Researchers find novel therapeutic target for specific cancer treatment

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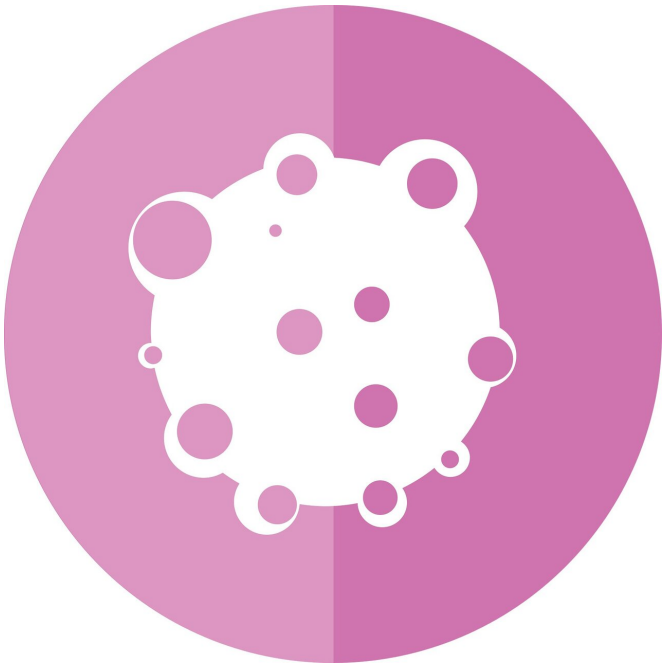

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Mount Sinai researchers uncovered a mechanism that tumor cells exploit selective autophagy for metabolic reprogramming that benefits tumor cell growth and offers resistance to glucose deprivation. The study suggests that AKAP220-mediated autophagy as a novel therapeutic target for specific cancer treatment.

Autophagy is a lysosome degradation pathway that is cytoprotective through recycling of intracellular cargoes and supplying the breakdown products. The researchers now show a novel mechanism that autophagy selectively degrades PKA inhibitory subunit RIa, which is mediated through AKAP11 receptor in response to energy crisis. The AKAP11-mediated degradation of RIa and cAMP/PKA activation result in heightened mitochondrial metabolism in response to glucose starvation and subsequent protection of cell survival. Importantly, they show that suppression of AKAP11 levels in tumor cells prevents the degradation of RIa and blocks PKA activation, therefore causing inhibition of tumor cell growth.

The study shows a new concept of autophagy-mediated cell protection and tumor growth by disinhibiting protein kinase A (PKA), a master regulator of cell metabolism, and promoting mitochondria metabolic rewiring. Multiple lines of evidence demonstrate activation of PKA in tumors and activation of PKA drives tumorigenesis. These studies reveal a novel therapeutic target in the treatment of certain cancers by blocking autophagy-mediated PKA activation.

This study uncovers a cytoprotection mechanism whereby autophagy controls cell metabolism beyond production of digested nutrient for cell replenishment and survival. the authors identify a critical role of autophagy in boosting the activity of cAMP/PKA, a master regulator of cell metabolism, to maintain cell survival during energy crisis. They show that autophagy selectively degrades PKA inhibitory subunit RI?, which is mediated through AKAP11 receptor. The AKAP11—mediated cAMP/PKA activation result in heightened mitochondrial metabolism in response to glucose starvation and subsequent protection of cell survival. They also show that suppression of AKAP11 levels in tumor cells prevents the degradation of RI? and consequently blocks PKA activation, therefore causing inhibition of tumor cell growth. They conclude that tumor cells exploit selective autophagy that degrades AKAP11 and activates PKA for their growth and resistance to glucose deprivation."

Said Mount Sinai's Dr. Zhenyu Yue of the research:"Our results thed a light on autophagy protection mechanism by demonstrating a critical function of autophagy in fueling the mitochondrial metabolism and conferring cell resistance to glucose deprivation in growth. Our studies thus

reveal a novel therapeutic target of AKAP11 selective autophagy in the treatment of certain cancers."

More information: Zhiqiang Deng et al, Selective autophagy of AKAP11 activates cAMP/PKA to fuel mitochondrial metabolism and tumor cell growth, *Proceedings of the National Academy of Sciences* (2021). DOI: 10.1073/pnas.2020215118

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