A MODEL TO EXPLORE INTERVERTEBRAL DISC CELL ACTIVITY IN ADVERSE BIOCHEMICAL ENVIRONMENTS

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Introduction

Intervertebral disc (IVD) degeneration (IDD) involves the imbalance between the anabolic and the catabolic processes that regulate the extracellular matrix of the disc. These processes are complex; redundant and feedback-looped, and improved integration of knowledge is needed. Accordingly, we present a nucleus pulposus cell (NPC) regulatory network model (RNM) that integrates critical biochemical interactions in IVD regulation and can replicate experimental results.

Methods

The RNM was built from a unique curated corpus of 130 journal articles in IVD research. Proteins were represented as nodes that interact among each other through activation and inhibition edges. Semi-quantitative steady states (SS) of the RNM (node activations) were calculated through a fuzzy interpolation of Boolean rules [1]. Simulation tests evidenced the limited literature knowledge to represent non-degenerate reference SS of NPC, and guided corpus enrichment through the STRING database (Fig.1).

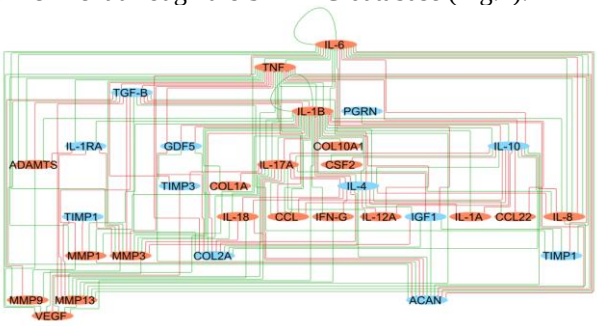

Figure 1: Topology of the enriched RNM.

Then, a full factorial sensitivity analysis (SA) was performed to identify which out of the RNM 15 cytokines, and 4 growth factors affected most the structural proteins and degrading enzymes. The RNM was further evaluated against metabolic events measured in non-healthy human NP explant cultures, after 2 days of 1ng/ml IL-1B catabolic induction.

Results and Discussion

The enriched RNM represented successfully an anabolic basal SS, as we would expect in non-degenerate IVD (Fig. 2, blue bars). IL-1B was able to increase catabolic markers and angiogenic factors and decrease matrix proteins (Fig.2). This shift of activity was confirmed by the explant culture measurements (Fig.3A-E).

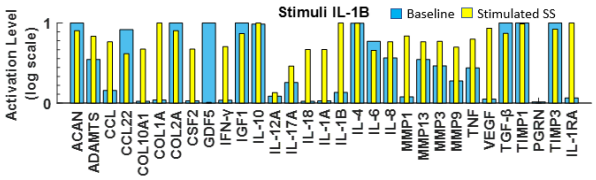

Figure 2: Baseline & IL1-1B Stimulated SS of the NPC RNM.

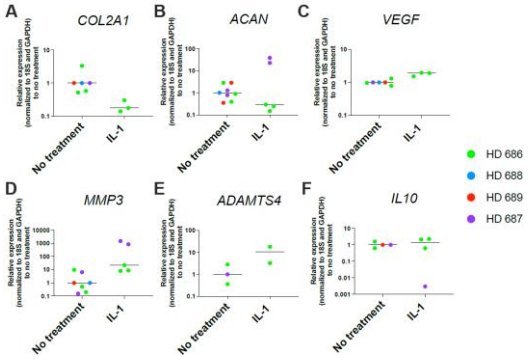

Figure 3: Relative gene expression of IVD anabolic (A, B, F) and catabolic (C-E) markers in human NP explants.

The SA identified TGF-β and IL-1RA as the two most powerful rescue mediators (Fig.4). Accordingly, TGF-β signaling-based treatments have been proposed for IDD [2] and IL-1RA gene therapy diminished the expression of MMP1, MMP3, MMP13 and ADAMTS4 [3]. Yet, it is challenging to simulate rescue strategies by IL-10 or IL-1RA, as both nodes are already activated by IL-1B in our RNM that mimics baseline activity of healthy NPC, according to our corpus. Interestingly, IL-1B could not induce IL-10 expression in the explant cultures (Fig.3F), and a non-healthy NPC RNM baseline may be needed.

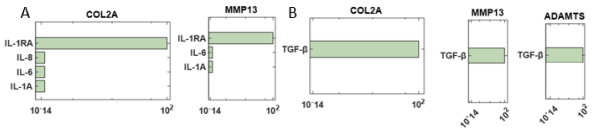

Figure 4: Sensitivity analysis with the A) cytokines and B) growth factors that most affected the RNM nodes.

The present RNM was successfully confronted to independent in vitro measurements and stands for a unique model, to integrate soluble protein signaling at the tissue level and explore IDD onsets.

References

1. Mendoza et al, Theor Biol Med Model, 3:1-13, 2006
2. Chen et al, Osteoarthritis Cartilage,27(8):1109-1117, 2019
3. Le Maitre et al, Arthritis Res Ther, 9(4): R83, 2007

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