A computational model of the human growth plate

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Introduction

Endochondral ossification is the differentiation process of cartilaginous into osseous tissue. A large variety of locally produced signaling molecules play a role in controlling this process. However, data from the literature suggest that PTHrP, Ihh and VEGF are the most important growth factors (GFs). Our aim was to quantitatively evaluate whether these three growth factors together can control the initiation and development of the fetal growth plate. For this purpose, we employed a new, temporo-spatial finite element model.

Material and methods

Once initial hypertrophiation has started in the center of the anlage, organized columns of proliferating (PZ), prehypertrophic (pHZ) and hypertrophic zones (HZ) emerge. PTHrP, Ihh and VEGF are produced in the articular perichondrium (PC), pHZ and HZ, respectively (Fig 1). These GFs need to be transported through the bone, as they have their effects on cells in a distinct zone.

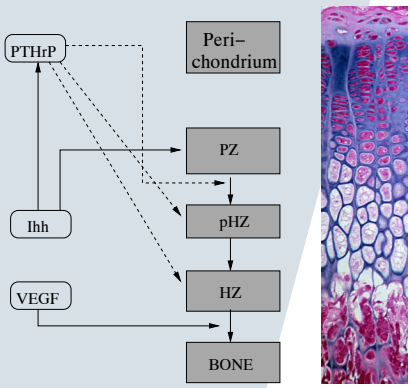

Figure 1: Left: Regulatory effects of GFs, depicted with solid (stimulatory) or dotted (inhibitory) lines. Arrows between zones indicate cell differentiation. Right: PZ, pHZ, HZ and bone in the growth plate.

A 1-D FE model was developed representing the distal half of a human femur. All interactions of GFs as depicted in Fig 1 were incorporated. All cells with surrounding extracellular matrix were represented by groups of elements.
Synthesis (s), diffusion (t) and decay (d) of all GFs determined the change in local GF concentration (c) per element:

$$\frac{dc}{dt} = s - t - d = s - \nabla.(D\nabla c) - \frac{ln2}{\tau}c \qquad (1)$$

in which half-life time (t) was assumed to be 10 minutes for all GFs [4]. The diffusion coefficient (D) was 63 mm^2/s for the PZ, based on FRAP measurements in porcine growth plate. The proliferation rate in PZ was semi-dependent on Ihh. All other processes, i.e. cell differentiation rate and ossification, were controlled by local GF concentration. All effects of GFs were concentration dependent following a Michaelis-Menten equation. Lengths of cells and zones were taken from human data [1, 2].

Results

A stable growth plate was formed, correctly simulating the human femoral growth plate. The number of cells varied cyclically within a small, physiological range (Fig 2). Bone growth was found to be constant and self-regulating during the simulation.

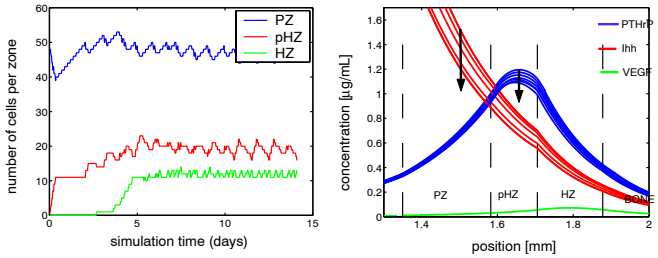

Figure 2: Left: Nr of cells per zone during the simulation. Right: PTHrP and Ihh profiles as a result of the transition of a cell from pHZ to HZ. The subsequent PTHrP and Ihh decreases lead to a transition of a cell from PZ to pHZ.

Discussion

The growth factors PTHrP, Ihh and VEGF together were able to control the initiation and development of the growth plate in a computational model, correctly simulating the development of the cartilage anlage to a mineralized bone at three months after birth.
Enhanced or decreased GF synthesis resulted in new steady states, which corresponded with changes seen in transgenic mice and with human growth plate pathologies (data not shown).
The approach to model endochondral ossification in a long bone based on growth factor effects, is new and is a promising addition to earlier computational models, which generally focussed on the mechanical environment in the tissue as a trigger for endochondral ossification.
Future developments enable extensions to later developmental stages, 2-D and 3-D representations, and incorporation of the interactions of mechanical loading and synthesis, transport and receptors of growth factors.

References:

[1] *Fazzalari, et al., 1997, The anat. record 248:1-12*
[2] *Kember, et al., 1976, JBJS 58-B: 426-35*
[3] *Hunziker, et al., 1987, JBJS 69:162-72*
[4] *Bailon-Plaza, et al., 2001, J. Theor. Biol. 212:191-209*
[5] *Stevens, et al., 1999, JBJS 17:646-53*