SOD and Skin Health

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Inhibition of the TPA-induced cutaneous inflammation and hyperplasia by EC-SOD.

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This study reports the roles of extracellular superoxide dismutase (EC-SOD) in the cutaneous inflammation and hyperplasia with 12-O-tetradecanoylphorbol-3-acetate (TPA) application in EC-SOD transgenic mice (Tg EC-SOD). Topical double TPA treatment induced the various inflammatory changes including the epidermal thickness, elevated the PCNA-labeling index, the edema formation, and increased production of hydrogen peroxide (H2O2) in wild type mice (WT). These changes were markedly suppressed in TPA-treated Tg EC-SOD. The expressions of the inflammatory cytokines, IL-1alpha and IL-1beta, were reduced in the TPA-treated Tg EC-SOD compared with those in TPA-treated WT. The expression of IL-1alpha was significantly increased in the skin of TPA-treated WT, especially in the basal and suprabasal layers, but it was restricted focally in basal layer of the skin of TPA-treated Tg EC-SOD. The number of infiltrating inflammatory cells and the IL-1beta expressing cells was obviously reduced in TPA-treated Tg EC-SOD in comparison with TPA-treated WT. The result suggests that EC-SOD might play an important role in the suppression of TPA-induced cutaneous inflammation and epidermal hyperplasia by regulating the expression of IL-1alpha and IL-1beta, although the mechanisms remain to be elucidated.

Publication Types:

- Research Support, Non-U.S. Gov't

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Modulation of skin tumorigenesis by SOD.

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Generation of reactive oxygen species (ROS) has been implicated in the development of cancer. Groundwork establishing mitochondria as a critical source of ROS generation and the role of manganese superoxide dismutase (MnSOD) in preventing mitochondria-mediated cell death have been well established. In a seemingly contradictory role, it also is well documented that increased MnSOD expression suppresses the carcinogenesis effect of ROS. Our recent studies demonstrated that overexpression of MnSOD reduced tumor incidence in the two-stage 7,12-dimethylbenz(a)-anthracene (DMBA)/12-O-tetradecanoylphorbol-13-acetate (TPA) skin carcinogenesis model. However, reduction of MnSOD by heterozygous knockout of the MnSOD gene (Sod 2+/-) did not lead to an increase in tumor incidence. Thus, how modulation of mitochondrial ROS levels alter the outcome of developing cancer is unclear. This review will provide background information on the sequence of ROS-mediated events in the mitochondria and evidence that suggests that the antioxidant and tumor suppressor functions of MnSOD are indeed inter-related. It also will offer insights into the mechanisms by which MnSOD modulates the outcome of early stage skin carcinogenesis.

Publication Types:

- Review

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Determination of oxidative stress in vitiligo by measuring superoxide dismutase and catalase levels in vitiliginous and non-vitiliginous skin.

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BACKGROUND: Vitiligo is an acquired disorder characterized by circumscribed depigmented macules devoid of identifiable melanocytes. Complex genetic, immunological, neural and self destructive mechanisms interplay in its pathogenesis. According to autocytotoxic hypothesis, oxidative stress has been suggested to be the initial pathogenic event in melanocyte degeneration. AIMS: The aim of our investigation was to evaluate the role of oxidative stress by measuring levels of the antioxidant enzymes superoxide dismutase (SOD) and catalase (CAT) in lesional and normal skin of patients with vitiligo and in the skin of normal controls. METHODS: We determined the activity of SOD in lesional and non-lesional skin and CAT in lesional skin only of 25 vitiligo patients and 25 controls by using the spectrophotometric assay and Aebi's method, respectively. RESULTS: There was statistically significant increase in the levels of SOD in vitiliginous and non vitiliginous skin of patient group compared to the control group ($P < 0.001$). No significant difference was found between the levels of SOD in lesional skin and non-lesional skin of vitiligo patients. The levels of CAT in the skin of patients were found to be significantly lower than those of controls ($P < 0.001$). CONCLUSIONS: There is increased oxidative stress in vitiligo as is indicated by high levels of SOD and low levels of CAT in the skin of vitiligo patients.

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J Burn Care Res. 2009 Mar-Apr;30(2):321-8.

Lecithinized superoxide dismutase suppresses free radical substrates during the early phase of burn care in rats.

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Severe hypovolemia is caused by an increase in blood vessel permeability in the early phase after an extensive burn; massive fluid volume replacement has been used for the treatment of this condition. The release of oxygen free radicals and chemical mediators, especially from skin tissue, induces the increase in blood vessel permeability. Free radical burst is associated with ischemia-related skin tissue injury. Although various antioxidant therapies have been used to inhibit the consequences of hypovolemia, an effective method has not been established. To elucidate the protective effects of lecithinized superoxide dismutase (PC-SOD) as an antioxidant agent. Each rat sustained a 30% total body surface area burn (n = 20) on the back by the Walker and Mason method were allocated into three groups: (1) no treatment group (n = 6), (2) a low dose of PC-SOD (0.67 mg/kg) group (n = 7), and (3) a high dose of PC-SOD (1.33 mg/kg) group (n = 7). The concentrations of malondialdehyde and SOD in the serum, skin tissue, and lung tissue were measured in each group 1 hour after burning. Both low and high doses of PC-SOD prevented malondialdehyde concentration associated with free radical burst after burning compared with the no treatment group ($P < .05$); serum (27.7 +/- 6.8, 10.8 +/- 2.7, and 12.1 +/- 2.8 nmol/L), skin tissue (2251.3 +/- 560.5, 802.7 +/- 228.8, and 790.1 +/- 188.3 nmol/wet.g), and lung (157.3 +/- 19.5, 109.1 +/- 23.9, and 81.9 +/- 20.3 nmol/wet.g). These data suggest that PC-SOD may be a protective agent against free radical-induced vasodilatation caused by severe, extensive burns.

