Apoptosis

**Major finding:** BAP1 and PTEN prevent IP3R3 degradation, increasing Ca\(^{2+}\)-flux and apoptosis to suppress tumor growth.

**Mechanism:** BAP1 deubiquitinates IP3R3 and PTEN competes with FBXL2 for IP3R3 binding to promote IP3R3 stabilization.

**Impact:** Inhibiting IP3R3 degradation may be a potential therapeutic strategy in BAP1- or PTEN-deficient tumors.

**BAP1 AND PTEN STABILIZE IP3R3 TO PROMOTE CA\(^{2+}\)-MEDIATED APOPTOSIS**

The type 3 inositol-1,4,5-triphosphate receptor (IP3R3) controls calcium (Ca\(^{2+}\)) release from the endoplasmic reticulum (ER) to the mitochondria. Persistent Ca\(^{2+}\) release overloads the mitochondria and results in apoptosis. Related studies identified two tumor suppressor proteins, BAP1 and PTEN, that promote IP3R3-mediated Ca\(^{2+}\) flux to promote apoptosis and suppress oncogenic transformation. Bononi and colleagues found that BAP1 binds to and deubiquitinates IP3R3 at the ER, thereby stabilizing IP3R3, enhancing Ca\(^{2+}\) flux, and promoting apoptosis. BAP1+ fibroblasts exhibited reduced IP3R3 protein levels, decreased mitochondrial Ca\(^{2+}\) uptake, and reduced apoptosis compared to wild-type fibroblasts. BAP1 also exhibited nuclear activity, and BAP1 depletion impaired DNA damage repair, resulting in enhanced DNA damage. Although these cells accumulated increased DNA damage, they could not execute apoptosis due to reduced mitochondrial Ca\(^{2+}\). In primary human mesothelial cells, asbestos exposure promoted malignant transformation, which was increased by depletion of IP3R3 or BAP1, although BAP1 depletion had a stronger effect due to its additional nuclear function. Kuchay, Giorgi, and colleagues found that PTEN also prevents IP3R3 degradation. Mechanistically, PTEN competed with FBXL2 for IP3R3 binding, and, as FBXL2 promoted proteasome-mediated degradation of IP3R3, PTEN binding stabilized IP3R3. FBXL2 depletion increased Ca\(^{2+}\) release from the ER and sensitized cells to apoptosis. Conversely, PTEN loss promoted FBXL2-mediated degradation of IP3R3, and PTEN reconstitution, irrespective of its phosphatase activity, stabilized IP3R3 to induce Ca\(^{2+}\) mobilization and apoptosis. Moreover, expression of PTEN and IP3R3 were correlated in human prostate cancer. In prostate cancer xenografts, a nondegradable IP3R3 mutant or an inhibitor that disrupted FBXL2 membrane localization sensitized tumors expressing low levels of PTEN to photodynamic therapy, which induces Ca\(^{2+}\)-dependent cytotoxicity. Taken together, these studies elucidate mechanisms by which BAP1 or PTEN stabilize IP3R3 to promote mitochondrial Ca\(^{2+}\) overload and apoptosis, thereby limiting tumor growth. These findings suggest the possibility for drugs that stabilize IP3R3 to treat BAP1- or PTEN-deficient tumors.

**Metabolism**

**Major finding:** mTORC2 controls glutamate and glutathione metabolism in cancer cells by phosphorylating xCT.

**Mechanism:** Phosphorylation at serine 26 inhibits xCT activity, reducing glutamate secretion and cystine uptake.

**Impact:** mTORC2-mediated regulation of xCT links growth factor signaling to amino acid metabolism in cancer.

**mTORC2 REGULATES THE CYSTEINE–GLUTAMATE ANTIPORTER xCT**

Amino acid metabolism is often dysregulated in cancer, but the underlying molecular mechanisms have not been fully elucidated. The cystine–glutamate antipporter xCT (encoded by SLC7A11) is a transmembrane protein that interacts with CD98 to form the system x\(_{\text{c}}\)-transporter, which takes up cystine in exchange for glutamate, and xCT is highly expressed in multiple tumor types. To uncover potential mechanisms of xCT regulation, Gu and colleagues performed an unbiased mass spectrometry screen to identify xCT binding partners. In glioblastoma, lung cancer, and triple-negative breast cancer cell lines, xCT was associated with the mTORC2 complex components mTOR and Rictor, but not mTORC1 complex–specific components, suggesting that mTORC2 may regulate xCT activity. Indeed, in response to EGFR signaling, mTORC2 phosphorylated xCT at serine 26 in the cytosolic N terminus, resulting in inhibition of xCT activity and reduced glutamate secretion. Conversely, in cancer cell lines with high levels of xCT and mTORC2 activity, mTORC2 inhibition, via Rictor depletion or treatment with the mTOR kinase inhibitor Torin1, increased glutamate secretion and cystine uptake, suggesting enhanced xCT activity. Further, Torin1 treatment increased the incorporation of cystine into glutathione, which plays a critical role in buffering reactive oxygen species in nutrient-depleted conditions and in anabolic reactions when nutrients are available. Thus, reducing glutathione levels via xCT knockdown and Torin1 treatment promoted glioblastoma cell death. Collectively, these findings reveal a mechanism by which mTORC2 regulates cystine uptake and glutathione metabolism via xCT phosphorylation, thereby linking growth factor signaling to amino acid metabolism in cancer.


---

*Published OnlineFirst June 30, 2017; DOI: 10.1158/2159-8290.CD-RW2017-122*
BAP1 and PTEN Stabilize IP3R3 to Promote Ca\textsuperscript{2+}-Mediated Apoptosis

*Cancer Discov* 2017;7:793. Published OnlineFirst June 30, 2017.

Updated version  Access the most recent version of this article at:
doi:10.1158/2159-8290.CD-RW2017-122

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, use this link http://cancerdiscovery.aacrjournals.org/content/7/8/793.1. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.