand, sumoylation of Rac1 by PIAS3, a SUMO ligase, stimulates its activation and lamellipodium protrusions. Smurf1-mediated ubiquitination of TRAF4 also promotes Rac1 activation.

**HACE1**

The gene of **HACE1** (HECT domain and ankyrin repeat-containing E3 ubiquitin-protein ligase 1) is mapped to a region of chromosome 6q21 implicated in multiple human malignancies. **HACE1** encodes a 102 kDa protein, featuring six ankyrin protein–protein interaction motifs with sequence similarity to those of INK4A, and a C-terminal HECT ubiquitin-protein ligase domain.

The active small GTPase Rac1 is a substrate for HACE1. HACE1 binds preferentially active (GTP-bound) Rac1. The binding of HACE1 to Rac1 is stimulated by hepatocyte growth factor (HGF) signaling, resulting in the poly-ubiquitylation of Rac1 at lysine 147, and consequently, its proteasomal degradation. Overexpression of HACE1 stimulates Rac1 ubiquitylation, whereas depletion of HACE1 by RNAi blocks the ubiquitylation of active Rac1 and increases GTP-bound Rac1 cellular levels and accumulation of Rac1 in membrane ruffles. Furthermore, an ubiquitination-resistant Rac1 mutant rescues the migration defect of Rac1-null cells to a greater extent than wild-type Rac1. These findings indicate that HACE1 suppresses cell migration through ubiquitinating active Rac1.

HACE1 is widely expressed in human tissues, with strong expression in heart, brain, placenta, kidney, and pancreas. It localizes predominantly in the endoplasmic reticulum (ER) and the cytoplasm, although it also presents in other fractions of cells.

HACE1 is epigenetically inactivated in human Wilms’ tumors. The expression of HACE1 is markedly downregulated in a variety of human cancers. HACE1 also inhibits the Rac1-dependent DNA damage. Genetic deletion of HACE1 in mice or HACE1 inactivation in human tumor cell lines result in an increase in Rac1 levels, consequently leading to an increase in the NADPH oxidase-dependent reactive oxygen species and DNA damage responses. Also, genetic deletion of HACE1 in mice results in spontaneous tumor development or renders mice susceptible to environmental and genetic cancer triggers, probably through Rac1-mediated increase in DNA damage and tumor growth. These studies indicate that HACE1 is a tumor suppressor. However, it remains to be determined whether HACE1-regulated cell migration is involved tumor progression and metastasis.

**XIAP**

XIAP is a member of the inhibitor of apoptosis family of proteins (IAP). XIAP contains three N-terminal baculoviral IAP repeat (BIR) domains, followed by an UBA domain and a C-terminal RING finger. The well-known function of XIAP is to inhibit caspases and prevent cell death, but it has been shown that it suppresses cell migration through causing Rac1 ubiquitination. Oberoi et al. reported that XIAP bound to Rac1 and ubiquitinated it at K147, leading to its degradation. Depletion of XIAP caused an increase in Rac1 protein levels and promoted cell migration, indicating that XIAP suppresses cell migration through mediating Rac1 ubiquitination. On the other hand, it has also been reported that either knockout or knockdown of XIAP significantly inhibits cell migration. Thus, the role of XIAP in cell migration remains to be clarified.

