

SOD and Arthritis

[Arthritis Rheum.](#) 2005 Nov;52(11):3479-91.

Extracellular superoxide dismutase and oxidant damage in osteoarthritis.

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OBJECTIVE: To use human cartilage samples and a mouse model of osteoarthritis (OA) to determine whether extracellular superoxide dismutase (EC-SOD) is a constituent of cartilage and to evaluate whether there is a relationship between EC-SOD deficiency and OA. **METHODS:** Samples of human cartilage were obtained from femoral heads at the time of joint replacement surgery for OA or femoral neck fracture. Samples of mouse tibial cartilage obtained from STR/ort mice and CBA control mice were compared at 5, 15, and 35 weeks of age. EC-SOD was measured by enzyme-linked immunosorbent assay, Western blotting, and immunohistochemistry techniques. Real-time quantitative reverse transcription-polymerase chain reaction was used to measure messenger RNA for EC-SOD and for endothelial cell, neuronal, and inducible nitric oxide synthases. Nitrotyrosine formation was assayed by Western blotting in mouse cartilage and by fluorescence immunohistochemistry in human cartilage. **RESULTS:** Human articular cartilage contained large amounts of EC-SOD (mean +/- SEM 18.8 +/- 3.8 ng/gm wet weight of cartilage). Cartilage from patients with OA had an approximately 4-fold lower level of EC-SOD compared with cartilage from patients with hip fracture. Young STR/ort mice had decreased levels of EC-SOD in tibial cartilage before histologic evidence of disease occurred, as well as significantly more nitrotyrosine formation at all ages studied. **CONCLUSION:** EC-SOD, the major scavenger of reactive oxygen species in extracellular spaces, is decreased in humans with OA and in an animal model of OA. Our findings suggest that inadequate control of reactive oxygen species plays a role in the pathophysiology of OA.

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The therapeutic effect of extracellular superoxide dismutase (EC-SOD) mouse embryonic fibroblast (MEF) on collagen-induced arthritis (CIA) mice.

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Rheumatoid arthritis is a chronic inflammatory disease. The generation of reactive oxygen species (ROS) within an inflamed joint has been suggested as playing a significant pathogenic role. Extracellular superoxide dismutase (EC-SOD) is a major scavenger enzyme of ROS, which has received growing attention for its therapeutic potential. To investigate the therapeutic effect of EC-SOD in mice with collagen-induced arthritis (CIA), we used mouse embryonic fibroblast (MEF) of transgenic mice that overexpresses EC-SOD on the skin by using hK14 promoter. DBA/1 mice that had been treated with bovine type II collagen were administered subcutaneous injections of EC-SOD transgenic MEF (each at 1.4×10^6 cells) on days 28, 35, and 42 after primary immunization. To test EC-SOD activity, blood samples were collected in each group on day 49. The EC-SOD activity was nearly 1.5-fold higher in the transgenic MEF-treated group than in the nontransgenic MEF-treated group ($p < 0.05$). The severity of arthritis in mice was scored in a double-blind manner, with each paw being assigned a separate clinical score. The severity of arthritis in EC-SOD transgenic MEF-treated mice was significantly suppressed in the arthritic clinical score ($p < 0.05$). To investigate the alteration of cytokine levels, ELISA was used to measure blood samples. Levels of IL-1beta and TNF-alpha were reduced in the transgenic MEF-treated group ($p < 0.05$). Abnormalities of the joints were examined by H&E staining. There were no signs of inflammation except for mild hyperplasia of the synovium in the transgenic MEF-treated group. The proliferation of CII-specific T cells was lower in the transgenic MEF-treated mice than in those in the other groups. The transfer of EC-SOD transgenic MEF has shown a therapeutic effect in CIA mice and this approach may be a safer and more effective form of therapy for rheumatoid arthritis.

Publication Types: [Research Support, Non-U.S. Gov't](#)

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SOD and Arthritis

[J Control Release](#). 2005 Mar 21;103(2):419-34. Epub 2005 Jan 15.

Developments in the rat adjuvant arthritis model and its use in therapeutic evaluation of novel non-invasive treatment by SOD in Transfersomes.

