Letter to the Editor

Cancer Research

Extracellular Citrate and Cancer Metabolism—Response

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In response to our recent article showing that cancer cells take up extracellular citrate through the plasma membrane-specific variant (pmCiC) of the mitochondrial citrate transporter and that depriving cancer cells of extracellular citrate by blocking pmCiC activity results in a decreased tumor growth (1), Icard and colleagues (2) have raised the interesting point that very high concentrations (50× physiologic levels) of extracellular citrate lead to cancer cell overloading, which also deters cancer growth. Although these approaches seem contradictory, they are actually based on the same ability of cancer cells to specifically import extracellular citrate (1). Both the "low" and "high" citrate uptake approaches do make sense, because low uptake limits citrate availability for critical cancer cell metabolic processes such as fatty acid synthesis (1), and high intracellular citrate levels inhibit glycolysis and disturb other cellular functions, which are also important for cancer cells (2). Therefore, disturbing intracellular citrate levels in either direction can have detrimental effects on cancer cells.

The question is then how to therapeutically manipulate extracellular citrate uptake. Simply aiming to therapeutically decrease or increase citrate levels in blood could result in some unwanted side effects *in vivo* by upsetting divalent ion chelation (3), or by affecting specialized healthy cells such as hepatocytes and neurons, which also depend on extracellular citrate, but via completely different families of citrate transporters (4, 5). Importantly, we suggest that a promising way to specifically attack cancer cells in this respect is to target the pmCiC by either decreasing (1) or enhancing its function. We have found that gluconate blocks the pmCiC, but so-called therapeutic "openers" may eventually be found that cause excessive citrate uptake. The advantage of targeting the pmCiC is that its expression is mainly restricted to cancer cells in humans, and is particularly high in metastases and sites of invasion (1).

Therefore, we agree with Icard and colleagues (2) that either decreasing or increasing extracellular citrate uptake by cancer cells is an interesting option for cancer therapy. In addition, we suggest that therapeutically targeting the pmCiC is a scientifically sound option for achieving tumor-specific effectiveness.

Disclosure of Potential Conflicts of Interest

M.E. Mycielska and E.K. Geissler have ownership interest (including stock, patents, etc.) in a patent titled "plasma membrane citrate transporter for use in the diagnosis and treatment of cancer" (patent application; no. EP15767532.3 and US15/514,255; status patent pending.

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References

1. Mycielska ME, Dettmer K, Rümmele P, Schmidt K, Prehn C, Milenkovic VM, et al. Extracellular citrate affects critical elements of cancer cell metabolism and supports cancer development *in vivo*. Cancer Res 2018;78:2513–23.
2. Icard P, Fournel L, Alifano M, Lincet H. Extracellular citrate and cancer metabolism—letter. Cancer Res 2018;78:5176.
3. Mycielska ME, Milenkovic VM, Wetzel CH, Rümmele P, Geissler EK. Extracellular citrate in health and disease. Curr Mol Med 2015;15:884–91.
4. Wada M, Shimada A, Fujita T. Functional characterization of Na+-coupled citrate transporter NaC2/NaCT expressed in primary cultures of neurons from mouse cerebral cortex. Brain Res 2006;1081:92–100.
5. Gopal E, Miyauchi S, Martin PM, Ananth S, Srinivas SR, Smith SB, et al. Expression and functional features of NaCT, a sodium-coupled citrate transporter, in human and rat livers and cell lines. Am J Physiol Gastrointest Liver Physiol 2007;292:G402–8.

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