Melanoma

Major Finding: Melanoma cells exploit both genetic and nongenetic mechanisms of resistance to MAPK inhibition.

Concept: Cells persisting during treatment exhibit a neural crest–like state and can be targeted by FAK inhibition.

Impact: Resistance to MAPK inhibition is governed by the cellular composition of minimal residual disease.

MELANOMA ENGAGES GENETIC AND NONGENETIC DRUG RESISTANCE TRAJECTORIES

Resistance to cancer drugs emerging from minimal residual disease (MRD) or drug-tolerant cells happens via both genetic and nongenetic mechanisms. However, little is currently known about the molecular features that determine which of these routes will prevail and lead to relapsed disease. Marin-Bejar, Rogiers, and colleagues analyzed whole-exome sequencing data from 64 *BRAF*-mutant melanoma samples that progressed after treatment with MAPK pathway inhibitors, finding that 20% of samples contained no known genetic alterations conferring resistance. RNA sequencing of samples from 49 matched untreated and RAF/MEK inhibitor–treated patients with melanoma showed that 28% of patients showed enrichment of a neural crest stem cell (NCSC) signature post-treatment that was present in patients who had partially responded, but absent in nonresponders. *BRAF*-mutant patient-derived xenograft (PDX) models exposed to MAPK pathway inhibitors initially experienced inhibition of tumor growth, followed by eventual progression. Targeted sequencing of these tumors revealed both genetic and nongenetic drug resistance trajectories, with IHC analysis of key NCSC markers showing no enrichment in lesions from genetic resistance PDXs. Further analysis of the NCSC-like cell population in nongenetic resistance PDXs showed selective activation of focal adhesion kinase (FAK) signaling with GDNF-dependent AKT activation. Treatment of PDX-bearing mice with FAK inhibitors ablated the NCSC population, delaying the emergence of MAPK-therapy resistance and relapse. Sequencing of these samples upon relapse revealed a trajectory switch, with 8 of 9 samples showing the emergence of genetic alterations indicative of reactivation of ERK signaling that conferred increased sensitivity to ERK inhibition compared with MAPK inhibitor–only resistant primary samples. In addition to demonstrating the ability of melanoma cells to evolve genetic and nongenetic pathways of treatment resistance, these findings point to a potential therapeutic approach to target the nongenetic resistance trajectory in melanoma. ■

Marin-Bejar O, Rogiers A, Dewaele M, Femel J, Karras P, Pozniak J, et al. Evolutionary predictability of genetic versus nongenetic resistance to anticancer drugs in melanoma. Cancer Cell 2021 Jun 17 [Epub ahead of print].

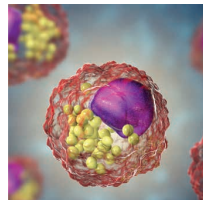
Metabolism

Major Finding: Omega-3 polyunsaturated fatty acids (PUFA) selectively killed cancer cells in acidic conditions.

Mechanism: PUFAs exceeded lipid droplet buffering capacity, inducing lipid peroxidation–mediated ferroptosis.

Impact: This work sheds light on PUFA supplementation and suggests dietary PUFA as an adjuvant strategy.

EXCESS POLYUNSATURATED FATTY ACIDS INDUCE DEATH IN ACIDIC CANCER CELLS



Therapeutic modalities that exploit tumor metabolic reprogramming are of increasing interest, with researchers exploring dietary modification and supplementation to control nutrient utilization in tumors. Although an association has been reported between consumption of dietary omega-3 (n-3) polyunsaturated fats (PUFA) and lower cancer-associated deaths in certain cohorts, the potential efficacy of dietary PUFAs is not well understood. To investigate how supplementation of specific PUFAs might exert cytotoxic effects, Dierge and colleagues cultured cancer cells in acidic (pH 6.5) or neutral (pH 7.4) media to mimic tumor acidosis and found that acid-adapted cancer cells had a higher capacity to accumulate n-3 and n-6 PUFAs into lipid droplets. Long-term exposure to PUFAs inhibited cancer cell growth in monolayer culture, whereas PUFAs caused cytotoxicity in three-dimensional tumor spheroids, in which cells at the spheroid core were exposed to acidosis. Culturing spheroids in media containing bicarbonate or buffered at a more alkaline pH abrogated the cytotoxic effect of PUFAs. PUFA exposure increased levels of lipid peroxidation, suggesting that excess PUFA uptake led to cytotoxicity attributable to lipid peroxidation damage. Given that lipid peroxidation is associated with ferroptosis, the ferroptosis inducer erastin enhanced PUFA-mediated cytotoxicity, whereas ferroptosis inhibitors including ferrostatin-1 inhibited cytotoxicity, supporting ferroptosis as the primary mode of cell death. To understand the function of PUFA accumulation, lipid droplet formation was blocked by diacylglycerol *O*-acyltransferase 1 inhibitors (DGAT1i), which prevented PUFA buffering and therefore increased lipid peroxidation. Indeed, DGAT1i enhanced the anticancer effects of n-3 or n-6 PUFAs, increasing ferroptosis-dependent cytotoxicity. In a murine xenograft model of colorectal carcinoma, mice were fed isocaloric diets based on olive oil (monounsaturated fatty acid) or concentrated fish oil (PUFA). A PUFA-rich diet inhibited tumor growth and extended survival, whereas the combination of a PUFA-rich diet and DGAT1i administration enhanced these phenotypes. Together, this work highlights dietary n-3 PUFA supplementation as a potential anticancer strategy to combine with other pharmacologic approaches. ■

Dierge E, Debock E, Guilbaud C, Corbet C, Mignolet E, Mignard L, et al. Peroxidation of n-3 and n-6 polyunsaturated fatty acids in the acidic tumor environment leads to ferroptosis-mediated anticancer effects. Cell Metab 2021 Jun 11 [Epub ahead of print].