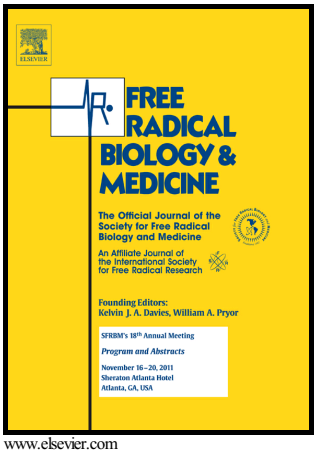
Pharmacologic ascorbate induces neuroblastoma cell death by hydrogen peroxide mediated DNA damage and reduction in cancer cell glycolysis

Enlong Ma, Ping Chen, Heather M. Wilkins, Tao Wang, Russell H. Swerdlow, Qi Chen



www.elsevier.com

PII: S0891-5849(17)30752-9
DOI: http://dx.doi.org/10.1016/j.freeradbiomed.2017.09.008
Reference: FRB13446

To appear in: *Free Radical Biology and Medicine*

Received date: 26 April 2017
Revised date: 6 September 2017
Accepted date: 9 September 2017

Cite this article as: Enlong Ma, Ping Chen, Heather M. Wilkins, Tao Wang, Russell H. Swerdlow and Qi Chen, Pharmacologic ascorbate induces neuroblastoma cell death by hydrogen peroxide mediated DNA damage and reduction in cancer cell glycolysis, *Free Radical Biology and Medicine,* http://dx.doi.org/10.1016/j.freeradbiomed.2017.09.008

Pharmacologic ascorbate induces neuroblastoma cell death by hydrogen peroxide mediated DNA damage and reduction in cancer cell glycolysis

Enlong Ma[1,2], Ping Chen[1], Heather M. Wilkins[3], Tao Wang[1], Russell H. Swerdlow[3], Qi Chen[11*]

[1] Department of Pharmacology, Toxicology and Therapeutics, University of Kansas Medical Center

[2] Department of Pharmacology, Shenyang Pharmaceutical University, Shenyang 110016, China

[3]Kansas University Alzheimer's Disease Center, University of Kansas Medical Center, 3901 Rainbow Blvd., Kansas City, KS 66160

***Corresponding author**: Qi Chen, Department of Pharmacology, Toxicology and Therapeutics, University of Kansas Medical Center, 3901 Rainbow Blvd., Kansas City, KS 66160 USA. Telephone: (913) 588-3690; E-mail: qchen@kumc.edu

ABSTRACT

An ascorbate-mediated production of oxidative stress has been shown to retard tumor growth. Subsequent glycolysis inhibition has been suggested. Here, we further define the mechanisms relevant to this observation. Ascorbate was cytotoxic to human neuroblastoma cells through the production of H_2O_2, which led to ATP depletion, inhibited GAPDH, and non-apoptotic and non-autophagic cell death. The mechanism of cytotoxicity is different when PARP-dependent DNA repair machinery is active or inhibited. Ascorbate-generated H_2O_2 damaged DNA, activated PARP, depleted NAD+, and reduced glycolysis flux. NAD+ supplementation prevented ATP depletion and cell death, while treatment with a PARP inhibitor, olaparib, preserved NAD+ and

[1] The corresponding author is also the lead contact for the paper.