



































Dietary pro-oxidant therapy by a vitamin K precursor targets PI 3-kinase VPS34 function

MANOJIT M. SWAMYNATHAN , SHAN KUANG, KAITLIN E. WATRUD, MARY R. DOHERTY, CHARLOTTE GINESTE , GRINU MATHEW , GRACE Q. GONG , HILARY COX , EILEEN CHENG , DAVID REISS, JUDE KENDALL, DIYA GHOSH , COLLEEN R. RECZEK , XIANG ZHAO , TALI HERZKA, SAULÉ ŠPOKAITÉ , ANTOINE N. DESSUS , SEUNG TEA KIM , OLAF KLINGBEIL, JUAN LIU, DAWID G. NOWAK , HABEEB ALSUDANI, TSE-LUEN WEE , YOUNGKYU PARK , FRANCESCA MINICOZZI , KEITH RIVERA , ANA S. ALMEIDA , KENNETH CHANG , RAM P. CHAKRABARTY , JOHN E. WILKINSON , PHYLLIS A. GIMOTTY , SARAH D. DIERMEIER , MIKALA EGEBLAD , CHRISTOPHER R. VAKOC, JASON W. LOCASALE , NAVDEEP S. CHANDEL , TOBIAS JANOWITZ , JAMES B. HICKS, MICHAEL WIGLER , DARRYL J. PAPPIN , ROGER L. WILLIAMS , PAOLO CIFANI , DAVID A. TUVESON , JOCELYN LAPORTE , AND LLOYD C. TROTMAN 

fewer

[Authors Info & Affiliations](#)

SCIENCE 25 Oct 2024 Vol 386, Issue 6720 DOI: 10.1126/science.adk9167

729 1

    CHECK ACCESS

Editor's summary

In light of emerging evidence that antioxidants can have cancer-promoting effects, Swamynathan *et al.* tested potential pro-oxidant interventions (see the Perspective by Pannia and Dowling). In particular, the authors focused on menadione sodium bisulfite, a water-soluble precursor of vitamin K. As the authors anticipated, this menadione derivative suppressed prostate cancer growth. The researchers then examined its mechanism of action and identified the kinase VPS34 (phosphatidylinositol 3-kinase catalytic subunit type 3) as its target. Fortuitously, they realized that a fatal genetic muscle disease called X-linked myotubular myopathy is also linked to a relative excess of VPS34 activity owing to the loss of its antagonist, and dietary supplementation with menadione proved beneficial in a mouse model of this genetic disorder. —Yevgeniya Nusinovich

Structured Abstract

INTRODUCTION

Prostate cancer (PC) is the most commonly diagnosed cancer in men, with more than 299,000 new cases anticipated in the United States in 2024. The majority of these men will present with slow-growing disease that can turn into life-threatening PC that resists all available treatment options. Therefore, there is a strong interest in defining well-informed lifestyle, dietary, and supplement choices that can slow down disease progression. This has spawned large-scale human trials, including one on the benefits of dietary antioxidants: The SELECT trial (Selenium and Vitamin E Cancer Prevention Trial) followed 35,533 healthy men for more than 10 years. Against expectations, SELECT showed significantly increased risk of developing PC among men who took the antioxidant vitamin E supplements.

