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Collagen Mutant Mouse Models Provide an Important Tool to Study Osteoarthritis

Brandon J Rose[1], **Robert E Seegmiller**[2], **Laura C Bridgewater**[3] **and David L Kooyman**[1*]

[1]*Department of Physiology and Developmental Biology, Brigham Young University, 4005 LSB, Provo, USA*

[2]*College of Dental Medicine, Roseman University of Health Sciences, South Jordan, USA*

[3]*Department of Microbiology and Molecular Biology, Brigham Young University, 4007 LSB, Provo, USA*

[*]**Corresponding author:** David L Kooyman, Department of Physiology and Developmental Biology, Brigham Young University, 4005 LSB, Provo, UT 84602, USA, Tel: 801-422-6399; Fax: 801-422-0004; E-mail: david_kooyman@byu.edu

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Collagen Mutant Mouse Models

Mutations in the human type II (COL2A1) collagen gene appear to be the basis for many skeletal disorders such as spondyloepiphyseal dysplasia [1], achondrogenesis, Kniest, and Stickler syndrome [2]. Several of these conditions include early-onset osteoarthritis in addition to the chondrodysplasia phenotype [3]. Other collagen genes are also involved etiologically in the chondrodysplasias, e.g., an autosomal dominant form of Stickler syndrome, characterized by mild spondyloepiphyseal dysplasia (SED) and early-onset osteoarthritis, results from a mutation involving the COL11A2 gene that encodes the α2 (XI) chain of the quantitatively minor fibrillar type XI collagen [4]. Multiple epiphyseal dysplasia in humans involving flattening of the epiphyses, shortening of endochondral bones, and early-onset osteoarthritis has been linked to a mutation in type IX collagen [5], and mice made transgenic for α1 (IX) mutation have been shown to develop osteoarthritis and intervertebral disc degeneration prematurely [6]. The Disproportionate micromelia (Dmm) mouse has a mutation that causes lethal dwarfism in the homozygote and mild dwarfism in the heterozygote. This strain of mouse has a three-nucleotide deletion in the C-propeptide region of the Col2a1 gene, a gene highly conserved with its human homologue, COL2A1 [7]. Both genes encode for type II collagen, the most abundant protein in hyaline cartilage [8]. As a result of the Col2a1 deletion, Dmm/+ mice have a decrease of proteoglycan production in the hyaline cartilage that typically yields early onset degradation and OA. We have previously reported OA-like changes in a mouse model that bears a mutation in the Col2a1 gene, similar to that found in humans, that behaves as a recessive mutation resulting in no obvious phenotype in the heterozygote [9]. The mouse mutation was named spondyloepiphesial dysplasia congenita (sedc) [10] because when homozygous it produces features that resemble the most common clinical phenotypes of SED congenita in humans [11]. Thus in both mouse and human it is known that collagen gene mutations that lead to a wide variety of disorders of the skeletal system can also lead to premature osteoarthritis.

While chondrodysplasia models of OA have been important in advancing our understanding of OA, the majority of OA cases in humans are not associated with any recognizable features of chondrodysplasia. This raises the question of whether the cartilage collagen genes play a significant role in the majority of human OA, or are only relevant in the minority of cases associated with chondrodysplasias. It has been shown that, in fact, at least two different heterozygous point mutations in the triple helical domain of the COL2A1 gene can cause degenerative joint disease in humans in the absence of other phenotypic abnormalities [12]. We have also shown that the heterozygous sedc mouse, although morphometrically normal, exhibits early onset OA [9]. This puzzle was solved, in part, when we demonstrated using electron microscopy that compared with controls, mutant articular cartilage displayed decreased fibril diameter concomitant with increases in size of the pericellular space, Mankin and OARSI scores, cartilage thickness, chondrocyte clustering, proteoglycan staining and horizontal fissuring [13]. We concluded that collagen in the mutant's articular cartilage (both heterozygote and homozygote) fails to provide the normal meshwork required for matrix integrity and overall cartilage stability.

However, one area that mouse chondrodysplasia models may have particular importance is OA associated with apoptosis [14]. The unfolded protein stress response (UPR) has been implicated in OA progression. We and others have reported that collagen mutant mouse strains Dmm, Cho and Sedc exhibit distended ER and Golgi, consistent with the mis-folded type II collagen being trapped in the ER rather than secreted to the extracellular matrix [15,16]. We have previously reported a 1.66 fold increase in BiP expression in Dmm/+ newborn articular cartilage compared to wild type ($p = 0.01$). We have also observed increased expression of caspase-3 signaling in the Sedc mouse model knee and TMJ sections in association with a substantial decrease in cellularity.

Chondrodysplasia mouse models are an important tool to study OA, given that they can help elucidate key bio-molecular pathways associated with the hypo-cellularity that is characteristic of this debilitating disease.

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