mTOR is a central cell growth–modulating kinase in all eukaryotes. mTOR exists in two different complexes, mTORC1 and mTORC2, which are distinguished by unique accessory proteins RAPTOR and RICTOR, respectively. In addition, SIN1 is also a component uniquely present in the mTORC2 and is required for mTORC2 complex formation and function (1–3). Compared with the well-defined regulation and function of mTORC1, mTORC2 is less understood. AKT/PKB, a member of the AGC kinase family, is a key signaling hub in the PI3K pathway and regulates multiple cellular processes, such as growth, proliferation, metabolism, and survival. AKT is one of the most important substrates of mTORC2, which promotes AKT activation by directly phosphorylating its hydrophobic motif (S473), a site required for AKT maximum activation (4). Phosphorylation at S473 primes AKT for further phosphorylation at T308 in the catalytic domain by PDK1, thus leading to full activation of AKT. mTORC2 also phosphorylates other AGC kinases, including serum- and glucocorticoid-regulated kinase (SGK; ref. 5) and protein kinase C (PKC; ref. 6). It is generally accepted that mTORC2 is activated by growth factors via PI3K signaling; however, the precise molecular mechanism of mTORC2 activation remains elusive thus far.

Accumulating evidence suggests that SIN1 may play a key role in the regulation of mTORC2. It was found that alternatively spliced SIN1 isoforms in the cell define distinct mTORC2 pools; of these, only two are regulated by insulin (1). This suggests that SIN1 may function as a mediator between growth factor signaling and mTORC2. SIN1 contains a phospholipid-binding pleckstrin homology (PH) domain that may function as a mediator of mTORC2 localization, thereby revealing a mechanistic link between PI3K and mTORC2 (8).

Recently, Wei and colleagues reported that mTORC2 complex is directly regulated by mTORC1–S6K axis through SIN1 phosphorylation (Fig. 1; ref. 8). Phosphorylation of SIN1 at T86 and T398 by either S6K or AKT dissociates SIN1 from mTORC2, thus resulting in mTORC2 inhibition. Importantly, the authors also demonstrated a link between SIN1 phosphorylation and a cancer-derived mutation in SIN1 R81T, providing clinical significance of SIN1 phosphorylation in cell growth control. The R81T mutation attenuates SIN1 T86 phosphorylation and sustains mTORC2 activity and AKT tyrosine phosphorylation upon physiologic stimulation, thus bypassing SIN1 phosphorylation–mediated negative regulation of mTORC2 activity in response to upstream PI3K activation (Fig. 1; ref. 8).

The significance of this study is further expanded by genetic analysis of cancer-associated mutations in the SIN1-PH domain. Analysis of The Cancer Genome Atlas database revealed several somatic mutations in the SIN1-PH domain.

Summary: The mTOR complex 2, mTORC2, is a critical downstream effector of PI3K that stimulates AGC kinase members, including AKT, PKC, and SGK. Liu and colleagues reported that the pleckstrin homology domain of SIN1, an essential component of mTORC2, directly binds the PI3K product PtdIns(3,4,5)P3 to promote mTORC2 kinase activation and membrane localization, thereby revealing a mechanistic link between PI3K and mTORC2. Cancer Discov; 5(11): 1127–9. ©2015 AACR.

See related article by Liu and colleagues, p. 1194 (9).
domain. Biochemical characterizations showed that these cancer-associated mutations compromise SIN1-PH binding to the mTOR kinase domain, thereby leading to increased mTORC2-dependent AKT\(^{S473}\) phosphorylation (Fig. 1). Among these mutations, D412G shows the most robust enhancement of mTORC2 activity even under nonstimulation conditions, thus identifying a key residue important for interaction with the mTOR kinase domain. Interestingly, the cancer mutation analyses show that the D412G mutation and R81T with the mTOR kinase domain. Interestingly, the cancer mutation analyses show that the D412G mutation and R81T with the mTOR kinase domain, leading to membrane recruitment as well as relief of inhibition of mTORC2 by SIN1. The active mTORC2 phosphorylates and activates membrane-associated AKT. SIN1 can be phosphorylated by S6K and AKT to confer negative regulation on mTORC2. Cancer-associated mutations in SIN1 can potentiate mTORC2 activity by disrupting the inhibitory phosphorylation in SIN1 or interaction with mTOR.

Finally, compared with SIN1-WT, introduction of SIN1\(^{D412G}\) mutant into ovarian cancer cells that are depleted of endogenous SIN1 significantly increased AKT phosphorylation. These cells also show stronger oncogenic features, such as resistance to apoptosis-inducing and chemotherapeutic drugs, enhanced colony formation ability, and increased tumor growth in xenograft. Given that SIN1 phosphorylation is also compromised by a cancer patient–derived mutation, D412G, these observations support a notion that mutations in PI3K, AKT, and SIN1 affect a common pathway important for cancer development.

In summary, SIN1 can regulate mTORC2 in multiple ways: (i) it facilitates mTORC2 complex formation (1–3); (ii) it is responsible for recruiting certain mTORC2 substrates, including AKT and SGK (10); (iii) its PH domain directly receives the PI3K signal to activate mTORC2 (9); and (iv) its PH domain recruits mTORC2 to plasma membrane (9). Notably, SIN1 regulates mTORC2 activity in both positive and negative manners. The switch between negative and positive is dictated by PtdIns(3,4,5)\(^3\). Upon activation of PI3K, binding of the SIN1-PH domain by PtdIns(3,4,5)\(^3\) not only relieves its inhibition on the mTOR kinase but also promotes mTORC2 translocation to plasma membrane for phosphorylation of its physiologic substrates. The current study together with previous results establishes SIN1 as a critical signaling integrator for mTORC2 activity.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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REFERENCES

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