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Letter to the Editor

Cancer Research

Extracellular Citrate and Cancer Metabolism—Letter

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Dr. Mycielska and colleagues have recently reported that extracellular citrate supports cancer development (1). Using different cell lines, including human pancreatic and gastric cancer cells, they observed that cancer cells cultured in standard conditions with adjunction of physiologic concentrations of citrate (200 μmol/L), take up greater amounts of citrate than normal cells, in particular, under hypoxia and low glucose concentrations. Citrate is taken up by the citrate plasma membrane carrier pmCiC, which is inhibited by gluconate. Inhibition of pmCiC reduces growth of human pancreatic tumors implanted subcutaneously in mice. Thus, citrate metabolism is suggested as a possible target for development of new cancer therapies, in particular, by inhibition of its specific plasma membrane carrier.

An apparently opposite strategy merits however to be discussed. Although inhibition of transportation of citrate at physiologic concentration has an antineoplastic effect, administration of high concentrations of citrate (approximately 50-fold higher) also has an antineoplastic effect.

The rationale of this strategy considers that the Warburg effect decreases the mitochondrial production of citrate. Thus, increasing intracellular concentration of citrate could arrest glycolysis, proliferation, dedifferentiation, and aggressiveness of cancer cells (4). Several studies (2–5) showed that citrate inhibits proliferation of multiple cultured cancer cells (ovarian, mesothelioma, pancreas, lung, stomach, melanoma, etc.) at the concentration of 10 mmol/L by (i) activation of caspases 2 or 8 and inhibition of Mcl-1, promoting apoptosis; (ii) decreasing ATP production through inhibition of key enzymes of glycolysis and of tricarboxylic acid cycle; and (iii) increasing sensitivity of tumor cells to cisplatin. Recent findings made by Ren and colleagues (5) confirmed that citrate decreases chemoresistance to cisplatin, in particular, by reducing the expression of MUC-1 (5). Citrate inhibits the proliferative IGF-1R/PI3K/AKT axis, thus activating the suppressive PTEN-eIF2α pathway, and induces tumor cell differentiation (expression of E-cadherin). Importantly, daily oral administration of citrate for 7 weeks at dose of 4 g/kg/day reduces tumor growth of several xenografts in mice [Ras-driven lung tumor, pancreatic tumor (Pan02), and Her2/Neu mammary cancer] and increases significantly the number of infiltrating tumor T cells, with no significant side effect. Plasma level of citrate associated with tumor regression was 3 mmol/L, roughly 8-fold of what was noted in noncitrate-treated animals (5).

All these studies provide arguments to consider that increasing intracellular concentration of citrate (either by administration of high-dose citrate and/or by ATP-citrate lyase inhibition) may be also an interesting anticancer approach.

Further studies are needed to define the place of each of these apparently opposite strategies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Mycielska ME, Dettmer K, Rümmele P, Schmidt K, Prehn C, Milenkovic, et al. Extracellular citrate affects critical elements of cancer cell metabolism and supports cancer development *in vivo*. Cancer Res 2018;78:2513–23.
2. Zhang X, Varin E, Allouche S, Lu Y, Poulain L, Icard P. Effect of citrate on malignant pleural mesothelioma cells: a synergistic effect with cisplatin. Anticancer Res 2009;29:1249–54.
3. Kruspig B, Nilchian A, Orrenius S, Zhivotovsky B, Gogvadze VCitrate kills tumor cells through activation of apical caspases. Cell Mol Life Sci 2012;69:4229–37.
4. Icard P, Lincet H. The reduced concentration of citrate in cancer cells: an indicator of cancer aggressiveness and a possible therapeutic target. Drug Resist Updat 2016;29:47–53.
5. Ren JG, Seth P, Ye H, Guo K, Hanai JL, Husain Z, et al. Citrate suppresses tumor growth in multiple models through inhibition of glycolysis, the tricarboxylic acid cycle and the IGF-1R pathway. Sci Rep 2017;3:4537.

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