ces are important, and that was enough to get the job. However, the insights presented by the experiments of Lu *et al.* show that the expert was partly right.

Admittedly, there have been many demonstrations of the connection between magnetism and superconductivity, in particular when superconductors containing a magnetic element were found: for instance, in the rare-earth nickel borocarbides (*8*), in ferromagnetic superconductors (*9*), or in the recent Fe-based materials (*10*). In these cases, time-inversion symmetry is broken in some form, particularly in the ferromagnetic superconductors, where triplet Cooper pairs are required (with spins of the same orientation). However, the spin locking in MoS_2 preserves time-reversal symmetry. The same occurs in systems with so-called Rashba spin-orbit coupling. Such coupling arises in the absence of inversion symmetry and in materials with heavy elements and again locks electron's spin and momenta. It is related to the electric-field gradient leading to spin-orbit coupling. The "fictitious" magnetic field generated by Rashba spin-orbit coupling is oriented in the plane of the Cooper pair electrons' momentum. This can eventually favor mixtures of singlet and triplet Cooper pairs (*11*). Estimates for the size of this effect, however, provide very small values for MoS_2 (*2, 3*). By contrast, the effect discussed in MoS_2 is a direct consequence of the inequivalence of K and K′ sites on the Fermi surface.

Monolayers of the related material $NbSe_2$, another transition-metal dichalcogenide, show similar behavior (*12*). Yet another recent work discovers amazing properties of 2D vortices in ionic gate-induced superconductivity in ZrNCl (*13*). It seems that a gate is being opened, likely showing beautiful vistas of superconductivity through a looking glass, where the crystal lattice is trump. ■

REFERENCES AND NOTES

1. D. van Delft, P. Kes, *Phys. Today* **63**, 38 (2010).
2. J. M. Lu *et al.*, *Science* **350**, 1353 (2015).
3. Y. Saito *et al.*, http://arxiv.org/abs/1506.04146 (2015).
4. K. F. Mak *et al.*, *Phys. Rev. Lett.* **105**, 136805 (2010).
5. D. Xiao *et al.*, *Phys. Rev. Lett.* **108**, 196802 (2012).
6. R. Roldán *et al.*, *Phys. Rev. B* **88**, 054515 (2013).
7. A. I. Buzdin, *Rev. Mod. Phys.* **77**, 935 (2005).
8. P.C. Canfield *et al.*, *Phys. Today* **51**, 40 (1998).
9. D. Aoki, J. Flouquet, *J. Phys. Soc. Jap.* **81**, 011003 (2011).
10. A. Chubukov, P. J. Hirschfeld, *Phys. Today* **68**, 46 (2015).
11. E. Bauer, M. Sigrist, Eds., *Non-Centrosymmetric Superconductors*, Lecture Notes in Physics 847 (Springer, Berlin, 2012).
12. X. Xi *et al.*, *Nat. Phys.* 10.1038/nphys3538 (2015).
13. Y. Saito *et al.*, *Science* **350**, 409 (2015)

ACKNOWLEDGMENTS

Supported by Mineco (FIS2014-54498-R) and Region of Madrid (S2013/MIT-2850).

10.1126/science.aad7086

CANCER

Revisiting vitamin C and cancer

A high dose of vitamin C kills certain colon cancer cells

By **Colleen R. Reczek** *and* **Navdeep S. Chandel**

In the early 1970s, the two-time Nobel Prize–winning chemist Linus Pauling proposed that high doses of vitamin C (ascorbic acid) can act as an antioxidant to reduce cancer. Pauling and his colleague Ewan Cameron reported that cancer patients given intravenous vitamin C (10 g/day) followed by oral delivery had an increased rate of survival (*1*). This led to two large clinical trials carried out by the Mayo Clinic in the late 1970s and mid-1980s (*2, 3*), which demonstrated that oral administration of a high dose of vitamin C had no efficacy as a cancer therapeutic. Furthermore, dietary antioxidants have failed as anticancer agents in clinical trials (*4*). However, on page 1391 in this issue, Yun *et al.* (*5*) show that high doses of vitamin C selectively kill colorectal cancer cells carrying activating mutations in the oncogenes *KRAS* or *BRAF*, which are often refractory to approved targeted therapies.

