Models for Studying Cartilage Biology in the Context of Osteoarthritis

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Proteins produced in response to excessive mechanical loading and inflammation in joints not only stimulate the production of enzymes that break down the cartilage but also impair the ability of the chondrocyte, the unique cell type in adult cartilage, to repair the damage. We have used several strategies for identifying and characterizing mediators involved in the pathogenesis of osteoarthritis (OA), including culture models of primary human and mouse chondrocytes and cell lines, mouse models, and human cartilage samples. Human cartilage is a complex tissue of matrix proteins that varies from superficial to deep layers and from loaded to unloaded zones. During OA development the normally quiescent chondrocytes with low matrix turnover undergo phenotypic modulation resulting in matrix destruction and abnormal repair. We have identified new genes, not known previously to act in cartilage, including growth arrest and DNA damage (GADD) 45β and the ETS transcription factor, ESE1/ELF3, induced in chondrocytes by bone morphogenetic protein (BMP)-2 and inflammatory cytokines, respectively. Both GADD45β and ESE1/ELF3 are induced by NFκB and in turn, upregulate matrix metalloproteinase (MMP)-13 and suppress type II collagen gene (COL2A1) gene expression (1). A microarray study to compare IL-1β and BMP-2-induced genes resulted in the discovery of a novel role for GADD45β, an anti-apoptotic factor during genotoxic stress and cell cycle arrest, as a mediator of MMP-13 and type X collagen (Col10a1) gene expression during hypertrophic chondrocyte differentiation (2). Since GADD45β is present in quiescent chondrocytes in normal cartilage and in early OA cartilage at sites peripheral to the lesion in chondrocyte clusters and in deep zone chondrocytes, it may promote chondrocyte survival, while promoting hypertrophy during tidemark advancement (3). Current studies involve both in vitro analysis of signaling and transcriptional mechanisms that regulate the expression and activities of GADD45β and ESE-1 and in vivo analysis of the consequences of knockout and transgenic overexpression of these genes in mouse models, using surgical OA (good matrix with abnormal loading) and genetic models with OA-like pathology (bad matrix with normal loading) during aging. In further studies, we are examining the epigenetic regulation of MMP-13 and using proteomics and genomics approaches to map the signaling networks and microRNA targets that impact on gene expression programs during the onset and progression of OA. These studies may to lead to the identification of critical targets for therapy to block cartilage damage and promote effective cartilage repair.

Selected Publications:

1. Peng H, Tan L, Osaki M, Zhan Y, Ijiri K, Tsuchimochi K, Otero M, Wang H, Choy BK, Grall FT, Gu X, Libermann TA, Oettgen P, Goldring MB. ESE-1 is a potent repressor of type II collagen gene (COL2A1) transcription in human chondrocytes. J Cell Physiol 2008; 251: 562-573.
2. Ijiri K, Zerbini LF, Peng H, Otu HH, Tsuchimochi K, Otero M, Dragomir C, Walsh N, Bierbaum BE, Mattingly D, van Flandern G, Komiya S, Aigner T, Libermann TA, Goldring MB. Differential expression of GADD45β in normal and osteoarthritic cartilage: Potential role in homeostasis of articular chondrocytes. Arthritis Rheum 2008; 58:2075-2087.
3. Ijiri K, Zerbini LF, Peng H, Correa RG, Lu B, Walsh N, Zhao Y, Taniguchi N, Huang XL, Otu H, Wang H, Wang JF, Komiya S, Ducy P, Rahman MU, Flavell RA, Gravallese E, Oettgen P, Libermann TA, Goldring MB. A novel role for GADD45β as a mediator of MMP-13 gene expression during chondrocyte terminal differentiation. J Biol Chem 2005; 280:38544-38555.