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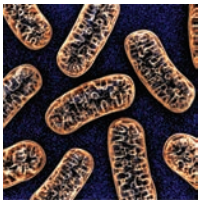
Metabolism

Major Finding: The ability of mitochondrial complex III to oxidize ubiquinol was essential to tumor growth *in vivo*.

Concept: Long thought dispensable for tumor growth, the mitochondrial electron transport chain was critical.

Impact: This work bolsters ongoing phase III trials of mitochondrial complex I and TCA cycle inhibitors.

MITOCHONDRIAL OXIDATION OF UBIQUINOL IS REQUIRED FOR TUMORIGENESIS



Although mitochondrial metabolism has typically been viewed as dispensable for cancer cells, recent evidence suggests that function of the mitochondrial electron transport chain (ETC) is required for tumor growth. Martínez-Reyes and colleagues investigated the mechanism underlying this phenomenon using mouse lung adenocarcinoma cells, a human osteosarcoma cell line, and Notch transformed leukemic cells that were deficient in mitochondrial ETC complex III. These cells were not capable of establishing tumors in mice, implying an important role for mitochondrial complex III for tumor growth *in vivo*. Ectopic expression of sea squirt (*Ciona intestinalis*) alternative oxidase (AOX), which can substitute for the function of mitochondrial complex III in oxidizing ubiquinol (an electron-rich form of Coenzyme Q10) to ubiquinone, rescued the phenotype of cytochrome b–deficient osteosarcoma cells, restoring their oxygen consumption rate, tricarboxylic acid (TCA) cycle function, and ability to develop into tumors *in vivo*. The ubiquinone normally produced by mitochondrial complex III is essential for the function of mitochondrial complex I, and loss of mitochondrial complex I function caused by an inactivating mutation affecting the essential mitochondrial complex I component NDUFS2 rendered AOX-rescued, cytochrome b–deficient osteosarcoma cells incapable of growing tumors *in vivo*. This effect was dependent on NAD^+ and not mitochondrial ATP generation: Tumor growth potential was restored in NDUFS2-null AOX-rescued cytochrome b–deficient osteosarcoma cells that were capable of NAD^+ regeneration due to ectopic expression of *Lactobacillus brevis* NADH oxidase. Collectively, these data suggest a critical role for mitochondrial complex III and the ETC in tumor growth due to TCA cycle function but not ATP production. Further, these results support the ongoing investigation of mitochondrial complex I inhibitors and TCA cycle inhibitors as chemotherapeutic agents in phase III clinical trials. ■

Martínez-Reyes I, Cardona LR, Kong H, Vasan K, McElroy GS, Werner M, et al. Mitochondrial ubiquinol oxidation is necessary for tumour growth. Nature 2020 Jul 8 [Epub ahead of print].

Clinical Trials

Major Finding: The ATR inhibitor berzosertib produced responses with or without the DNA-damaging agent carboplatin.

Concept: In this 40-patient phase I trial, one patient in the monotherapy group showed a complete response.

Impact: Berzosertib appears safe, and ATR inhibitors warrant further study with or without DNA-damaging drugs.

BERZOSERTIB IS SAFE, WITH SIGNS OF EFFICACY AGAINST ADVANCED SOLID TUMORS

Inhibitors of the serine/threonine protein kinase ATR, a mediator of the DNA-replication stress response, are under investigation for a variety of malignancies. Preclinical evidence has suggested that ATR inhibitors may synergize with chemotherapeutic drugs that inhibit DNA repair, prompting Yap and colleagues to initiate a phase I trial of the ATR inhibitor berzosertib (M6620) with or without carboplatin in patients with advanced solid tumors. One patient in the monotherapy group experienced a complete response with no progression by the time of last assessment (29 months) and one patient in the combination-therapy group experienced a partial response lasting 6 months. Notably, heavily pretreated disease was the norm among these patients, including the one who experienced a complete response and the one who experienced a partial response. The patient who experienced a complete response had immunohistochemistry-confirmed loss of ARID1A (along with *ARID1A* mutation) and ATM, and had mismatch-repair deficiency. Additionally, the patient experiencing a partial response had a germline *BRCA1* mutation, and her ovarian cancer was platinum-refractory and had progressed twice on two different PARP inhibitor regimens. Stable disease was the best response among 29.4% of those who received berzosertib alone and 71.4% of those who received the combination treatment. The most common treatment-emergent adverse events deemed to be related to treatment were flushing, nausea, pruritus, headache, and infusion reactions in the berzosertib monotherapy group and hematologic abnormalities (including neutropenia, thrombocytopenia, and anemia) in the group receiving combination therapy. In summary, the ATR inhibitor berzosertib appears safe alone or in combination with carboplatin and shows signs of efficacy in patients with heavily pretreated advanced solid tumors, suggesting that further study of this or other ATR inhibitor–DNA-damaging drug combinations is warranted. ■

Yap TA, O'Carrigan B, Penney MS, Lim JS, Brown JS, de Miguel Luken MJ, et al. Phase I trial of first-in-class ATR inhibitor M6620 (VX-970) as monotherapy or in combination with carboplatin in patients with advanced solid tumors. J Clin Oncol 2020 Jun 22 [Epub ahead of print].

AACR American Association for Cancer Research

CANCER DISCOVERY

Berzosertib Is Safe, with Signs of Efficacy against Advanced Solid Tumors

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