TMBIM6 regulates the assembly and activation of mTORC2

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Mechanistic target of rapamycin (mTOR) is a central regulator of signals controlling cellular growth and metabolism. Although mTORC1 signalling has been frequently studied, the molecular basis and signalling for mTORC2 activation remain to be clarified. Here, we identified that mTORC2 activation is regulated through transmembrane BAX inhibitor motif containing 6 (TMBIM6) on the endoplasmic reticulum (ER). TMBIM6 is directly binding to RICTOR as a central protein of mTORC2 signalling pathway. TMBIM6 is as a crucial component in ER-associated mTORC2 activation manner, and its expression increases in several cancers. We demonstrate that TMBIM6-associated mTORC2 activation enhances glycolysis, the pentose phosphate pathway, protein synthesis, and the expression of lipid synthesis genes and glycosylated proteins. TMBIM6 ablation or knockdown restricts primary tumour growth and stimulates regression. A new small molecule inhibitor of TMBIM6, BIA, reduces its binding to mTORC2, decreasing mTORC1 and mTORC2 activity. Notably, this compound suppresses the formation and maintenance of tumours in a breast cancer cell implanted model. Our results uncover a new signalling cascade that enhances mTORC2 activity through its interaction with TMBIM6 and has implications for understanding tumorigenesis.