

## Cell Mechanics and Mechanobiology in the Intervertebral Disc

Lori A. Setton

Departments of Biomedical Engineering and Surgery, Duke University

*Durham, North Carolina USA*

**INTRODUCTION:** Substantial biological remodeling of the intervertebral disc occurs in response to altered mechanical loading, changes that may contribute to the health or degeneration of the intervertebral disc. Work in our laboratory has focused on understanding the responses of isolated intervertebral disc cells to physical stimuli, and both the factors and mechanisms that play a role in regulating those responses *in vivo*.

**CELL MICROMECHANICS:** Modeling has predicted that cells within the intervertebral disc experience spatially-varying mechanical stimuli, including hydrostatic pressure, fluid-flow, deformations and osmotic pressure changes, that may vary depending on cell morphology, mechanical properties of both cell and extracellular matrix, and the means for physical interaction between cell and matrix. Work in our group has studied the biological responses of isolated cells when exposed to these representative stimuli *in vitro*. Cells of the annulus fibrosus are generally responsive to short-term periods of direct compression and osmotic pressure change, as quantified by altered gene expression profiles for cytoskeletal and matrix proteins and cytoskeletal organization. Cells of the immature nucleus pulposus exhibit fewer responses to these same stimuli *in vitro*, differences that may be partly attributed to the more extensive cytoskeletal network and stiffer properties of these cells.

**CELL-MATRIX INTERACTIONS:** To determine the mechanisms that govern these spatial differences in cell mechanobiology, our work has recently focused on studying how mechanical stimuli are transduced to cells within the disc. Integrins are known to be important mediators of cell-matrix interactions in other systems, with demonstrated roles in regulating cell survival, adhesion, cytokine responses, and mechano-biology. In the intervertebral disc, we observe a spatially varying pattern of integrin expression with integrins that interact with collagens, laminins and fibronectin for most cells. These integrins are shown to play a role in mediating

intervertebral disc cell adhesion to particular matrix substrates that are similar for both annulus fibrosus and nucleus pulposus cells; however, the observations differ from findings for both fibroblasts and chondrocytes, pointing to a phenotypic difference for cells of the intervertebral disc.

**COLLAGEN KNOCKOUT MODELS OF DISC DEGENERATION:** Evidence for human disc disease points to a role for mutations in the genes encoding type IX collagen, a molecule that may mediate cell-matrix interactions. In order to better understand



*Figure: IVD from (left) wild-type and (right) Col9a1<sup>-/-</sup> mouse aged 9 months*

this interplay, our laboratory has begun to study mice with an inactivated *Col9a1* gene that express no type IX collagen. Discs exhibit more degenerative changes compared to wild-type littermates (Figure). Stiffness of the knee joint cartilage was measured to be significantly less in the mutant mouse; however, similar matrix changes have not yet been evaluated for the intervertebral discs. Our laboratory is investigating two potential hypotheses to explain the observed disc changes in the *Col9a1*<sup>-/-</sup> mice: (1) a mechanically compromised extracellular matrix is associated with elevated wear-and-tear of the disc, which leads to premature degenerative onset; or (2) altered cell-matrix interactions with the collagen deletion alter transduction of mechanical signals from matrix to cell, and hence alter cell mechanobiology.

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