RESEARCH ARTICLE METABOLISM

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

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

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

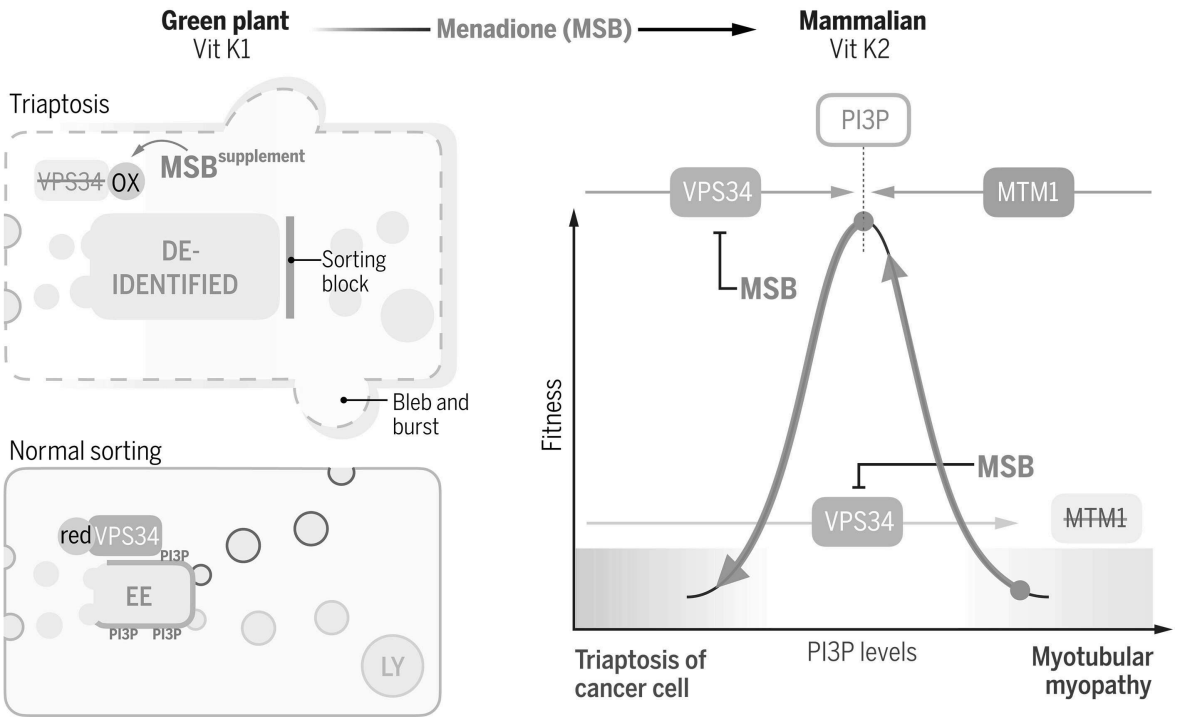
The PC-promoting effect of antioxidant vitamin E supplements immediately raised the question whether, conversely, pro-oxidant supplements can help prevent the disease. Genetically engineered mouse (GEM) models of PC provide a platform to ask this question. Specifically, we use the RapidCaP GEM model, 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.

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