*In silico* screening to predict chondrocyte hypertrophy using a semiquantitative gene network model

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PURPOSE: In development, chondrocyte hypertrophy is a crucial and well-studied step in endochondral ossification. Hypertrophy may also play a role in pathophysiological processes, including osteoarthritis. We employ a computational approach to estimate the effect of individual factors in this complex process.

METHODS: We have combined information gleaned from a high number of publications on chondrocyte differentiation into a gene regulatory network of 46 factors and over 150 interactions. This network can estimate the stability of proliferative chondrocytes/permanent cartilage (stable state with SOX9 activity) and hypertrophic chondrocytes (stable state with RUNX2 activity) by employing 2 measures. A first measure is a Monte Carlo analysis that assesses stability in the face of random initial conditions, the second modifies stable states to estimate the sensitivity to perturbation.

RESULTS: For each factor, these qualitative measures are calculated *in silico* under knockout and overexpression conditions and compared to the wild type situation. This enables screening of the effects of all incorporated factors on cartilage homeostasis, differentiation and pathogenesis via the initiation of hypertrophy. Indeed, our gene network analysis indicated multiple candidate genes for the development of osteoarthritis. Factors that amplify the SOX9 attractor basin include TGFβ, PPR, IGF-I, and PKA. The presence of RAS, IHH, GLI2 and FGF is required for the Runx2 stable state. Using a literature study, we corroborated several of the proposed factors.

CONCLUSIONS: *In silico* screening of overexpression and knockout presents a novel strategy to improve bone and cartilage tissue engineering approaches, and can be used to propose a list of putative therapeutic targets for e.g. osteoarthritis.