RATIONALE

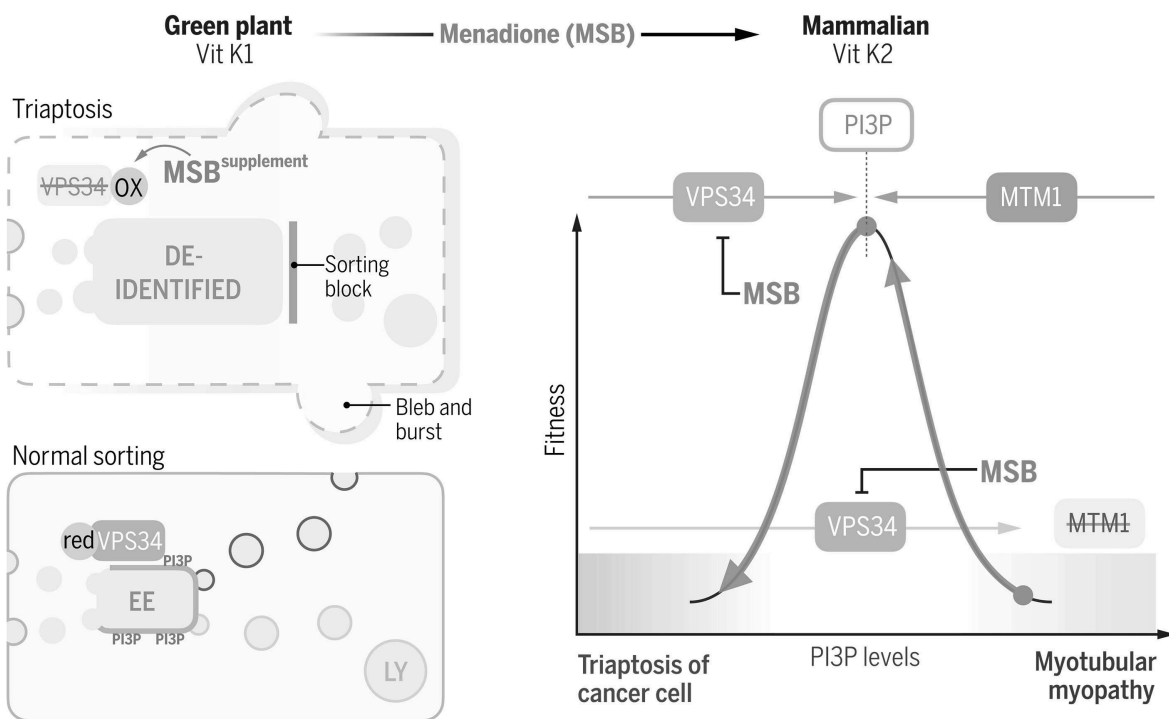
The PC-promoting effect of antioxidant vitamin E supplements immediately raised the question whether, conversely, pro-oxidant supplements can help prevent the disease. Genetically engineered mouse (GEM) models of PC provide a platform to ask this question. Specifically, we use the RapidCaP GEM model, which allowed us to determine whether and how fast a cancer in the prostate progresses to the metastatic form.

RESULTS

We treated RapidCaP animals with the pro-oxidant menadione supplement [menadione sodium bisulfite (MSB)], a precursor of mammalian vitamin K that is present in circulation after consumption of plant vitamin K from greens. Daily MSB supplementation in drinking water suppressed PC progression, yielding durable responses. Systematic analysis of cell death pathways revealed that MSB kills cancer cells through a distinct oxidative cell death mechanism that we propose to call triaptosis. We used genome-wide CRISPR screens to understand the underlying biological principle and found that MSB depletes the early endosomal (EE) membrane lipid phosphatidylinositol 3-phosphate [PI(3)P]. PI(3)P defines the EE compartment, allowing sorting of derived vesicles back to the plasma membrane or into the lysosomal degradation system. Video microscopy revealed that the distinctive feature of triaptosis is the accumulation of large PI(3)P-negative, deidentified endosomes followed by cell blebbing and plasma membrane rupture. We found that MSB directly oxidizes essential cysteines on class III PI 3-kinase VPS34, thus inactivating the PI(3)P-producing enzyme. Notably, supplementing cells with extra reducing agents completely abrogates cell death induced by MSB. The ability of menadione to suppress PI(3)P production prompted us to test whether it could suppress a fatal inherited disorder: X-linked myotubular myopathy. This incurable disease is caused by inherited mutation of the *MTM1* gene. MTM1 is the phosphatase that directly antagonizes PI 3-kinase VPS34. Therefore, boys with this disease suffer from unopposed PI(3)P production, causing a failure of muscle buildup. *Mtm1* knockout mice recapitulate the most severe phenotype, lethality of infant boys. Supplementing MSB in drinking water doubled the overall survival of these mice to a median of 2 months. The treatment also improved animal weight gain and muscle histology.

CONCLUSION

Our results suggest that dietary menadione could form the basis of new therapeutic approaches in multiple disease settings. This is because MSB is an oxidative antagonist of PI 3-kinase VPS34, the enzyme that produces the phospholipid PI(3)P. In PC cells, the oxidative stress lowers PI(3)P, causing cell death by triaptosis. We infer from our data that normal cells have sufficient reserves in reducing power to withstand this insult. In myotubular myopathy, menadione may curb the unopposed VPS34 kinase activity and bring PI3P back to levels that can improve muscle development. Collectively, our findings contribute to the emerging understanding of pro-oxidant agent selectivity and show how definition of the pathways that they impinge on can give rise to unexpected therapeutic opportunities.



Dietary pro-oxidant therapy using a vitamin K precursor.

(Top) Green plant foods are a major source of vitamin K (Vit K1), which mammals convert to Vit K2. The intermediate is menadione, which can be supplemented to diets (MSB). (Left) MSB oxidizes VPS34 kinase. This causes triaptosis, a distinct cell death mechanism based on depletion of PI3P, which deidentifies the EE compartment. LY, lysosomal degradation system. (Right) Concept of therapy approaches using PI3P reduction by MSB in two disease settings.

