of amino acids, localizes Rheb to the lysosome, where it can interact with mTORC1, Ragulator and the v-ATPase.[128]

In contrast to amino acid signaling, which regulates the localization of mTORC1, growth factor signaling is primarily mediated by the tuberous sclerosis complex (TSC). TSC is a GAP for Rheb, which inhibits the ability of Rheb to activate mTORC1; this inhibition is relieved by the action of insulin, which inhibits TSC activity.[129,130] TSC is phosphorylated by a number of kinases, including AKT, which regulates its activity. In the absence of growth factor signaling, TSC is localized to the lysosome; insulin stimulates the disassociation of TSC from the lysosomal surface.[131] While it was originally reported that amino acids do not alter the subcellular localization of TSC,[128] subsequent work suggests that numerous other stresses, including a lack of amino acids, promote the lysosomal accumulation of TSC.[132,133]

At least some of the many stimuli that regulate mTORC1 activity function by co-opting parts of these two regulatory mechanisms. For example, glucose activates mTORC1, an effect mediated by activation of the Rag proteins and that requires both Ragulator and the v-ATPase.[134] At least some other stimuli that regulate TSC, including oxygen and cellular energy levels, are likely to regulate TSC localization. Some stimuli regulate mTORC1 at multiple levels; for example, AMPK phosphorylates both Raptor and TSC2, which physically destabilizes mTORC1 while activating TSC to inhibit mTORC1 activity.[135,136] Adiponectin is an example of a hormonal stimulus that inhibits mTORC1 *via* activation of AMPK and the subsequent post-translational modification of TSC2 and Raptor (Figure 14.1).[137]

AKT is a major effector of PI3K signaling and regulates mTORC1 signaling *via* an inactivating phosphorylation of TSC2 as well as phosphorylation of PRAS40, which frees mTORC1 from inhibition by this protein.[13] As such, mTORC2, which phosphorylates AKT at three separate sites, is putatively upstream of mTORC1 in the insulin/IGF-1/PI3K signaling pathway.[75] mTORC2 is an effector of PI3K signaling—it was recently shown that mTORC2 is directly stimulated by phosphatidylinositol (3,4,5)-trisphosphate (PIP_3)[138]—and as such mTORC2 is activated by stimuli including insulin, IGF-1, and leptin (Figure 14.1).[28,139] mTORC2 is also stimulated by palmitoleic acid, a substrate for fatty acid elongase-5 (Elovl5),[140] by substrates of glycerol-3-phosphate acyltransferase-1 (Gpat1),[141] and by association with ribosomal protein subunits.[142] While mTORC2 has been shown to localize to the ribosome-rich mitochondria-associated endoplasmic reticulum,[143] mTORC2 was also recently identified at the lysosome,[144] suggesting the possibility that both mTOR complexes might be regulated by lysosomal-mediated nutrient sensing.

14.7 How Can mTORC1 Be Specifically Targeted?

One possible way to approach the development of mTORC1-specific inhibitors is to focus on the regulatory steps required to activate mTORC1. Notably, mTORC1 activation seems to require the lysosomal localization of mTORC1,