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Topical transduction of superoxide dismutase mediated by HIV-1 Tat protein transduction domain ameliorates 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced inflammation in mice.

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A domain (RKKRRQRRR) derived from HIV-1 Tat is one of the most efficient protein transduction domains (PTD) for delivering macromolecules including proteins into cells and tissues. Antioxidant enzymes such as superoxide dismutase (SOD) and catalase are major cellular defenses against oxidative stress which results in various diseases including skin inflammation. In this study, we examined the effect of SOD fused with HIV-1 Tat PTD (Tat-SOD) on TPA-induced skin inflammation in mice. Topical application of Tat-SOD to mice ears 1h after TPA application once a day for 3 days dose-dependently inhibited TPA-induced ear edema in mice. Topical application on mice ears of Tat-SOD also suppressed TPA-induced expression of proinflammatory cytokines such as TNF-alpha, IL-1beta, and IL-6 as well as cyclooxygenase-2 (COX-2) and production of PGE(2). Furthermore, topical application of Tat-SOD resulted in significant reduction in activation of NF-kappaB and mitogen-activated protein kinases (MAPK) in the mice ears treated with TPA. These data demonstrates that Tat-SOD inhibits TPA-induced inflammation in mice by reducing the levels of expression of proinflammatory cytokines and enzymes regulated by the NF-kappaB and MAPK and can be used as a therapeutic agent against skin inflammation related to oxidative damage.

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Antinecrotic and antioxidant effects of superoxide dismutase during skin ischemia.

[Article in English, Russian]

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Antinecrotic activity of SOD was studied in rats with experimental skin ischemia. Treatment with SOD increased activity of endogenous SOD in skin homogenates (by 70 and 26% compared to the ischemic and intact skin, respectively). However, the rate of superoxide anion generation remained unchanged after SOD treatment. Creatine phosphate content and NAD/NADH redox potential increased by 16 and 21%, respectively, on day 3 after SOD administration. The increase in functional activity of the energy supply system and rise in the reserve capacity of the antioxidant protection system contribute to inhibition of lactate dehydrogenase and creatine phosphokinase and decrease in the cytolysis index under the influence of SOD. Our results indicate that SOD produces the antinecrotic effect and holds much promise for the therapy of skin ischemia.

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Assessment of physical and antioxidant activity stability, in vitro release and in vivo efficacy of formulations added with superoxide dismutase alone or in association with alpha-tocopherol.

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A topical formulation was added with different concentrations of superoxide dismutase (SOD) alone or in association with alpha-tocopherol (alpha-TOC). The physical stability was evaluated by rheological behavior of formulations stored at 4 degrees C, 30 degrees C/60% RH and 40 degrees C/70% RH for 6 months. SOD alone and formulations containing SOD 0.2%, 0.4% or 0.6% or SOD and alpha-TOC were stored in the same conditions and the enzymatic activity was evaluated by the superoxide anion scavenging using chemiluminescence measurement. In vitro release study was carried out using modified Franz diffusion cell and SOD formulations photoprotection against skin erythema was observed for 72 h. SOD and alpha-TOC formulation proved to be instable, since the interaction between the antioxidants led to both physical and enzymatic activity instability. SOD formulations showed to be physically stable and maintained the enzymatic activity for 6 months when stored at 4 and 30 degrees C/60% RH. Despite the fact of low SOD release from the formulation, it was effective in inhibiting the UVB-induced skin erythema for 48 h after a single application. Topical administration of antioxidants provides an efficient way to enrich the endogenous cutaneous protection system, and SOD formulations could be used for improving photoprotection of skin.

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Cancer Res. 2005 Feb 15;65(4):1401-5.

A mechanism-based antioxidant approach for the reduction of skin carcinogenesis.

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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-PyP(5+)) 12 hours after each TPA treatment. Biochemical studies showed that MnTE-2-PyP(5+) 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-PyP(5+) suppressed mitosis without interfering with apoptosis. Remarkably, the incidence and multiplicity of skin tumors were reduced in mice that received MnTE-2-PyP(5+) before cell proliferation. These results show a novel strategy for an antioxidant approach to cancer intervention.

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Extracellular superoxide dismutase tissue distribution and the patterns of superoxide dismutase mRNA expression following ultraviolet irradiation on mouse skin.

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Superoxide dismutases (SODs) are believed to play a crucial role in protecting cells against oxygen toxicity. There are three forms of SOD: cytosolic Cu-Zn SOD, mitochondrial Mn SOD, and extracellular SOD (EC SOD). Extracellular SOD is primarily a tissue enzyme, but the role of EC SOD in skin is unclear. Therefore, this study investigated the distribution of EC SOD in the skin using immunohistochemistry and examining the patterns of EC SOD gene expression following ultraviolet (UV) irradiation in comparison with those of Cu-Zn SOD and Mn SOD in mouse dorsal skin using Northern blot analysis. Immunohistochemical analysis showed that EC SOD was abundantly located in the epidermis as well as in the dermis, but the gene expression of EC SOD mRNA was more abundant in the dermis than in the epidermis. The gene expression levels of all three types of SODs after UV irradiation were induced differently according to the type and UV irradiation dose. The EC SOD mRNA expression level was increased relatively later than that of Cu-Zn SOD and Mn SOD. The EC SOD mRNA level was significantly higher at 6 h and 48 h after UVA irradiation and psoralen plus ultraviolet-A treatment, respectively. Ultraviolet-B irradiation increased the EC SOD mRNA expression level, with maximum at 48 h. These suggest that EC SOD participates in the majority of antioxidant systems in the skin, and it may have different defensive roles from Cu-Zn SOD and Mn SOD against UV-induced injury of the skin.

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