Abstract

Men taking antioxidant vitamin E supplements have increased prostate cancer (PC) risk. However, whether pro-oxidants protect from PC remained unclear. In this work, we show that a pro-oxidant vitamin K precursor [menadione sodium bisulfite (MSB)] suppresses PC progression in mice, killing cells through an oxidative cell death: MSB antagonizes the essential class III phosphatidylinositol (PI) 3-kinase VPS34—the regulator of endosome identity and sorting—through oxidation of key cysteines, pointing to a redox checkpoint in sorting. Testing MSB in a myotubular myopathy model that is driven by loss of *MTM1*—the phosphatase antagonist of VPS34—we show that dietary MSB improved muscle histology and function and extended life span. These findings enhance our understanding of pro-oxidant selectivity and show how definition of the pathways they impinge on can give rise to unexpected therapeutic opportunities.

RELATED PERSPECTIVE

A pro-oxidant suppresses unrelated diseases

BY EMANUELA PANNIA, JAMES J. DOWLING • SCIENCE • 25 OCT 2024

Get full access to this article

View all available purchase options and get full access to this article.

CHECK ACCESS

ALREADY A SUBSCRIBER OR AAAS MEMBER? SIGN IN AS AN [INDIVIDUAL](#) OR VIA YOUR [INSTITUTION](#)

Supplementary Materials

The PDF file includes:

Materials and Methods

Figs. S1 to S13

References (84–104)

DOWNLOAD

34.35 MB

Other Supplementary Material for this manuscript includes the following:

MDAR Reproducibility Checklist

DOWNLOAD

158.43 KB

Movies S1 to S9

DOWNLOAD

156.88 MB

Data S1 to S6

DOWNLOAD

18.37 MB

References and Notes

- 1 R. L. Siegel, A. N. Giaquinto, A. Jemal, Cancer statistics, 2024. *CA Cancer J. Clin.* **74**, 12–49 (2024).
[CROSSREF](#) • [PUBMED](#) • [WEB OF SCIENCE](#) • [GOOGLE SCHOLAR](#)
- 2 S. M. Lippman, E. A. Klein, P. J. Goodman, M. S. Lucia, I. M. Thompson, L. G. Ford, H. L. Parnes, L. M. Minasian, J. M. Gaziano, J. A. Hartline, J. K. Parsons, J. D. Bearden 3rd, E. D. Crawford, G. E. Goodman, J. Claudio, E. Winquist, E. D. Cook, D. D. Karp, P. Walther, M. M. Lieber, A. R. Kristal, A. K. Darke, K. B. Arnold, P. A. Ganz, R. M. Santella, D. Albanes, P. R. Taylor, J. L. Probstfield, T. J. Jagpal, J. J. Crowley, F. L. Meyskens Jr., L. H. Baker, C. A. Coltman Jr, Effect of selenium and vitamin E on risk of prostate cancer and other cancers: The Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA* **301**, 39–51 (2009).
[CROSSREF](#) • [PUBMED](#) • [WEB OF SCIENCE](#) • [GOOGLE SCHOLAR](#)
- 3 E. A. Klein, I. M. Thompson Jr., C. M. Tangen, J. J. Crowley, M. S. Lucia, P. J. Goodman, L. M. Minasian, L. G. Ford, H. L. Parnes, J. M. Gaziano, D. D. Karp, M. M. Lieber, P. J. Walther, L. Klotz, J. K. Parsons, J. L. Chin, A. K. Darke, S. M. Lippman, G. E. Goodman, F. L. Meyskens Jr., L. H. Baker,

SHOW ALL REFERENCES

eLetters (0)

eLetters is a forum for ongoing peer review. eLetters are not edited, proofread, or indexed, but they are screened. eLetters should provide substantive and scholarly commentary on the article. Embedded figures cannot be submitted, and we discourage the use of figures within eLetters in general. If a figure is essential, please include a link to the figure within the text of the eLetter. Please read our [Terms of Service](#) before submitting an eLetter.

LOG IN TO SUBMIT A RESPONSE

No eLetters have been published for this article yet.

Recommended articles from TrendMD

Sociolinguistics and Language Planning

Wolfgang Wölck, Science, 1973

Müller-Pouillet, Lehrbuch der Physik. Edited by Leopold Pfaundler. Tenth edition. Volume 1. Vieweg, Brunswick. 1905.

