Free Radic Biol Med. 2015 Dec;89:1231-47. doi: 10.1016/j.freeradbiomed.2015.10.416. Epub 2015 Oct 20.

Anticancer therapeutic potential of Mn porphyrin/ascorbate system.

Tovmasyan A[1], Sampaio RS[2], Boss MK[3], Bueno-Janice JC[2], Bader BH[4], Thomas M[4], Reboucas JS[5], Orr M[6], Chandler JD[6], Go YM[6], Jones DP[6], Venkatraman TN[7], Haberle S[7], Kyui N[8], Lascola CD[7], Dewhirst MW[1], Spasojevic I[9], Benov L[4], Batinic-Haberle I[10].

Author information

[1]Department of Radiation Oncology, Duke University School of Medicine, Durham, NC 27710, United States.
[2]Department of Radiation Oncology, Duke University School of Medicine, Durham, NC 27710, United States; Departamento de Quimica, CCEN, Universidade Federal da Paraiba, Joao Pessoa, PB 58051-900, Brazil.
[3]Department of Molecular Biomedical Sciences, North Carolina State University College of Veterinary Medicine, Raleigh, NC 27607, United States.
[4]Department of Biochemistry, Faculty of Medicine, Kuwait University, Kuwait.
[5]Departamento de Quimica, CCEN, Universidade Federal da Paraiba, Joao Pessoa, PB 58051-900, Brazil.
[6]Division of Pulmonary, Allergy and Critical Care Medicine, Department of Medicine, Emory University, Atlanta, GA, United States.
[7]Department of Radiology, Duke University School of Medicine, Durham, NC 27710, United States.
[8]Canadian Economic Analysis Department, Bank of Canada, Ottawa, ON K1A 0G9, Canada.
[9]Department of Medicine, Duke University School of Medicine, Durham, NC 27710, United States; Duke Cancer Institute, Pharmaceutical Research Shared Resource, PK/PD Core laboratory, Durham NC 27710, United States.
[10]Department of Radiation Oncology, Duke University School of Medicine, Durham, NC 27710, United States. Electronic address: ibatinic@duke.edu.

Abstract

Ascorbate (Asc) as a single agent suppressed growth of several tumor cell lines in a mouse model. It has been tested in a Phase I Clinical Trial on pancreatic cancer patients where it exhibited no toxicity to normal tissue yet was of only marginal efficacy. The mechanism of its anticancer effect was attributed to the production of tumoricidal hydrogen peroxide (H2O2) during ascorbate oxidation catalyzed by endogenous metalloproteins. The amount of H2O2 could be maximized with exogenous catalyst that has optimized properties for such function and is localized within tumor. Herein we studied 14 Mn porphyrins (MnPs) which differ vastly with regards to their redox properties, charge, size/bulkiness and lipophilicity. Such properties affect the in vitro and in vivo ability of MnPs (i) to catalyze ascorbate oxidation resulting in the production of H2O2; (ii) to subsequently employ H2O2 in the catalysis of signaling proteins oxidations affecting cellular survival pathways; and (iii) to accumulate at site(s) of interest. The metal-centered reduction potential of MnPs studied, E1/2 of Mn(III)P/Mn(II)P redox couple, ranged from -200 to +350 mV vs NHE. Anionic and cationic, hydrophilic and lipophilic as well as short- and long-chained and bulky compounds were explored. Their ability to catalyze ascorbate oxidation, and in turn cytotoxic H2O2 production, was explored via spectrophotometric and electrochemical means. Bell-shape structure-activity relationship (SAR) was found between the initial rate for the catalysis of ascorbate oxidation, vo(Asc)ox and E1/2, identifying cationic Mn(III) N-substituted pyridylporphyrins with E1/2>0 mV vs NHE as efficient catalysts for ascorbate oxidation. The anticancer potential of MnPs/Asc system was subsequently tested in cellular (human MCF-7, MDA-MB-231 and mouse 4T1) and animal models of breast cancer. At the concentrations where ascorbate (1mM) and MnPs (1 or 5 μM) alone did not trigger any alteration in cell viability, combined treatment suppressed cell viability up to 95%. No toxicity was observed with normal human breast epithelial HBL-100 cells. Bell-shape relationship, essentially identical to vo(Asc)oxvs E1/2, was also demonstrated between MnP/Asc-controlled cytotoxicity and E1/2-controlled vo(Asc)ox. Magnetic resonance imaging studies were conducted to explore the impact of ascorbate on T1-relaxivity. The impact of MnP/Asc on intracellular thiols and on GSH/GSSG and Cys/CySS ratios in 4T1 cells was assessed and cellular reduction potentials were calculated. The data indicate a significant increase in cellular oxidative stress induced by MnP/Asc. Based on vo(Asc)oxvs E1/2 relationships and cellular toxicity, MnTE-2-PyP(5+) was identified as the best catalyst among MnPs studied. Asc and MnTE-2-PyP(5+) were thus tested in a 4T1 mammary mouse flank tumor model. The combination of ascorbate (4 g/kg) and MnTE-2-PyP(5+) (0.2mg/kg) showed significant suppression of tumor growth relative to

either MnTE-2-PyP(5+) or ascorbate alone. About 7-fold higher accumulation of MnTE-2-PyP(5+) in tumor vs normal tissue was found to contribute largely to the anticancer effect.

KEYWORDS: Ascorbate; Cancer cells; Catalysis; Cytotoxicity; Hydrogen peroxide; Mn porphyrin; MnTE-2-PyP; SOD mimics; Tumor growth suppression

PMID: 26496207 PMCID: PMC4684782 [Available on 2016-12-01] DOI: 10.1016/j.freeradbiomed.2015.10.416

[PubMed - indexed for MEDLINE]

MeSH Terms, Substances, Grant Support

LinkOut - more resources

PubMed Commons

PubMed Commons home

0 comments

How to join PubMed Commons

You are here: NCBI > Literature > PubMed

Support Center

GETTING STARTED
NCBI Education
NCBI Help Manual
NCBI Handbook
Training & Tutorials
Submit Data

RESOURCES
Chemicals & Bioassays
Data & Software
DNA & RNA
Domains & Structures
Genes & Expression
Genetics & Medicine
Genomes & Maps
Homology
Literature
Proteins
Sequence Analysis
Taxonomy
Variation

POPULAR
PubMed
Bookshelf
PubMed Central
PubMed Health
BLAST
Nucleotide
Genome
SNP
Gene
Protein
PubChem

FEATURED
Genetic Testing Registry
PubMed Health
GenBank
Reference Sequences
Gene Expression Omnibus
Map Viewer
Human Genome
Mouse Genome
Influenza Virus
Primer-BLAST
Sequence Read Archive

NCBI INFORMATION
About NCBI
Research at NCBI
NCBI News
NCBI FTP Site
NCBI on Facebook
NCBI on Twitter
NCBI on YouTube

National Center for Biotechnology Information, U.S. National Library of Medicine
8600 Rockville Pike, Bethesda MD, 20894 USA

Policies and Guidelines | Contact