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NETWORK MODELLING FOR NUCLEUS PULPOSUS CELL ACTIVITY IN EARLY INTERVERTEBRAL DISC DEGENERATION

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Summary: Low back pain (LBP) is a major cause of disability worldwide. It is often related to intervertebral disc (IVD) degeneration (IDD), characterized by loss of water, proteoglycans, and type-II collagen, in the nucleus pulposus (NP) of the IVD. Extracellular matrix (ECM) degradation results from complex biochemical processes, with redundant and feedback-looped processes that further interact with physical factors. Accordingly, IDD has a strong inertia and might only be tackled if apprehended sufficiently early. While its pathogenesis remains poorly understood, several numerical and experimental models explore underlying biomechanical and biochemical processes. Yet, the integration of knowledge about IVD cell regulation in health and disease still needs to be improved. Accordingly, a new NP cell (NPC) regulatory network model (RNM) is presented, incorporating critical biochemical interactions in IVD regulation. First, a unique corpus of 120 articles was built about the biochemical stimuli in the NP and their activation and/or inhibition effect on the regulation of soluble cytokines, proteases, and ECM proteins by NPC. Due to the limited knowledge about IDD and the lack of experiments with healthy human IVD material, the corpus was enriched through the STRING database, including general protein-protein interactions in Homo Sapiens. In particular, relevant interactions in chondrocyte regulation were retained. To build the RNM, proteins were represented as nodes that interacted among each other through a directed network of inhibition and activation edges. Nodal activations were calculated through a system of ordinary differential equations that semi-quantitatively interpolates Boolean rules and provide the stable steady states (SSS) of the RNM. Finally, two experimental studies, using healthy human and bovine IVD NPC, were simulated to evaluate the model. Simulations revealed an anabolic basal SSS of the RNM . According to the experimental measurements related to the simulated NPC perturbation, initial activation of IL-17A enhanced slightly COL1A and MMP13, while inactivating almost completely the anabolic ECM components, indicating its negative role in the IVD regulation. In contrast, initial activation of GDF5 up-regulated not only the expression of ACAN and COL2A, but also important growth factors and anti-inflammatory cytokines that play an important anabolic role in the IVD. Interestingly though, the increase of MMP-13 activation with IL-17A was very low, which seems to be supported by some evidence that this protease might not play a clear role in IDD, in contrast to osteoarthritis. Further experiments with anti-inflammatory IL-4 and TGF-B showed a significant increase of the anabolic factors and a decrease but not depletion of the catabolic ones, emphasizing the complexity of the IVD regeneration. IL-1B initial activation increased the activation levels of ADAMTs, the primary enzymes that cleave proteoglycans in IDD progression, whereas the activation of MMP3, believed to increase in advanced stages of IDD, remained low. Despite, the relatively limited amount of knowledge about IDD, compared to other diseases, e.g., such as osteoarthritis, an enriched RNM was built and successfully assessed against independent experiments. This directed RNM in IDD stands for a unique basis to further integrate both mechano-regulation and biochemical knowledge and enrich existing dose-dependent NPC activity model.