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The aim of this study was firstly to refine a rat model of arthritis, the adjuvant arthritis (AA) model, by studying the time course of the disease, introducing new evaluation methods such as haematological and biochemical parameters in order to identify the main stages of the disease. An optimisation of treatment schedule and evaluation criteria was developed. This refinement provided novel non-invasive anti-inflammatory treatment of the AA with SOD by using mixed lipid vesicles specially developed for transdermal delivery, Transfersomes (Tfs), this being the second major aim. The time course of AA includes a first stage: 1 day after the disease induction, the induced paw volume more than doubled and the paw circumference increased by approx. 50%. Two weeks later, another stage occurred where the disease shifted from the local arthritis form towards polyarthritis: an additional increase of volume and circumference of the induced and non-induced paws, occurred. The animals also started to loose weight around day 14 after the disease induction. Radiographic observable lesions increased correspondingly. Treatment of animals, started at day 1 after induction, by epicutaneous application of SOD-Tfs showed that 1 mg SOD/kg body weight is more efficient than 0.66 mg SOD /kg body weight. As a positive control, SOD liposomes intravenously injected were used for comparison and confirmed the biological efficiency of epicutaneously applied SOD in Tfs. SOD solution and empty Tfs epicutaneously applied exerted no effect. In addition, epicutaneous application of SOD-Tfs used prophylactically was able to suppress the induced rat paw oedema. Radiographic images showed less joint lesions in SOD-Tfs treated animals in comparison with control and placebo treated rats. It was shown for the first time that SOD incorporated into Tfs and applied onto a skin area not necessarily close to the inflamed tissue is able to promote non-invasive treatment of induced arthritis.

Publication Types:

- [Research Support, Non-U.S. Gov't](#)

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SOD and Arthritis

[Activity of superoxide dismutase (CuZn-SOD) in erythrocytes of patients after hips alloplasty]

[Article in Polish]

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Hip osteoarthritis leads, among others, to abnormally decreased physical activity (hypokinesia). Adverse effect of physical inactivity can cause inhibition of anabolic processes in favour of enhancement of protein, carbohydrate, and lipid catabolic reactions, as well as inadequate metabolism of polyunsaturated fatty acids. These alterations can induce an increased lipid peroxide synthesis, overproduction of reactive oxygen species (ROS) and acceleration of lipid peroxidation processes. The aim of the study was to determine superoxide dismutase activity (CuZn-SOD) in red blood cells of patients suffering from hip osteoarthritis prior to and following total alloplasty as compared to healthy subjects, and also to evaluate effect of hypokinesia on oxidative stress.

MATERIAL AND METHODS; CuZn-SOD activity in red blood cells was determined according to the Misra and Fridovich method in 36 patients with hip osteoarthritis hospitalized at the Traumatic-Orthopaedic Department of the Ministry of Internal Affairs and Administration Hospital in Łódź. **RESULTS:** In patients with decreased physical activity in ten days after alloplasty, enzyme activity increased (+24.9%), one month since the operation it decreased, but it higher as compared to result activity of CuZn-SOD prior to surgery (+16.8%). **CONCLUSIONS:** The results activity of superoxide dysmutase leads to ROS generation and their overgeneration in hip osteoarthritis and in first time of treatment.

Publication Types:

- [English Abstract](#)

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Increased levels of autoantibodies against catalase and superoxide dismutase associated with oxidative stress in patients with rheumatoid arthritis and systemic lupus erythematosus.

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OBJECTIVE: To evaluate the level of autoantibodies against superoxide dismutase (SOD) and catalase (CAT) in the sera of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) Tunisian patients, to study the oxidative profile among the same patients and to establish a correlation between the two parameters in order to understand the role of each one in the genesis of the two diseases. **METHOD:** Using a standard enzyme-linked immunosorbent assay (ELISA), the levels of immunoglobulin G (IgG) and IgM directed against CAT and SOD in the sera of 39 RA patients, 40 SLE patients, and 50 control healthy individuals were evaluated. The oxidative/antioxidative profile was tested by measuring serum malondialdehyde (MDA), conjugated dienes (CD), CAT activity, and SOD activity. **RESULTS:** Our data showed increased levels of IgG antibodies (Ab) against CAT in both groups of patients ($p < 0.05$) compared to control subjects. However, the SLE patients displayed an increased level of anti-SOD IgG ($p < 0.05$). In all patients the lipid peroxidation was confirmed by high levels of MDA and conjugated dienes ($p < 0.05$). RA patients exhibited an increasing CAT and SOD activity in their sera ($p < 0.05$) with a positive correlation observed between CAT and IgG anti-CAT ($p < 0.05$). The same results were observed for SLE patients. In addition, a positive correlation was observed between anti-CAT Ab and anti-SOD Ab in SLE patients ($p < 0.05$). **CONCLUSION:** Collectively, these results suggested that the primary factor causing the oxidative stress observed in RA and SLE is excessive free radical production rather than impaired CAT or SOD activity due to autoantibody inhibition.

