Understanding the interactions between Wnt and BMP signalling pathways in human Periosteum Derived Cells

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INTRODUCTION

Wnt and BMP

- *Bone Morphogenetic Proteins (*BMPs) and *Wnt* are crucial for bone formation
- ***BMP canonical pathway*** signals through the Smad signalling cascade [1].
- ***Wnt canonical pathway*** starts with the activation of Dsh and ends with the entrance of β-catenin in the nucleus. Wnt/β-catenin pathway acts as a switching mechanism to determine the differential fate of mesenchymal cells in osteoblasts or chondrocytes during skeletogenesis. [2]

Crosstalks

- Crosstalks between both pathways highly depend on the cellular context [3]
- Mutual inhibition is well established in literature :
  - ✓ An interaction between Dsh and Smad1, resulting in the inhibition of Wnt pathway by BMP [4]
  - ✓ The acceleration of the phosphorylation process of active Smad1 leading to its degradation by Gsk, resulting in the inhibition of BMP pathway by Wnt [5]

Aim of this study

- Simulation and analysis of the interaction between Wnt and BMP pathways in human Periosteum derived cells in order to fully understand the mechanisms behind the fate of mesenchymal cells
- Design new/better experiments in order to reduce the number of experiments

MATERIALS & METHODS

Mathematical modeling :

- ✓ a **literature-based mathematical model** describing BMP and Wnt pathways and various cross-talks [6]
- ✓ **mutual inhibition** between BMP and Wnt
- ✓ **parameter values**
  - First : derived from previous models [6] and experiments reported in literature [7]
  - Second : optimized through in-house experiment results
- ✓ **Ordinary Differential Equations (ODEs)** describe the temporal evolution of the various model constituents
  - law of mass action and rate kinetics
  - Implemented and simulated in Matlab
  - 19 variables, 49 parameters

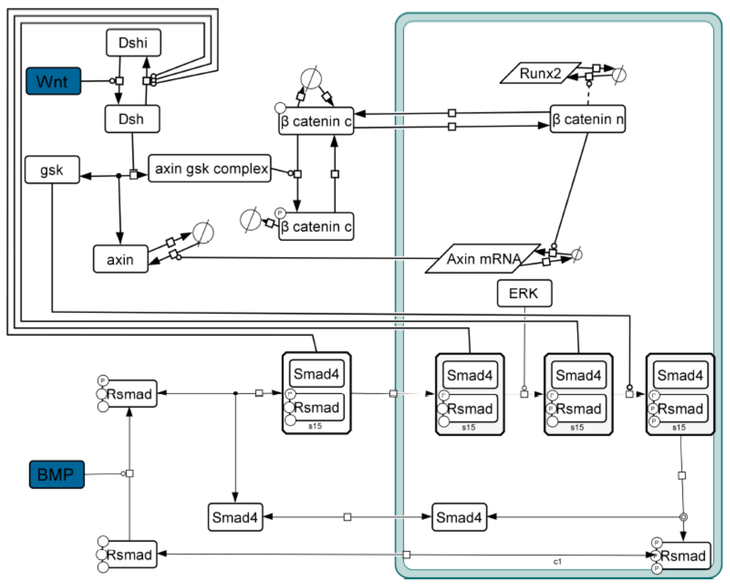

Figure 1 : Schematic representation of the pathways modeled

Experimental procedure :

- ✓ Cell type: human Periosteal Derived Cells
- ✓ Stimulation (100ng/well) for three conditions :
  - **C1** : Wnt3a
  - **C2** : BMP2
  - **C3** : Wnt3a + BMP2
- ✓ Procedure for each condition :

-24h	Minimal Medium
-12h	Serum starvation
0h	MM + **C1/2/3** WBlot & qPCR
5'/10'/30'/1h	WBlot
6h/12h/24h/ 48h/72h	qPCR

RESULTS

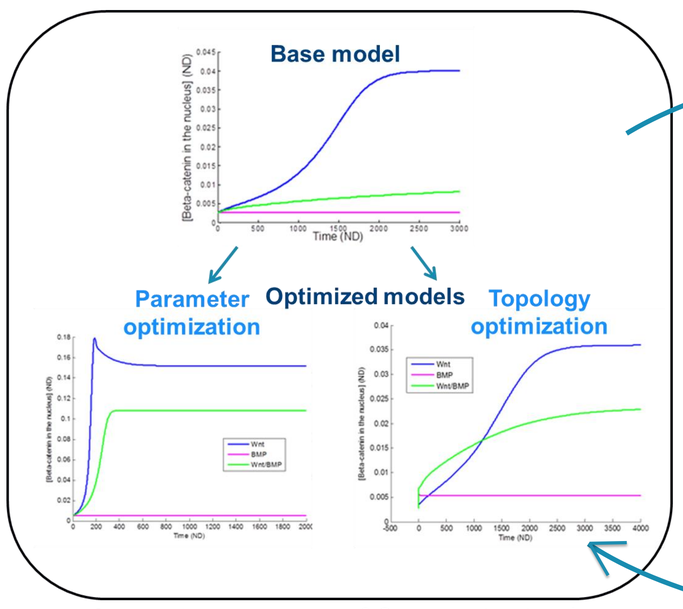

Figure 3 : Amount of β-catenin in the nucleus for the three conditions and for different optimized models.

Design of new experiments

- ✓ **Dynamics simulation** by adding Wnt, BMP or both at t=10
- ✓ **The model :**
  - Shows a mutual inhibition for most of the parameter values
  - Can show different behaviors depending of the parameters values and/or the topology
- ✓ **The experimental results :**
  - Give us the shape of the dynamics
  - Confirm a mutual inhibition for the long term behavior
  - Show an unexpected intermediate behavior

Model optimization

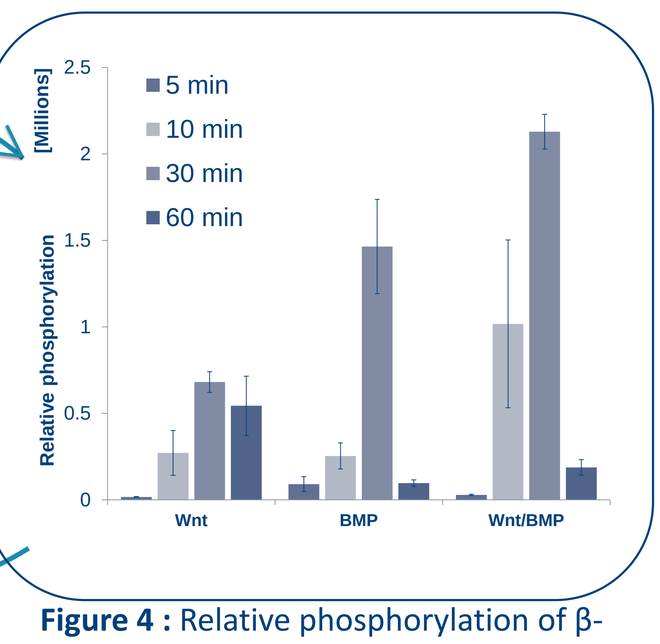

Figure 4 : Relative phosphorylation of β-catenin in the nucleus at 5, 10, 30 and 60 min after stimulation.

DISCUSSION

- ✓ In absence of quantitative parameter information, the presented ODE model provides qualitative predictions on changes in the concentrations of all modelled components
- ✓ The model is able to capture the preliminary experimental observations such as the long term behavior or the intermediate peak of β-catenin
- ✓ The experimental results have been used to optimized the model and additional *e*xperimental work is underway to guide further model development and to validate the first results

REFERENCES

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