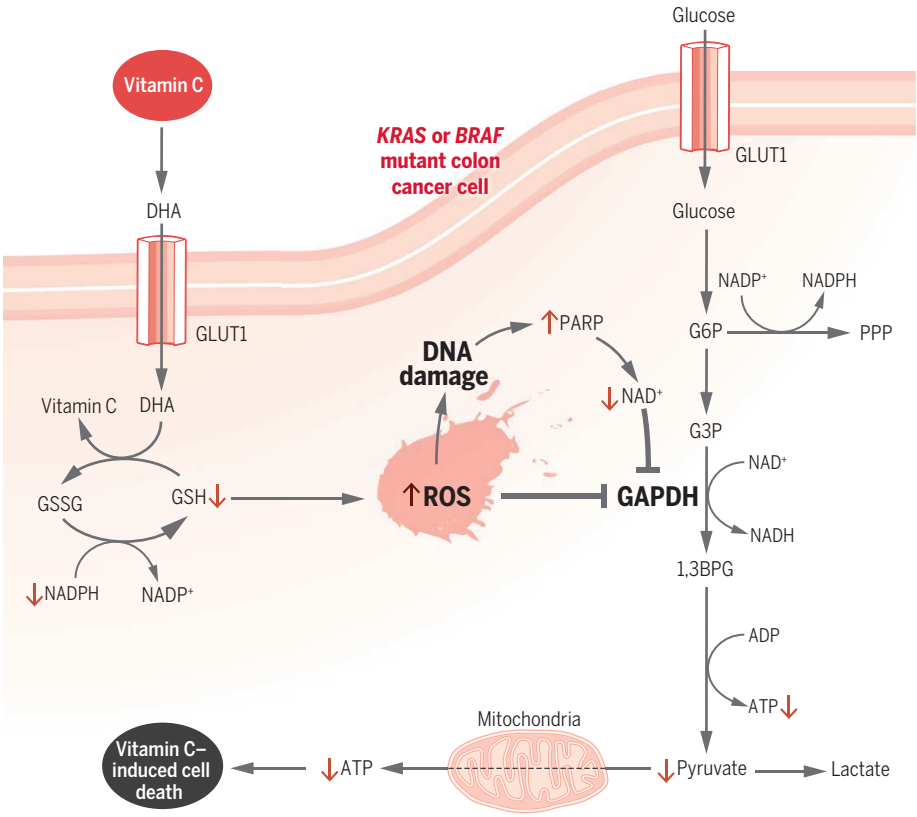
> ***"...the study...provides a mechanistic rationale for how vitamin C selectively kills...cancer cells."***

Vitamin C is taken up by cells through sodium-dependent vitamin C transporters, whereas the oxidized form of vitamin C, dehydroascorbate (DHA), moves into cells via glucose transporters such as GLUT1 (*5, 6*). Once inside the cell, DHA is reduced back to vitamin C by glutathione (GSH), which consequently becomes oxidized glutathione (GSSG). Subsequently, GSSG is converted back to GSH by reduced nicotinamide adenine dinucleotide phosphate (NADPH) (see the figure). High doses of vitamin C can increase the amount of reactive oxygen species (ROS) in cancer cells and exert antitumorigenic activity (*7*). However, the molecular mechanisms by which vitamin C inhibits tumorigenesis remained unknown.

Yun *et al.* observed that vitamin C was oxidized to DHA in cell culture media lacking reducing agents, and was subsequently imported into human colon cancer cells harboring oncogenic *KRAS* or *BRAF* mutations by GLUT1. Moreover, the authors showed that high doses of vitamin C that resulted in a peak plasma concentration of 30 mM when administered intraperitoneally reduced the intestinal tumor burden in mice bearing conditional oncogenic activating forms of *Kras* and *adenomatous polyposis coli* (*Apc*) mutations, but not in mice with the conditional *Apc* mutation alone. Tumors from the double conditional *Kras* and *Apc* mutant mice expressed more GLUT1 than tumors from mice harboring only the *Apc* mutation. Furthermore, the pan-antioxidant *N*-acetylcysteine prevented the vitamin C–mediated decrease in tumor burden, indicating that elevated ROS amounts due to vitamin C were responsible for reducing tumorigenesis in vivo.