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Reactive oxygen species and superoxide dismutases: role in joint diseases.

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Reactive oxygen species (ROS) are produced in many normal and abnormal processes in humans, including atheroma, asthma, joint diseases, aging, and cancer. The superoxide anion $O_2^{(-)}$ is the main ROS. Increased ROS production leads to tissue damage associated with inflammation. Superoxide dismutases (SODs) convert superoxide to hydrogen peroxide, which is then removed by glutathione peroxidase or catalase. Thus, SODs prevent the formation of highly aggressive ROS, such as peroxynitrite or the hydroxyl radical. Experimental models involving SOD knockout or overexpression are beginning to shed light on the pathophysiological role of SOD in humans. Although the antiinflammatory effects of exogenous native SOD (orgotein) are modest, synthetic SOD mimetics hold considerable promise for modulating the inflammatory response. In this review, we discuss new knowledge about the role of the superoxide anion and its derivatives as mediators of inflammation and the role of SODs and SOD mimetics as antioxidant treatments in joint diseases such as rheumatoid arthritis, osteoarthritis, and crystal-induced arthropathies.

Publication Types:

- [Research Support, Non-U.S. Gov't](#)
- [Review](#)

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Targeted delivery of catalase and superoxide dismutase to macrophages using folate.

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Reactive oxygen species (ROS) secreted by activated macrophages play a central role in causing rheumatoid arthritis, and therapeutics that can inhibit the production of ROS by macrophages have great clinical potential. Superoxide dismutase (SOD) and catalase (CAT) are two enzymes that scavenge ROS and have great potential for treating rheumatoid arthritis. However, clinical trials with these enzymes have been ineffective, due to drug delivery problems, and effective SOD and CAT delivery vehicles are greatly needed. In this communication, we demonstrate that CAT and SOD can be effectively targeted to activated macrophages, via the folate receptor. Folate was conjugated to CAT and SOD using NHS/EDC chemistry with high efficiency. Cell culture experiments demonstrated that folate conjugation increased their ability to scavenge ROS, produced by the macrophages, and also enhanced their uptake into activated macrophages. We anticipate numerous applications of folate-conjugated CAT and SOD in treating inflammatory diseases, based on their efficacy and straightforward synthesis.

Publication Types:

- [Research Support, N.I.H., Extramural](#)
- [Research Support, Non-U.S. Gov't](#)
- [Research Support, U.S. Gov't, Non-P.H.S.](#)

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Enzymosomes with surface-exposed superoxide dismutase: in vivo behaviour and therapeutic activity in a model of adjuvant arthritis.

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Acylated Superoxide Dismutase (Ac-SOD) enzymosomes, liposomal enzymatic systems expressing catalytic activity in the intact form, were previously characterized. The main scope of the present work was to investigate the biological behaviour of Ac-SOD inserted in the lipid bilayer of liposomes, in comparison with SOD located in the aqueous compartment of liposomes. Two types of liposomes were used: conventional liposomes presenting an unmodified external surface and long circulating liposomes coated with poly (ethylene glycol) (PEG). Liposomal formulations of Ac-SOD and SOD were prepared and labelled with indium-111 and their in vivo fate compared. Data obtained led us to the conclusion that, for liposomes coated with PEG the in vivo fate was not influenced by the insertion of Ac-SOD in the lipid bilayers. The potential therapeutic effect of Ac-SOD enzymosomes was compared with SOD liposomes in a rat model of adjuvant arthritis. A faster anti-inflammatory effect was observed for Ac-SOD enzymosomes by monitoring the volume of the inflamed paws. The present results allowed us to conclude that Ac-SOD enzymosomes are nano-carriers combining the advantages of expressing enzymatic activity in intact form and thus being able to exert therapeutic effect even before liposomes disruption, as well as acting as a sustained release of the enzyme.

