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MECHANOTRANSDUCTION COMPUTATIONAL APPROACH OF CHONDROCYTES

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Summary: Osteoarthritis (OA) is a debilitating joint disease, characterized by articular cartilage degradation, local inflammation, and pain. An extensive range of *in vivo* and *in vitro* studies provide evidence that mechanical loads induce changes in chondrocyte gene expression, through a process known as mechanotransduction (MT). MT involves cascades of complex molecular interactions that, when triggered, convert physical signs to cellular response(s) that favor chondroprotection or cartilage destruction regarding the nature of loads. Systematic representations of those interactions can positively inform early strategies for OA management, and dynamic modelling allows semi-quantitative representations of the steady states (SS) of the system according to imposed initial conditions. In cell biology, we would compare long-term cell activity or phenotypes to these SS or attractors. To this end, a novel network-based model (NBM) in the form of a continuous dynamical system of CC activity is proposed. The NBM incorporates key interactions from a corpus of 82 peer-reviewed articles from indexed journals. Then, an interactome is developed, consisting of a set of 115 nodes, i.e., cellular receptors, second messengers, transcription factors and proteins, related to each other through a specific topology of 256 directed edges. It is converted into a semi-quantitative mathematical model through a system of differential equations. To simulate a healthy SS of a CC including MT, the network is first stimulated with a physio-osmotic initial condition (TRPV4 and ($alpha_5beta_1$ activation). We further assess its capability to predict expected SS under inflammation and injurious loads (under static compression (ST) or high hydrostatic compression (HC) when PIEZO channels and patched receptor (PTCH) become activated). To validate the model, a qualitative validation (QV) is performed: we look for reported experiments and then we have counted how many of them can be replicated with our NBM. Results show that under physio-osmotic conditions, an anabolic SS is reached with low levels of matrix metalloproteinases (MMPs), and high levels of structural proteins. Pro-inflammatory and HC perturbations lead to a significantly different (t-test, a=0.05) CC expression profile, as a catabolic SS is reached, reflected by fully expressed pro-inflammatory cytokines and MMPs. ST does not have such a strong influence on chondrocyte metabolism, but it reduces the presence of anabolic indicators. Regarding transcription factors, healthy markers (Sox9 and CITED 2) are fully expressed under physio-osmotic conditions, and reduced under inflammation, HC and ST. Contrary, NF-kB and Runx2, characteristic of an osteoarthritic CC, are activated by inflammation, HC, and ST. Concerning the QV, our NBM can replicate 88% of the experiments tested, but PTCH related experiments could not be reproduced, suggesting the need for a targeted enrichment of the NBM.A regulatory network that maps intracellular signaling pathways of a CC was successfully developed. The model could predict expected MT and inflammation effects on general cell metabolism, revealing the potential of exploitation in OA.