Cross-talk Modeling of Wnt, BMP and ERK Pathways during Osteochondrogenic Differentiation

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Introduction

The in vitro engineering of tissues may be achieved by mimicking in vivo tissue development. Although multiple skeletal tissue engineering applications already exist, the underlying mechanisms at protein level are often poorly understood.

Growth factors and protein pathways precisely navigate mesenchymal stem cells (MSCs) through the correct cascades. Studies hypothesize that the Wnt/β-catenin pathway acts as a switching mechanism to determine the differential fate of MSCs during skeletogenesis. The concentration of β-catenin is a key factor in this mechanism. Wnt upregulates the production of β-catenin which in turn upregulates Runx2 and downregulates Sox9. High concentrations of Runx2 relative to Sox9 lead to osteoblasts, while the opposite situation leads to chondrocytes. Cross-talks of the Wnt pathway with other pathways such as that of BMP and ERK expand the amount of factors that can influence β-catenin, turning the linear signaling cascade into a complex network with multiple starting conditions.

Materials and Methods

A mathematical model was derived describing the pathways of BMP, Wnt and ERK as well as various cross talks between these pathways that were suggested in literature [1,2] (Fig. 1). CellDesigner™ was used to formulate, solve and visualize the Ordinary Differential Equations describing the temporal evolution of the various model constituents. Multiple starting conditions (various concentrations of BMP, Wnt and ERK) were examined to clarify the cross-talk effect.

Results

The model predicts an increasing β-catenin concentration when Wnt is active and a lowered concentration when BMP is active. When both Wnt and BMP are active the combined cross-talk model shows the effect of mutual inhibition, where Wnt inhibits the BMP effect trough Gsk, countering the inhibitory effect of BMP on β-catenin. This effect was independently described in literature.

Discussion and Conclusions

Mathematical models can be used to enhance our understanding of signaling cascades and their interactions. This will enable us to develop efficient and robust production methods, which are required for large scale TE applications.

References


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Disclosures

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