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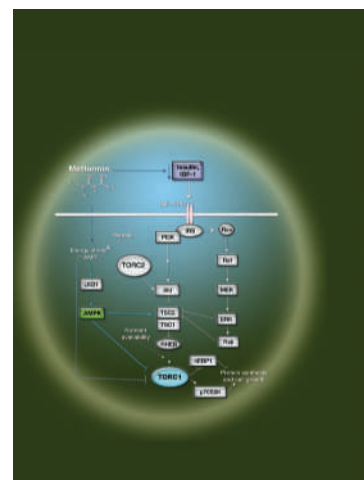
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## ABOUT THE COVER

The diagram reflects potential and known effects of the diabetes drug metformin (one of the most commonly used drugs in the world) on important molecular pathways of carcinogenesis in cells. The mammalian target of rapamycin (mTOR) exists in TOR complex 1 (TORC1) and TORC2. TORC1 controls cell growth through phosphorylating p70 S6 kinase (p70S6K) and 4E-binding protein 1 (4EBP1). Various inputs of TORC1 regulation appear to directly affect the TSC1-TSC2 complex, which controls activation of the Ras homologue enriched in brain (RHEB) protein that directly activates TORC1. Growth factor signaling (through phosphatidylinositol 3-kinase [PI3K]/Akt and extracellular signal-regulated kinase [ERK]/ribosomal S6 kinase [Rsk] signaling) and energy homeostasis (through AMP-activated protein kinase [AMPK]) directly phosphorylate TSC2. *In vivo*, metformin downregulates TORC1 possibly via both AMPK-dependent mechanisms and AMPK-independent mechanisms (dotted blue line from "Energy stress") or via its effect of decreasing levels of circulating insulin and insulin-like growth factor (IGF), which decreases activation of the IGF-1 receptor (IGF-1R)/insulin receptor (IR), leading in turn to suppression of PI3K and Ras signaling. See articles by Memmott et al. (beginning on page 1066), Hosono et al. (beginning on page 1077), Pollak (beginning on page 1060), and Engelman and Cantley (beginning on page 1049) for more information.



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