

PROTEIN KINASE SIGNALING CASCADE DURING NITRIC OXIDE-INDUCED APOPTOSIS, DEDIFFERENTIATION AND INFLAMMATORY RESPONSES OF ARTICULAR CHONDROCYTES

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Differentiated chondrocyte, which is the only cell type found in normal mature cartilage, synthesizes cartilage-specific extracellular matrix (ECM) to maintain matrix integrity. This homeostasis is destroyed in degenerative diseases, such as osteoarthritis and rheumatoid arthritis. Arthritis is characterized by structural and biochemical changes in chondrocytes and cartilage, including degradation of the cartilage matrix, insufficient synthesis of ECM due to loss of chondrocyte phenotype (i.e., de-differentiation), and increased numbers of apoptotic chondrocytes. It is now generally accepted that pro-inflammatory cytokines, such as interleukin-1 β and tumor necrosis factor- α , play a predominant role in structural and biochemical alterations in chondrocytes and cartilage by the stimulation of nitric oxide (NO) production via inducible NO synthase. NO causes cartilage destruction by inducing apoptosis, loss of differentiated phenotype (i.e. dedifferentiation), and inflammatory responses such as cyclooxygenase (COX)-2 expression and prostaglandin E₂ (PGE₂) production in articular chondrocytes. We, therefore, investigated the protein kinase signaling cascade involved in NO-induced apoptosis, dedifferentiation, and COX-2 expression in articular chondrocytes focused on the role of mitogen-activated protein (MAP) kinase and protein kinase C (PKC).

We demonstrated that direct production of NO by treating chondrocytes with an NO donor, sodium nitroprusside (SNP), induces apoptosis, dedifferentiation, and COX-2 expression in primary culture articular chondrocytes. NO-induced apoptosis and dedifferentiation of articular chondrocytes were regulated by opposite functions of MAP kinase subtypes, extracellular signal-regulated protein kinase (ERK) and p38 kinase [1,2]. NO-induced activation of ERK-1/-2 induces dedifferentiation with inhibitory effects on apoptosis, whereas activation of p38 kinase induces apoptosis and is responsible for maintenance of the differentiated phenotype. In addition to MAP kinase signaling, NO production also caused the inhibition of PKC α and - ζ activities [3]. The inhibition of PKC α activity is due to inhibition of its expression, which is independent of MAP kinase signaling. In contrast, PKC ζ activity is blocked as a result of p38 kinase activation, and inhibition of PKC ζ activity is followed by proteolytic cleavage by caspase-3. NO-induced activation of p38 kinase also activates nuclear factor (NF)- κ B [4]. NO-stimulated NF- κ B activation was inhibited by ectopic PKC α and ζ expression, whereas NO-stimulated inhibition of PKC α and ζ activity was not affected by NF- κ B inhibition. NO-induced NF- κ B activation leads to increased transcriptional expression of p53 that results in activation of caspase-3

to cause apoptosis. However, inhibition of NO-induced NF- κ B activity did not affect dedifferentiation, but did abrogate COX-2 expression and apoptosis [5,6]. Taken together, our results indicate that p38 kinase-dependent and -independent inhibition, of PKC ζ and α activity activates NF- κ B activity that regulates apoptosis and COX-2 expression, but not dedifferentiation in articular chondrocytes.

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