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Original Contribution

Protandim attenuates intimal hyperplasia in human saphenous veins cultured ex vivo via a catalase-dependent pathway

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Abstract

Human saphenous veins (HSVs) are widely used for bypass grafts despite their relatively low long-term patency. To evaluate the role of reactive oxygen species (ROS) signaling in intima hyperplasia (IH), an early stage pathology of vein-graft disease, and to explore the potential therapeutic effects of up-regulating endogenous antioxidant enzymes, we studied segments of HSV cultured ex vivo in an established ex vivo model of HSV IH. Results showed that HSV cultured ex vivo exhibit an ~ 3-fold increase in proliferation and ~ 3.6-fold increase in intimal area relative to freshly isolated HSV. Treatment of HSV during culture with Protandim, a nutritional supplement known to activate Nrf2

and increase the expression of antioxidant enzymes in several in vitro and in vivo models, blocks IH and reduces cellular proliferation to that of freshly isolated HSV. Protandim treatment increased the activity of SOD, HO-1, and catalase 3-, 7-, and 12-fold, respectively, and decreased the levels of superoxide ($O_2^{\bullet -}$) and the lipid peroxidation product 4-HNE. Blocking catalase activity by cotreating with 3-amino-1,2,4-triazole abrogated the protective effect of Protandim on IH and proliferation. In conclusion, these results suggest that ROS-sensitive signaling mediates the observed IH in cultured HSV and that up-regulation of endogenous antioxidant enzymes can have a protective effect.

Section snippets

Human vessel harvest and preparation

The Institutional Review Board at The Ohio State University approved all use of human tissue in this study and all patients provided written informed consent for tissue donation. Segments of the great saphenous vein that were in excess or unused at the end of CABG were obtained from consenting patients. Veins obtained from patients with documented varicosities of the long saphenous vein and communicable diseases such as HIV and hepatitis B or C were excluded. All vessels were removed by an

Protandim inhibits the formation of IH and the increase in cellular proliferation in HSV cultured ex vivo

Elastin staining revealed that HSV cultured ex vivo exhibited IH (Figs. 1B and 2A) and medial thickening (Fig. 2C) accompanied by increased cellular proliferation (Figs. 2B

and D) compared to freshly isolated (uncultured) HSV (Figs. 1A and 2A–D). These changes were attenuated by adding Protandim to HSV cultured ex vivo (Figs. 1C and 2A–D). Supplementation with NAC also inhibited the increase in intimal and medial areas as well as cellular proliferation (Fig. 2). All freshly isolated and

Discussion

The major findings of these studies are the following. (1) Treatment of HSV with Protandim or NAC blocks both IH and medial thickening as well as the increased cellular proliferation in an established ex vivo model of the early stages of vein-graft disease. (2) Protandim treatment results in a significant increase in activity and/or abundance of catalase, HO-1, and SOD, which is accompanied by a decrease in $O_2^{\bullet -}$ levels and the lipid peroxidation product 4-HNE. (3) Blocking catalase activity by

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Withaferin A induces heme oxygenase (HO-1) expression in endothelial cells via activation of the Keap1/Nrf2 pathway
2016, Biochemical Pharmacology
Citation Excerpt :
Some Nrf2 activating compounds have already been tested in animal models or even human clinical trials and were demonstrated to protect against moderate pulmonary hypertension, chronic kidney disease and multiple sclerosis [71–73]. Probably one of the best known Nrf2 activators is the dietary supplement Protandim®, also termed the Nrf2 synergizer, which by different laboratories was validated to activate Nrf2 and to reduce oxidative stress [71,74,75]. Interestingly, Ashwaganda extract is one of its ingredients suggesting that Nrf2 activation by Protandim® might be dependent on the presence of WA.
Show abstract
Nrf2 activation: A potential strategy for the prevention of acute mountain sickness
2013, Free Radical Biology and Medicine
Citation Excerpt :
All compounds were tested in a dose–response fashion (1–300 μg/ml) in the presence or absence of the PI3K inhibitor LY294002 (Cell Signaling Technologies, Cat. No. 9901) and evaluated with the Nrf2 activator Protandim [11,14–19]. Results are shown in Table 1.
Show abstract
Elucidating the Role of Protandim and 6-Gingerol in Protection Against Osteoarthritis
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MFAP4 Promotes Vascular Smooth Muscle Migration, Proliferation and Accelerates Neointima Formation
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Phytochemical activation of Nrf2 protects human coronary artery endothelial cells against an oxidative challenge

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