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Enhancement of collagen-induced arthritis in mice genetically deficient in extracellular superoxide dismutase.

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OBJECTIVE: To examine the influence of superoxide on the severity of collagen-induced arthritis (CIA) in mice. **METHODS:** CIA was induced in DBA/1J mice lacking the extracellular superoxide dismutase (EC-SOD) gene (knockout [KO]) and in normal DBA/1J mice (wild-type [WT]). **RESULTS:** The clinical disease activity score was significantly higher in EC-SOD-KO mice than in WT mice between days 36 and 53, and the histologic scores for joint damage on day 53 increased 2-fold or more in the EC-SOD-KO mice. There were no significant differences between the 2 groups of mice in proliferation indices of spleen or lymph node cells in vitro after stimulation with type II collagen. Although both IgG1 and IgG2a anticollagen antibody levels increased in both groups of mice between days 21 and 53, there were no significant differences between the 2 groups. Lipopolysaccharide-stimulated spleen cells from EC-SOD-KO mice produced greater levels of tumor necrosis factor alpha (TNFalpha) over 48 hours in culture compared with cells from WT mice. Increased steady-state levels of messenger RNA (mRNA) for interferon-gamma (IFNgamma), TNFalpha, and interleukin-1beta (IL-1beta), and lower levels of IL-1 receptor antagonist (IL-1Ra) mRNA were present in the joints of the EC-SOD-KO mice compared with the WT mice. **CONCLUSION:** The absence of EC-SOD leads to more severe CIA, which may be accompanied by enhanced production of the proinflammatory cytokines IFNgamma, TNFalpha, and IL-1beta, and decreased production of the antiinflammatory cytokine IL-1Ra in the joints.

Publication Types:

- [Research Support, U.S. Gov't, P.H.S.](#)

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Correlation between soluble intercellular adhesion molecule 1 level and extracellular superoxide dismutase activity in rheumatoid arthritis: a possible association with disease activity.

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OBJECTIVE: We investigated serum levels of soluble intercellular adhesion molecule-1 (sICAM-1) and the activity of extracellular superoxide dismutase (EC-SOD) in rheumatoid arthritis (RA). We also considered whether there was a correlation between sICAM-1 and EC-SOD and disease activity. **METHODS:** Levels of sICAM-1 were measured in serum from 42 patients with active RA and 30 control subjects by enzyme-linked immunosorbent assay (ELISA). EC-SOD activity was determined in sera isolated from patients with active RA and from controls. **RESULTS:** The serum levels of sICAM-1 were significantly higher in patients with RA than in control subjects ($p < 0.001$). In contrast, the activity of EC-SOD was significantly lower in RA patients than in healthy controls ($p < 0.001$). A significant negative correlation was found between the levels of sICAM-1 and EC-SOD activity ($r = -0.39$, $p < 0.01$). There was a statistically positive correlation between sICAM-1 levels with Ritchie articular index (RAI) score and C-reactive protein (CRP) ($r = 0.32$, $p < 0.05$; $r = 0.44$, $p < 0.01$, respectively). **CONCLUSIONS:** These results show that the increased levels of sICAM-1 present in active RA patients might be due to the decreased activity of EC-SOD, and increased levels of sICAM-1 may also reflect disease status or activity.

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[Extracellular superoxide dismutase (EC-SOD)--structure, properties and functions]

[Article in Polish]

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EC-SOD catalyzes the dismutation of superoxide radical to hydrogen peroxide and oxygen in the interstitial spaces of tissues and in extracellular fluids (plasma, lymph, and synovial fluid). It eliminates superoxide radicals from the cell environment and prevents the formation of reactive oxygen species and their derivatives. EC-SOD is a secretory, tetrameric glycoprotein containing copper and zinc, with a high affinity to certain glycosaminoglycans, such as heparin and heparan sulfate. It plays an important role in maintaining vascular tone, lung function, and the metabolism of NO, and in the pathology of such diseases as atherosclerosis, diabetes, and arthritis. This paper describes EC-SOD structure, function in tissues, and possibilities of therapy with application of this enzyme.

Publication Types:

- [English Abstract](#)
- [Review](#)

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