**Skp1-Cullin-F-box**

Skp1-Cullin-F-box (SCF)-containing complex is a multi-protein E3 ubiquitin ligase complex. SCF contains three core subunits: Skp1, Cullin, and F-box protein. Skp1 contributes to the recognition and binding of the F-box. Cullin (CUL1), as the major structural scaffold of the SCF complex, links the skp1 domain with the Rbx1 domain. The F-box protein functions as the bridge linking the ligase complex and specific substrates via its F-box domain and substrate-binding motif. FBXL19, an orphan member of the Skp1-Cullin-F-box family of E3 ubiquitin ligases, ubiquitinates Rac1 at Lys166, resulting in its proteasomal degradation. Overexpression of FBXL19 caused a reduction in Rac1 levels and...
leammellipodium formation and inhibited cell migration. Phosphorylation of Rac1 at Ser71 by Akt was required for FBXL19-mediated Rac1 ubiquitination and degradation. Substitution of either Ser71 with Ala or Lys66 with Arg blocked FBXL19-mediated Rac1 ubiquitination and degradation. Furthermore, expression of FBXL19 inhibited migration of the cells expressing the WT Rac1, but not that of the cells that express mutant Rac1. Thus, SCF/FBXL19 targets Rac1 for ubiquitination and degradation, which is in turn regulated by AKT, thus inhibiting lamellipodium protrusions and cell migration.

PIAS3

PIAS3, an E3 SUMO ligase, bound to Rac1 and caused sumoylation within the polybasic regions of Rac1 in response to hepatocyte growth factor (HGF) stimulation. Furthermore, PIAS3-mediated SUMOylation was essential for Rac1 activation and Rac1-mediated lamellipodium extension, cell migration, and invasion.

Smurf1 and TRAF4

TRAF4 is a member of the TNF receptor-associated factor (TRAF) family. However, unlike other family members that function as scaffolds for TNF receptor, Toll-like receptor and IL-1 receptor signaling complexes, TRAF4 does not interact with TNF receptors. Instead, TRAF4 bound the nicotinamide adenine dinucleotide phosphate reduced (NADPH) oxidase adaptor p47phox and localized to nascent, focal complex-like structures in motile endothelial cells. Active TRAF4 initiated robust membrane ruffling through activating Rac1, pAK1, and the oxidase, thus promoting cell migration. Most recently, Zhang’s group reported that TRAF4 was ubiquitinated at K90 by Smurf1. TRAF4 ubiquitination by Smurf1 was essential for TRAF4-dependent rac1 activation and migration of both normal mammary epithelial and breast cancer cells. However, the molecular mechanism by which TRAF4 ubiquitination regulates Rac1 activation remains to be elucidated.

E3 Ubiquitin Ligases Regulate Cell Adhesion Dynamics

Cell migration is a dynamic process that requires focal adhesion (FA) assembly at the front of cells with concomitant disassembly at the trailing edges of cells. Talin, an actin and β-integrin tail-binding protein, is essential for integrin activation. Talin is cleaved by calpain into an N-terminal head domain and a C-terminal rod domain. The talin head domain contains a FERM (band fourpoint-one, ezrin, radixin, moesin homology) domain, and is responsible for the binding of talin to β-integrin tail and integrin activation. Phosphatidylinositol 4 phosphate 5-kinase type 1 γ (PIPKIγ90) is an enzyme that catalyzes the production of phosphatidylinositol 4,5-bisphosphate (PIP2), a molecule that is well implicated in FA formation. PIPKIγ90 interacts with talin and localizes at FAs. Both talin and PIPKIγ90 are essential for FA dynamics and cell migration. We recently showed that E3 ubiquitin ligases Smurfl and HECTD1 regulate FA assembly and disassembly during cell migration (Fig. 1).

Smurf1

The role of Smurf1 in regulating FA dynamics has been reviewed previously. Briefly, the talin head (TH) domain, when released by calpain, stimulates integrin activation. Smurf1 binds to TH and causes TH ubiquitination and degradation, consequently leading to FA disassembly. Thus, Smurf1 in concert with calpain mediates FA disassembly during cell migration. This action of Smurf1 likely occurs during the tail retraction, a migration step where calpain is required, because the role of Smurf1 at the leading edges is prevented by Cdk5-mediated phosphorylation of talin. Since this function of Smurf1 is dependent of calpain, we expect it mainly plays a role in FA disassembly in those cells where calpain prevails.

