14c Elucidation of Intracellular Signaling Pathways in Shear-Activated Chondrocytes: a Role in Arthritis

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COX-2 expression, inflammation and apoptosis preferentially occur in areas of cartilage exposed to prolong periods of high laminar shear flow (20 dyn/cm^2, 48 hrs). Recent evidence has linked COX-2 inhibitors to an increased likelihood of cardiovascular anomalies, thus demanding alternative therapeutics for inflammatory diseases. Using cDNA microarray technology coupled with novel bioinformatics tools, we have identified a target set of genes repressed during extended shear loading including several Phase II genes, which contain an antioxidant-response element (ARE) in their promoter region and function to protect cells against oxidant stress. Promoter activity assays indicate both a time- and shear stress-dependent decrease in ARE promoter activity in chondrocytic cells, signifying a potential mechanism for the observed increase of reactive oxygen radicals present in osteoarthritic tissue. The use of Phase II inducers sulforaphane (1.25 μM) and D3T (5 μM) are capable of restoring phase II enzyme activity and inhibiting COX-2 transcription and PGE_2 production, while also abrogating apoptosis in sheared chondrocytes. Additionally, CAY10404, a specific COX-2 inhibitor, was able to restore Phase II activity levels and abrogate inflammatory signaling, indicating potential feedback between pro- and anti-inflammatory pathways. Phase II inducers represent a novel therapeutic tool for arthritis, lacking the potentially harmful side-effects associated with COX-2 inhibitors, while conveying many atheroprotective effects to the vascular wall, making such therapeutics extremely attractive.