Yun *et al.* report that the increased uptake of DHA into the *KRAS* or *BRAF* mutant cancer cells, which express more GLUT1 compared to normal cells, leads to the rapid conversion of DHA to vitamin C, resulting in the depletion of GSH and NADPH and an increase in ROS. Metabolite analysis revealed an increase in glucose carbons into the oxidative pentose phosphate pathway, a major cytosolic mechanism to generate NADPH. Indeed, increases in ROS have been shown to activate the oxidative pentose phosphate pathway within minutes (*8*). Additionally, metabolite analysis revealed an increase in glycolytic intermediates such as glyceraldehyde-3-phosphate (G3P) upstream of glyceraldehyde 3-phosphate dehydrogenase (GAPDH). Concomitantly, Yun *et al.* observed a decrease in metabolites downstream of the GAPDH reaction, suggesting GAPDH inhibition by ROS as a result of the increased DHA flux into *KRAS* or *BRAF* mutant colon cancer cells. GAPDH is a redox-sensitive protein, as its active-site cysteine residue can be targeted by ROS. Inhibition of GAPDH decreases the generation of glycolytic adenosine 5′-triphosphate (ATP) and pyruvate, a major substrate required to drive ATP production in the mitochondria. However, pyruvate supplementation can rescue the cell death and energetic

Department of Medicine and Robert H. Lurie Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611, USA. E-mail: nav@northwestern.edu



Vitamin C and cell metabolism. The uptake of vitamin C by *KRAS* and *BRAF* mutant colon cancer cells is shown. The resulting increase in ROS production blocks glucose metabolism (in addition to other effects shown). Cells shift their glycolytic flux into the pentose phosphate pathway (PPP), but ultimately, the cells become depleted of ATP, inducing an energetic crisis that leads to cell death.

crisis caused by GAPDH inhibition. Thus, these results suggest that high doses of vitamin C impair glycolysis and could be combined with the antidiabetic drug metformin, which can also diminish tumor burden by inhibiting mitochondrial complex I (*9*).

In addition to oxidizing GAPDH, the elevated ROS amounts induced by vitamin C cause DNA damage, resulting in poly(ADP-ribose) polymerase (PARP) activation and NAD^+ consumption. Notably, the GAPDH enzymatic reaction utilizes NAD^+ to convert G3P to 1,3-bisphosphoglycerate (1,3BPG). Therefore, the decrease in NAD^+ due to PARP activation further diminishes the GAPDH reaction. Inhibition of PARP or administration of nicotinamide mononucleotide, a precursor of NAD^+ synthesis, partially rescued cell viability after vitamin C treatment in vitro. Collectively, these findings suggest that in *KRAS* and *BRAF* mutant cells, vitamin C–induced endogenous ROS inhibits the GAPDH reaction directly (oxidizing GAPDH) as well as indirectly (reducing the NAD^+ pool), leading to an energetic crisis that triggers cell death.

High GLUT1 expression alone, however, does not make a cell more susceptible to vitamin C cytotoxicity. Wild-type *KRAS* and *BRAF* colon cancer cells overexpressing GLUT1 were resistant to vitamin C–induced cell death, implying that oncogenic *KRAS*- or *BRAF*-induced metabolic reprogramming, in addition to high GLUT1 expression, is needed for toxicity. One metabolic liability of oncogenic *KRAS*-driven tumors is their increased rate of mitochondrial and cytosolic NADPH oxidase–generated ROS compared to wild-type cells, which initiate localized signaling pathways necessary for tumor cell proliferation and tumorigenesis (*10*). Consequently, these cancer cells increase their antioxidant defense system by up-regulating the expression of the transcription factor nuclear factor (erythroid-derived 2) related factor-2 (NRF2) to buffer the accumulation of ROS and prevent damage (*4*). The impairment of NRF2 or disabling antioxidant proteins in oncogenic *KRAS*-driven cancer cells would allow for excessive amounts of ROS to accumulate and incur cell death, resulting in reduced tumor growth (*11, 12*). The results by Yun *et al.* are consistent with previous findings that increasing endogenous ROS with high doses of vitamin C reduces the tumor growth of oncogenic *KRAS*-driven pancreatic cancer cells (*13*). Thus, tumors that exhibit a high rate of ROS generation coupled with increased GLUT1 expression are likely to benefit from treatment with a high dose of vitamin C.

