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Investigation of the combined effects of a catabolic microenvironment and complex mechanical loading on intervertebral disc degeneration (101209)

Katherine Crump [1 2], Kim de Graaf [1], Paola Bermudez Lekerika [1 2], Christine Le Maitre [3], Jérôme Noailly [4], Benjamin Gantenbein [1 5]

1. *Tissue Engineering for Orthopaedics and Mechanobiology, Bone & Joint Program, Department for BioMedical Research (DBMR), University of Bern, Bern, Switzerland*
2. *Graduate School for Cellular and Biomedical Sciences (GCB), University of Bern, Bern, Switzerland*
3. *Division of Clinical Medicine, School of Medicine and Population Health, University of Sheffield, Sheffield, UK*
4. *BCN MedTech, Universitat Pompeu Fabra, Barcelona, Spain*
5. *Department of Orthopedic Surgery & Traumatology, , University of Bern, Bern, Switzerland*

INTRODUCTION

Intervertebral disc (IVD) degeneration is the cause of around half of all low back pain cases in young adults, however the initiating and risk factors are poorly understood, limiting development of personalized therapies[1,2]. The balance between anabolic and catabolic processes is essential for healthy turnover of IVD extracellular matrix (ECM), and disruption of this process through elevated catabolic activity leads to disease progression[2]. Although the effects of pro-inflammatory cytokines and mechanical loading has been investigated within the IVD[3], it is unknown how IVD response to complex mechanical loading is affected by the presence of cytokines. Thus, we aimed to investigate the combined effects of dynamic compression and torsion with catabolic cytokine interleukin 1 beta (IL-1β) and inhibitory cytokine interleukin 1 receptor antagonist (IL-1Ra), on bovine IVDs using *ex vivo* culture, magnetic resonance imaging (MRI), and finite element (FE) modeling.

METHODS

Whole bovine IVDs obtained within 3-4 hours port-mortem from a local abattoir were isolated and the IVDs cultured in a customized two degrees-of-freedom bioreactor applying diurnal dynamic compression (0.1-0.5 MPa) and torsion (6 degrees) under normal (HG DMEM), catabolic (10 ng/ml IL-1β) and inhibitory (10 ng/ml IL-1Ra) media conditions for one week. Static compression (0.1 MPa) under the same media conditions were used as a control. Before and after culture, the IVDs were imaged using 3T MRI, which was used to create subject-specific FE models. Downstream analyses included height measurement, qPCR, glycosaminoglycan (GAG) quantification, and cell metabolic activity. For statistical analysis (when n>3), nonparametric distribution was assumed and a Kruskal–Wallis test then Dunn's multiple comparisons test were performed, and a $P < 0.05$ considered statistically significant.

RESULTS

Following one week of culture, IVD height decreased in all conditions (Figure 1a & b), however, this disc height decreases was less pronounced within IVDs stimulated with IL-1Ra. Cellular metabolic activity in the nucleus pulposus (NP) decreased in all conditions, but the difference was only significant in IVDs stimulated with IL-1β and complex dynamic loading (Figure 1c). Similarly, the GAG content decreased in the NP of all conditions, but was not significant. Gene expression of anabolic genes, i.e. collagen type II (*COL II*) decreased (Figure 1e), while expression of catabolic genes, i.e. matrix metalloproteinase 3 (*MMP3*) increased in the NP tissue for all conditions except in the control static IVDs and in the IL-1Ra stimulated IVDs, respectively (Figure 1d).

DISCUSSION

We hypothesized that catabolic cytokines, i.e. IL-1β, in the microenvironment of the IVD are sufficient to negatively alter the cellular response to complex loading, leading to further downstream degeneration. However, markers of degeneration were found in all conditions, which could indicate that loading was supraphysiological and catabolic alone. This will be investigated further using subject-specific FE models developed from the MRI images. Additionally, short half-lives of cytokines could have prevented them from diffusing through the IVD effectively, thus limiting the cellular response. This will be further investigated using immunohistochemistry and ELISA. Nevertheless, the results convey that static or complex dynamic loading is sufficient to induce catabolism with or without cytokine stimulation.