HECTD1

The gene of HECTD1 (HECT domain containing 1) is mapped to a region of chromosome 14q12 (www.genecards.org). Deletion or duplication in this region is associated with severe mental retard and Rett-like syndrome. The human HECTD1 consists of 2610 amino acid residues, with apparent molecular weight 270 kDa, containing four N-terminal ankyrin repeats, a central MIB/HERC2 domain, and an unusual HECT ubiquitin-protein ligase domain at the C terminus. The HECTD1 protein is expressed in human blood cells, liver, and heart (from MOPED and PaxDb). Its presence in other tissues remains to be determined. HECTD1 has a cytoplasmic localization when it is epitopically expressed HEK293 cells. It has been reported that HECTD1 is localized to the leading edge in some cells. In fact, we found that HECTD1 partially co-localized with talin at the actin arcs immediately behind the leading edges, where FA in association with actin filaments and myosin, implying a role of HECTD1 in cell migration.

It has been well demonstrated that PIPKIγ90 plays a central role in focal adhesion assembly and disassembly, a key step in cell migration, but the underlying mechanism was unknown. We showed that PIPKIγ90 was ubiquitinated at K97 by HECTD1, resulting in its degradation, which was prevented by proteasome inhibitors. Depletion of HECTD1 by shRNAs resulted in an increase in endogenous PIPKIγ90 levels, indicating that HECTD1 is responsible for the ubiquitination of PIPKIγ90. HECTD1-mediated ubiquitination of PIPKIγ90 is required for focal adhesion dynamics and cell migration. Expression of PIPKIγ90 in MCF-7, an ubiquitination-resistant mutant that retains its ability for talin-binding, inhibited both FA assembly and disassembly. Also, depletion of HECTD1 significantly suppressed both FA assembly and disassembly. In contrast, expression of PIPKIγ90 in MCF-7, which is resistant to degradation but has a reduced binding capacity for talin, did not significantly impair FA assembly and disassembly rates. Based on these results, we conclude that PIPKIγ90 ubiquitination by HECTD1 and subsequently degradation cause a reduction in the production of PIP2, which is required for talin and vinculin.
activation, thus reducing the binding of the β integrin tail to talin and consequently leading to FA disassembly.

The role of PIPKιγ90 ubiquination in focal adhesion assembly is less clear. Either expression of ubiquitination-resistant PIPKιγ90 or knockdown of HECTD1 inhibited focal adhesion assembly; also overexpression of PIPKιγ90 suppressed integrin activation. Since PIPKιγ90 and the β integrin tail compete for the same site on talin, PIPKιγ90 ubiquitination and degradation might facilitate the talin-integrin interaction. However, it has been shown that talin-PIPKιγ90-B1 integrin exist as a complex in migrating cells. Thus, the mechanisms by which PIPKιγ90 ubiquitination regulates FA assembly remain to be determined. Nevertheless, PIPKιγ90 ubiquitination by HECTD1 and consequent degradation modulate the on-site production of PIP2, thus regulating focal adhesion dynamics and cell migration. The study provides new insights into the molecular mechanisms regulating cell adhesion and migration.

On the other hand, Zohn’s group reported that HECTD1 bound and ubiquitinated Hsp90 to form K63-linked poly-ubiquitin chains, thus inhibiting the ubiquitinated Hsp90 to form K63-linked ubiquitination and degradation. Therefore, PIPKIγ, which PIPKIγ90 regulates, will focus on determining how these E3 ubiquitin ligases are regulated by different signaling pathways. It is of great importance to examine how ubiquitin ligases temporally and spatially regulate the degradation of their substrates using advanced photo-manipulated methods. For example, photo convertible fluorescence protein could be used to determine the temporal and spatial protein degradation in live cells. For full understanding of the roles of E3 ubiquitin ligases, it is important to identify other E3 ubiquitin ligases and novel substrates that regulate these processes, particularly FA dynamics. Finally, identification of specific E3 ubiquitin ligase inhibitors will benefit basic and clinical studies.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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