An important difference between the study by Yun *et al.* and many previous studies is the mode of vitamin C delivery. Oral ingestion of high concentrations of vitamin C, 100 times the recommended dietary allowance, rarely exceeds a plasma concentration greater than 200 μM due to limited absorption and renal excretion. By contrast, vitamin C administered intravenously can reach a plasma concentration of up to 10 mM and is safe in humans. Yun *et al.* injected vitamin C intraperitoneally in mice that reached millimolar concentrations in the plasma. A recent pilot phase IIa clinical trial using intravenous administration of vitamin C in conjunction with conventional paclitaxel-carboplatin therapy demonstrated a benefit in a small number of patients (*14*). Furthermore, metastatic tumor cells can survive the hostile oxidizing environment of the blood by increasing their antioxidant defenses (*15*). Thus, infusion of vitamin C may be an effective therapeutic strategy to induce the cell death of circulating metastatic tumor cells.

One drawback of intravenous administration of vitamin C is that patients will have to visit the clinic for vitamin C infusions daily for months. However, the development of a new oral formulation of vitamin C that can achieve high plasma concentrations may circumvent this concern. Nevertheless, the study by Yun *et al.* provides a mechanistic rationale for how vitamin C selectively kills *KRAS* and *BRAF* mutant colorectal cancer cells. These findings warrant high-dose vitamin C clinical trials with selectivity for patients with a high GLUT1 expression combined with *KRAS* or *BRAF* oncogene–induced metabolic reprogramming. After all these years, it seems that Pauling may have been correct on the use of high doses of vitamin C for cancer therapy but for the wrong reasons—not as an antioxidant, but as a pro-oxidant anticancer agent. ■

REFERENCES

1. E. Cameron, L. Pauling, *Proc. Natl. Acad. Sci. U.S.A.* **73**, 3685 (1976).
2. C. G. Moertel *et al.*, *N. Engl. J. Med.* **312**, 137 (1985).
3. E. T. Creagan *et al.*, *N. Engl. J. Med.* **301**, 687 (1979).
4. N. S. Chandel, D. A. Tuveson, *N. Engl. J. Med.* **371**, 177 (2014).
5. J. Yun *et al.*, *Science* **350**, 1391 (2015).
6. W. Tian *et al.*, *J. Biol. Chem.* **289**, 3339 (2014).
7. Q. Chen *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **105**, 11105 (2008).
8. A. Kuehne *et al.*, *Mol. Cell* **59**, 359 (2015).
9. W. W. Wheaton *et al.*, *eLife* **3**, e02242 (2014).
10. F. Weinberg *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **107**, 8788 (2010).
11. G. M. DeNicola *et al.*, *Nature* **475**, 106 (2011).
12. A. Glasauer, L. A. Sena, L. P. Diebold, A. P. Mazar, N. S. Chandel, J. Clin. *Invest.* **124**, 117 (2014).
13. M. G. Espey *et al.*, *Free Radic. Biol. Med.* **50**, 1610 (2011).
14. Y. Ma *et al.*, *Sci. Transl. Med.* **6**, 222ra18 (2014).
15. E. Piskounova *et al.*, *Nature* **527**, 186 (2015).

10.1126/science.aad8671

ILLUSTRATION: K. SUTLIFF/*SCIENCE*

Revisiting vitamin C and cancer

Colleen R. Reczek and Navdeep S. Chandel

Science **350**, 1317 (2015);
DOI: 10.1126/science.aad8671

Science (print ISSN 0036-8075; online ISSN 1095-9203) is published weekly, except the last week in December, by the American Association for the Advancement of Science, 1200 New York Avenue NW, Washington, DC 20005.