



PI3-K/Akt signaling showing multiple inputs, outputs, and crosstalk. PI3K is activated by a number of mechanisms, including growth factor receptors, integrins, and Ras, converting phosphatidylinositols (*PIP*) to phosphatidylinositol-3-phosphates. This action of PI3K is antagonized by the tumor suppressor phosphatase and tensin homologue (*PTEN*). AKT (thymoma in AKR mouse/protein kinase B) binds through its pleckstrin homology domain to phosphatidylinositol-3-phosphates and is activated by phosphorylation by phosphoinositide-dependent protein kinase 1 (*PDK1*) and mammalian target of rapamycin (*mTOR*)/rictor. Heat shock protein 90 (*HSP90*) binds to Akt to regulate Akt levels. Akt phosphorylates multiple downstream targets, including focal adhesion kinase (*FAK*), inducible nitric oxide synthase (*iNOS*), and I kinase (*IKK*), thus regulating nuclear factor- B (NF- B), BAD, and Bcl-xl (B-cell lymphoma mutant, extra long), forkhead transcription factor (*FKHR*), glycogen synthase kinase-3 (*GSK-3*), murine double minute 2 (*MDM2*), mammalian target of rapamycin, and thus eukaryotic initiation factor 4E (eIF4E) binding protein (*4E-BP*) and ribosomal S6 protein kinase (*S6K*), Ras homologue enriched in brain (Rheb). RSK, ribosomal S6 kinase; PKC, protein kinase c; SGK, serum and glucocorticoid induced kinase; Glut-4, glucose transporter-4; RAC1, Ras-related C3 botulinum toxin substrate 1; CDC42, cell division cycle 42. The cell functions modulated by the different signaling pathways are indicated. There are a number of PI3K and Akt signaling inhibitors in development (*red ovals*) and cancer drugs with which they might be combined.

[Powis, G. et al. Clin Cancer Res 2006;12:2964-2966](#)