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Nitric oxide in apoptosis and differentiation of chondrocytes

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Nitric oxide (NO) is known to regulate cartilage destruction by causing de-differentiation and apoptosis of chondrocytes. We investigated aa the role of mitogen-activated protein (MAP) kinase subtypes, extracellular signal-regulated protein kinase (ERK)-1/-2 Erk-1 and -2and p38 kinase, in NO-induced apoptosis ofin the regulation of chondroc rabbit articular chondrocytes and its relationship with de-differentiation. Generation of NO with sodium nitroprusside (SNP) caused de-differentiation as indicated by stopping of type II collagen expression and proteoglycan synthesis. NO generation also caused apoptosis that is accompanied by p53 accumulation and caspase-3 activation. SNP treatment caused activation of ERK-1/-2 and p38 kinase. Inhibition of ERK-1/-2 with PD98059 rescued SNP-induced de-differentiation but enhanced apoptosis up to 2-fold, whereas inhibition of p38 kinase with SB203580 enhanced de-differentiation with complete blockade of apoptosis. The stimulatory effects of ERK inhibition on apoptosis accompanied increased p53 accumulation and caspase-3 activity, whereas the inhibitory effects of p38 kinase blockade accompanied reduced p53 accumulation and caspase-3 activity. Thus, the results indicated that NO-induced p38 kinase activity function as an induction signal for apoptosis and maintenance of chondrocytes phenotype, whereas ERK activity causes de-differentiation and function as anti-apoptotic signal. NO generation is much less pro-apoptotic in de-differentiated chondrocytes induced by a serial monolayer culture or phorbol ester treatment. Compared with differentiated chondrocytes, NO-induced p38 kinase activity is low in de-differentiated cells with less accumulation of p53 and activity of caspase-3. Taken together, our results indicated that ERK-1/-2 and p38 kinase oppositely regulate NO-induced apoptosis of chondrocytes in association with p53 accumulation, caspase-3 activation, and differentiation status