J. S. Ames, Science, 1906

Huge open-access journal deal inked by University of California and Springer Nature

Jeffrey Brainard, Science Now, 2020

Update: 'A bit chaotic.' Christening of new coronavirus and its disease name create confusion

Martin Enserink, Science Now, 2020

Russia mulls withdrawing from the International Space Station after 2024

Olga Dobrovidova, Science Now, 2021

South Africa first! Getting to Thuma Mina [↗](#)

Alanna Markle, ISS Southern Africa Report, 2020

Community-wide change towards positive parenting [↗](#)

Chandré Gould, ISS Southern Africa Report, 2022

The Traditional Courts Bill : a silent coup? [↗](#)

Nomboniso Gasa, SA Crime Quarterly, 2011

Without fear or favour : the Scorpions and the politics of justice [↗](#)

David Bruce, SA Crime Quarterly, 2008

Planning for nuclear security : design basis threats and physical protection systems [↗](#)

Cyrus Cyril Arwui, SA Crime Quarterly, 2017

Powered by **TREND MD**



CURRENT ISSUE

Indigenous groups push to control their own data p. 372

Vitamin K precursor may treat two diseases pp. 380 & 399

Mechanisms of radiation resistance in tardigrades p. 396

Science

\$15
25 OCTOBER 2024
Subscription

AAAS

FAST FIRES

The most destructive fires are spreading more rapidly p. 425

The landscape of RNA binding proteins in mammalian spermatogenesis

BY YANG LI, YUANYUAN WANG, ET AL.

Dietary pro-oxidant therapy by a vitamin K precursor targets PI 3-kinase VPS34 function

BY MANOJIT M. SWAMYNATHAN, SHAN KUANG, ET AL.

Multi-omics landscape and molecular basis of radiation tolerance in a tardigrade

BY LEI LI 李磊, ZHENGPING GE 葛正平, ET AL.

TABLE OF CONTENTS >

ADVERTISEMENT

Sign up for ScienceAdviser

Get *Science's* award-winning newsletter with the latest news, commentary, and research, free to your inbox daily.

SUBSCRIBE >

LATEST NEWS

NEWS | 25 OCT 2024

'Aerial arms race' with birds may have turned ancient cicadas into ace fliers

SCIENCEINSIDER | 25 OCT 2024

Can science and Islam coexist? A chemical engineer-turned-theologian sees common ground

SCIENCEINSIDER | 24 OCT 2024

Web of Science index puts *eLife* 'on hold' because of its radical publishing model

NEWS FEATURE | 24 OCT 2024

Buoyed by 'milestone' clinical result, RNA editing is poised to treat diseases

NEWS | 24 OCT 2024

Pregnancy wakes up viruslike 'jumping genes' to help make extra blood

NEWS FEATURE | 24 OCT 2024

'Not a free-for-all': Indigenous communities want limits on how their data are shared

ADVERTISEMENT

RELATED JOBS

TENURE-TRACK PROFESSOR IN EVOLUTIONARY BIOLOGY, HARVARD UNIVERSITY

Harvard University Department of Organismic and Evolutionary Biology
Cambridge, Massachusetts (US)

Postdoctoral Fellow in Vascular Cell Signaling

LSU Health Science Center - Shreveport
Shreveport, Louisiana

Research Assistant II

Baylor College of Medicine
Houston, TX

[MORE JOBS ►](#)

RECOMMENDED

REPORT | APRIL 2011

[AMP-Activated Protein Kinase Regulates Neuronal Polarization by Interfering with PI 3-Kinase Localization](#)

PERSPECTIVE | AUGUST 2012

[Precursor or Charge Supplier?](#)

NOVEMBER 2006

[PTEN Regulation, a Novel Function for the p85 Subunit of Phosphoinositide 3-Kinase](#)

SPECIAL VIEWPOINTS | MAY 2002

[The Phosphoinositide 3-Kinase Pathway](#)

[View full text](#) | [Download PDF](#)

Science

Science
Advances

Science
Immunology

Science
Robotics

Science
Signaling

FOLLOW US



GET OUR NEWSLETTER

NEWS

[All News](#)

[ScienceInsider](#)

[News Features](#)

[Subscribe to News from Science](#)

[News from Science FAQ](#)

[About News from Science](#)

[Donate to News](#)

COMMENTARY

[Opinion](#)

[Analysis](#)

[Blogs](#)

AUTHORS & REVIEWERS

[Information for Authors](#)

[Information for Reviewers](#)

ADVERTISERS

[Advertising Kits](#)

[Custom Publishing Info](#)

[Post a Job](#)

CAREERS

[Careers Articles](#)

[Find Jobs](#)

[Employer Hubs](#)

JOURNALS

[Science](#)

[Science Advances](#)

[Science Immunology](#)

[Science Robotics](#)

[Science Signaling](#)

[Science Translational Medicine](#)

[Science Partner Journals](#)

LIBRARIANS

[Manage Your Institutional Subscription](#)

[Library Admin Portal](#)

[Request a Quote](#)

[Librarian FAQs](#)

RELATED SITES

[AAAS.org](#)

[AAAS Communities](#)

[EurekAlert!](#)

ABOUT US

[Leadership](#)

[Work at AAAS](#)

[Prizes and Awards](#)

HELP

[FAQs](#)

[Access and Subscriptions](#)

[Order a Single Issue](#)

[Reprints and Permissions](#)

[TOC Alerts and RSS Feeds](#)

[Contact Us](#)