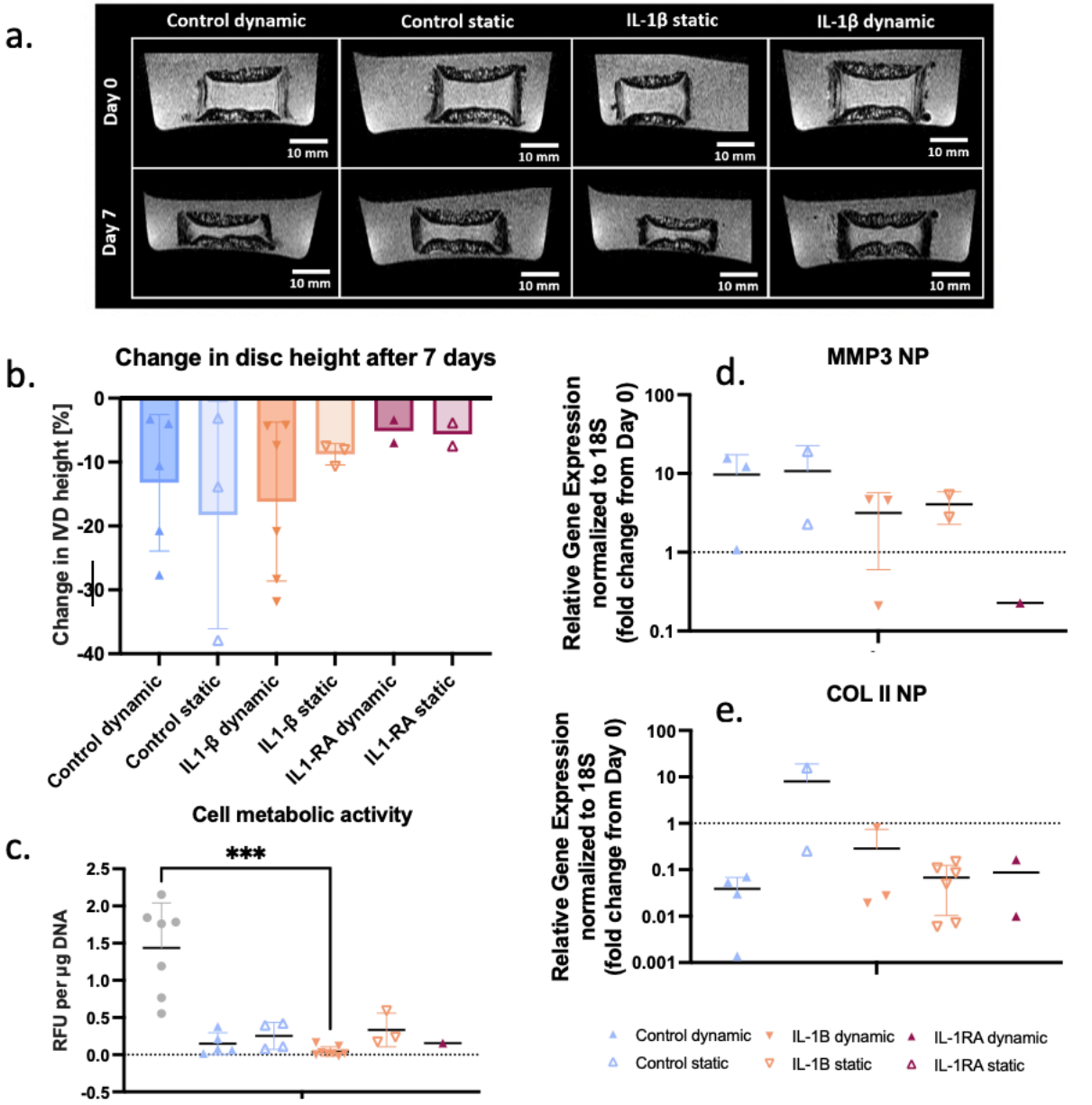

Figure 1. a. MRI images before and after 7 days of culture; b. change in disc height; c. cell metabolic activity in the NP; and the relative gene expression in the NP for d. *MMP3* and e. *COL II* after 7 days of culture under dynamic or static loading conditions and stimulation with IL-1b or IL-1Ra

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