A Mechanism-Based Antioxidant Approach for the Reduction of Skin Carcinogenesis

Yunfeng Zhao1, Luksana Chaiswing3,5, Terry D. Oberley3,4, Ines Batinic-Haberle6, William St. Clair2, Charles J. Epstein7 and Daret St. Clair1

1 Graduate Center for Toxicology, University of Kentucky, Lexington, Kentucky
2 Department of Radiation Medicine, University of Kentucky, Lexington, Kentucky
3 Department of Pathology, University of Wisconsin, Madison, Wisconsin
4 Veterans Affairs Medical Center, University of Wisconsin, Madison, Wisconsin
5 Faculty of Medical Technology, Mahidol University, Bangkok, Thailand
6 Department of Radiation Oncology, Duke University, Durham, North Carolina
7 Department of Pediatrics, University of California, San Francisco, California

Abstract

Studies in our laboratories showed that overexpression of manganese superoxide dismutase (MnSOD) reduced tumor incidence in a multistage skin carcinogenesis mouse model. However, reduction of MnSOD by heterozygous knockout of the MnSOD gene (MnSOD KO) did not lead to an increase in tumor incidence, because a reduction of MnSOD enhanced both cell proliferation and apoptosis. The present study extends our previous studies in the MnSOD KO mice and shows that apoptosis in mouse epidermis occurred prior to cell proliferation (6 versus 24 hours) when treated with tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA). To investigate the possibility that a timed administration of SOD following apoptosis but before proliferation may lead to suppression of tumor incidence, we applied a SOD mimetic (MnTE-2-PyP5+) 12 hours after each TPA treatment. Biochemical studies showed that MnTE-2-PyP5+ suppressed the level of protein carbonyls and reduced the activity of activator protein-1 and the level of proliferating cellular nuclear antigen, without reducing the activity of p53 or DNA fragmentation following TPA treatment. Histologic examination confirmed that MnTE-2-PyP5+ suppressed mitosis without interfering with apoptosis. Remarkably, the incidence and multiplicity of skin tumors were reduced in mice that received MnTE-2-PyP5+ before cell proliferation. These results show a novel strategy for an antioxidant approach to cancer intervention.

Key Words: oxidative stress • superoxide dismutase • tumor promotion • redox regulation • apoptosis

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