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The Role of Transcription Factor Nrf2 in Osteoarthritis by Protandim Induction

Purpose: Osteoarthritis (OA) is the most common joint disorder and a leading cause of physical disability. Over the past years, we studied the complex role of the lipid peroxidation product 4-hydroxynonenal (HNE) in osteoarthritis (OA). We are the first to demonstrate that HNE level was higher in patients with OA as compared to healthy subjects. Moreover, we demonstrated that HNE induces a cascade of catabolic and inflammatory events involved in OA process. We recently showed that the expression of glutathione-s-transferase A4-4 (*GSTA4-4*), a gene encoding the HNE-conjugating enzyme GSTA4-4, as well as nuclear factor erythroid 2-related factor 2 (Nrf2), which regulates *GSTA4-4* gene expression, is decreased in human OA cartilage compared to controls. **The objective of the present study is to explore the effects of Protandim, activator of Nrf2, on GSTA4-4 regulation, IL-1β-induced catabolic and inflammatory responses and H_2O_2-induced oxidative stress.**

Methods: Human OA chondrocytes were pre-treated with different concentrations of protandim for 1 hour followed by treatment with IL-1β or H2O2 for 24 hours. Metalloproteinase-13 (MMP-13), nitric oxide (NO), prostaglandin E2 (PGE2) and HNE were determined using commercial kits. GSTA4-4 mRNA level was assessed by real-time PCR

Results: Our findings showed that Protandim abolished IL-1β-induced MMP-13, NO, and PGE_2 production as well as H2O2-induced HNE generation. The effect of protandim is mediated, in part, by GSTA4-4 up-regulation

Conclusions: Collectively, these data strongly represent a new mechanism for the control of Nrf2 and GSTA4-4 expression in OA. Indeed, targeting mechanisms underlying their expression could be a promising avenue in OA treatment.