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PINK1/BRPK inhibits apoptotic cell death and enahances cellular invasiveness through an activation of mTORC2 pathway

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The PINK1/BRPK gene encodes a serine/threonine kinase with a mitochondrial localization signal. Mutations in the gene is causatively linked to an autosomal recessive form of Parkinson's disease (PD). We showed that PINK1/BRPK was expressed at a higher level in cancer cell lines with higher metastatic potential. When overexpressed, PINK1/BRPK blocked apoptotic cell death of cancer cells induced by various agents, including oxidative stress. Overexpression of wild-type PINK1/BRPK induced phosphorylation of Akt, an important anti-apoptotic protein. PINK1/BRPK protein is mostly localized in the mitochondria, but the protein is also detected in the cytoplasm and co-precipitated with Akt. Application of an Akt inhibitor abrogated the anti-apoptotic effect of PINK1/BRPK. Blocking the EGF receptor-PI3 kinase pathway, an authentic upstream pathway for Akt activation, did not affect phosphorylation of Akt by PINK1/BRPK, indicating that PINK1/BRPK activates Akt through a mechanism independent from the receptor-PI3 kinase pathway.

Another known upstream effector for Akt is mTORC2. We therefore examined mTORC2 in SH-SY5Y cells with overexpression of PINK1. PINK1/BRPK was co-precipitated with components of mTORC2 but not with a component of mTORC1. Prolonged treatment with rapamycin that is known to inhibit mTORC2 cancelled the effect of PINK1/BRPK, while brief treatment with rapamycin that is specific to mTORC1 showed no effect. Furthermore, overexpression of PINK1/BRPK enhanced cellular invasiveness in vitro. These results indicate that mTORC2 is a critical molecule to mediate the anti-apoptotic and pro-metastatic activity of PINK1/BRPK.

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