**AMPK directly activates mTORC2 in response to energetic stress and**

**promotes cell survival**

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The AMP-activated protein kinase (AMPK) is a sensor of energy status in the cell. Upon activation in response to metabolic stresses, AMPK maintains cellular energy balance by promoting energy generating catabolic pathways and suppressing ATP-consuming anabolic processes. mTOR (Mechanistic target of rapamycin) is a cytosolic signaling kinase which responds to a variety of environmental stimuli, including growth factors, such as insulin, nutrients, such as amino acids, and stresses, including energy stress. mTOR is the catalytic core of at least two, distinct multiprotein complexes called mTOR Complex 1 and mTOR Complex 2. mTORC1 has been studied a great deal. In contrast, mTORC2 is a poorly understood mTOR-containing complex, and knowledge of upstream activators of mTORC2 is very limited. We found that AMPK directly associates with mTORC2, phosphorylates mTOR and possibly other partner proteins within mTORC2 complex and activates mTORC2 in response to energetic stresses. A diverse array of AMPK activators increase mTORC2 signaling in an AMPK-dependent manner in cultured cells. Activation of AMPK with the type II diabetes drug metformin also increased mTORC2 signaling in primary hepatocytes in an AMPK dependent manner. AMPK-mediated activation of mTORC2 does not result from AMPK-mediated suppression of mTORC1 and thus reduced negative feedback on PI3K flux. By two-stage in vitro kinase assay, phosphorylation of mTORC2 by recombinant AMPK was sufficient to increase mTORC2 catalytic activity toward Akt. Hence, AMPK phosphorylates mTORC2 components directly to increase mTORC2 activity and downstream signaling. We have identified mTOR S1261 as a substrate of AMPK, but phosphorylation of mTOR S1261 is not required for AMPK-mediated activation of mTORC2. Functionally, inactivation of AMPK, mTORC2, and Akt increased apoptosis during acute energetic stress. By activating mTORC2 to increase cell survival, these data provide a mechanism for how AMPK paradoxically promotes tumorigenesis in certain contexts despite its tumor suppressive function through inhibition of growth promoting mTORC1. Collectively, these data unveil mTORC2 as a new target of AMPK and the AMPK-mTORC2 axis as a new promoter of cell survival during energetic stress.