TACCCing on new functions for the TSC2 tumor suppressor
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Tuberous sclerosis complex (TSC) is a rare disease marked by a confusing range of clinical symptoms that can include hamartomas, neurological symptoms, renal cysts and (in females only) the pulmonary syndrome lymph-angioleiomyomatosis (LAM). TSC arises from mutations in one of two genes: TSC1, encoding hamartin, and TSC2, encoding tuberin.1-3 Although the mechanistic basis by which mutations in TSC1 and TSC2 induce disease was for a long time obscure, studies appearing over the past several years have identified multiple roles for their encoded proteins in restricting cell proliferation (reviewed in ref. 4). Among these, the role of a hamartin-tuberin heterodimer in restraining the action of the mammalian Target Of Rapamycin (mTOR) cell growth-promoting kinase has been the target of intense interest, and has led to promising therapeutic advances arising from the application of mTOR inhibitors to treat TSC in the clinic.1 More recent studies have also shown the TSC proteins stabilize the cell cycle kinase inhibitor p27(Kip1) to limit cell cycle progression from G1 to S (see ref. 6), suggesting an independent means by which mutation of TSC genes induces abnormal proliferation. However, some aspects of the pathological presentation of TSC have remained obscure. For example, mutations in TSC2 are typically associated with more severe clinical symptoms than mutations in TSC1,7 suggesting potentially broader action of tuberin than can be accounted for based solely on its role as a component of the tuberin-hamartin heterodimer.

In the last issue of Cell Cycle, work by Gómez-Baldó et al. potentially identifies one such TSC2/tuberin-specific function.8 The goal of this study was initially to illuminate the function of TACC3, a member of the Transforming Acidic Coiled-Coil domain family of proteins.9 TACC proteins are evolutionarily conserved from yeast to humans. As their family name implies, changes in their expression have been associated with cell transformation, with each of the three human members of the family (TACC1-3) localized to genomic regions amplified in some cancers, and with changes in TACC expression noted even in tumors lacking obvious DNA rearrangements. The TACC proteins are apparently non-catalytic, but contain multiple protein interaction domains. Previously defined partners for the interaction domains include notably ch-TOG/CKAP1 and Aurora kinases. These evolutionarily conserved interactors connect TACC proteins to regulation of processes including centrosome-dependent microtubule assembly and chromosomal alignment in mitosis, and appropriate completion of cytokinesis.6,10 The present work began by utilizing extensive two-hybrid screening and network construction to more fully analyze the scope of TACC3 functional associations. While a number of previously known partners were isolated, as well as new partners plausibly linked to TACC3 functions at centrosomes and microtubules, one of the most intriguing hits was TSC2/tuberin.5

In their study, Gómez-Baldó et al. demonstrate that intracellular pools of TACC3 and tuberin (but not hamartin) localize to the nuclear membrane and copurify with the nuclear membrane component lamin-A, show that tuberin binds directly to the nuclear pore component NUP62, and also find that siRNA depletion of tuberin or TACC3 induces striking defects in nuclear morphology. In further work, they establish that TACC3 helps anchor a mitotically-phosphorylated pool of tuberin to the spindle poles in mitosis, and to the intercellular bridge in cytokinesis. They again use siRNA to demonstrate that depletion of these proteins leads to abnormalities of post-mitotic abscission and increased numbers of binucleate cells, and that depletion of TACC3 or tuberin leads to the triggering of a CHFR-dependent mitotic checkpoint. Although lesions in TSC1/hamartin have also been linked to changes in centrosomes and mitotic-specific regulation, to date, the mechanisms involved appear to be distinct, involving instead associations with Polo-like kinases (PLKs).11,12

Finally, the authors identify a number of new TACC3 interactors that point to new functions for this protein that may be relevant to TSC2 biology. As one example, they have now identified interactions between TACC3 and CP110 and CEP164, centrosomal proteins that also regulate formation of the primary cell cilium. The cilium provides a docking platform for receptors for Hedgehog and other cell-extrinsic growth-regulatory signals. Interestingly, both TSC213,14 and the TACC3 partner Aurora-A15 regulate ciliary dynamics, while Aurora-A is also a direct target of CHFR in checkpoint initiation12 and has broad action in regulation of centrosomally-anchored signaling functions.17 These connections raise the possibility that TSC2/tuberin is part of a signaling network that controls cytoskeletal dynamics and ciliary-based signaling systems in addition to better-studied roles with TSC1/hamartin. Such long reach would certainly help explain the more severe presentation of TSC cases derived from TSC2 mutations. Overall, the study beautifully exemplifies the value of considering extended interaction networks in considering complex protein functions in disease, and joins with other such studies (see ref. 18) in identifying links between centrosomal defects and cancer.

References