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VIEW ON NEWS

Revisiting vitamin C in cancer therapy: Is "C" for cure, or just wishful thinking?

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Abstract We devoted this short piece to highlight one recent article published in Science, which revisited the anti-cancer efficacy of high-dose vitamin C. Using isogeneic KRAS- and BRAF-mutated colorectal cell lines, the authors were able to demonstrate selective anti-tumor effects among the KRAS- and BRAF-mutated cells in culture and in ex-planted animal models treated with high-dose vitamin C. Their elegant and in-depth studies unequivocally tied the tumoricidal effect to the heightened sensitivity of the mutant cells due to the increased vitamin C uptake, leading to lethal accumulation of reactive oxygen species (ROS). This report will certainly rekindle enthusiasm in revisiting the case of vitamin C, pushing for more definitive cancer therapy trials.

For decades, high-dose vitamin C, in either the oral or intravenous form, has been examined for its efficacy in anti-cancer therapy.[1] So far, the studies of vitamin C have been plagued with inconsistencies. When it was used alone in *in vitro* and animal tests, high-dose vitamin C appeared to show beneficial effects in suppressing the growth of certain types of cancer cells. However, the combinations of vitamin C with other chemotherapeutic agents largely failed to show a complementary effect. Decades of clinical trials dating back to the late 1970s met the same ill fate. Vitamin C, either as a stand-alone agent or in combination with other clinically approved chemotherapeutic agents, has yet to prove itself a "cure" in anti-cancer therapy.

A substantial knowledge gap exists in understanding how vitamin C, as a redox agent, can potentially target malignant metabolic pathways to halt or kill cancer cells. To fill this gap, an article published in a recent issue of ***Science*** investigated the potential mechanism underlying the anti-cancer effects of vitamin C using isogenic KRAS- and BRAF-mutant colorectal cancer cell lines.[2] The authors were able to demonstrate selective anti-tumor effects among the KRAS- and BRAF-mutated cells in culture and in ex-planted animal models treated with high-dose vitamin C. Their elegant and in-depth studies unequivocally tied the tumoricidal effect to the heightened sensitivity of the mutant cells due to the increased vitamin C uptake. This, through intermediary biochemical steps, led to a lethal accumulation of reactive oxygen species (ROS) within the mutant cancer cells. In this outstanding work, the authors laid out a clear and compelling rationale that vitamin C has a promising role in cancer therapy, particularly in light of the fact that KRAS- and BRAF-mutated cancer cells are prone to resistance to certain classes of chemotherapeutic agents. This report will certainly rekindle enthusiasm in revisiting the case of vitamin C, pushing for more definitive cancer therapy trials.

Ample clinical trials have demonstrated that what worked in cell lines or mice may not be reproducible in human subjects. In addition, vitamin C is not totally free from side effects, especially when given in high doses. If KRAS- and BRAF-mutated cancer cells are indeed sensitive to ROS induced by high levels of intracellular vitamin C, which leads to the inactivation of glyceraldehyde 3-phosphate dehydrogenase (GAPDH), one would wonder if it may be more effective to explore strategies to target GAPDH

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directly without the need to administer high doses of vitamin C. Due to the controversial history of the previous vitamin C trials, especially those in conjunction with other chemotherapeutic agents, the question remains whether the "C" can stand for "cure" this time around.

Conflicts of interest

The authors declare no conflicts of interest.

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