A mathematical model of bone regeneration including angiogenesis: relevance for tissue engineering strategies

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INTRODUCTION: Angiogenesis is a key process in bone regeneration and bone engineering. Impaired angiogenesis may lead to non-union in the case of bone fractures. In this study we present a novel, mathematical model of bone regeneration in which angiogenesis has been explicitly implemented. Its relevance for bone engineering is demonstrated by applying it to the study of atrophic non-union.

METHODS: The model is based on [1], in which a bioregulatory model for fracture healing was developed. This model expresses the change of a number of continuum-type variables – growth factor concentrations, cell densities and matrix densities – as a function of time and spatial coordinates. Mathematical expressions for (the rate of) cell migration, proliferation, differentiation, growth factor and matrix synthesis were formulated and made dependent on local matrix density and/or growth factor concentration, leading to a coupled system of non-linear partial differential equations.

We extended the model, a.o. with expressions for angiogenesis and its relation with bone forming processes. Vascular growth factor density, endothelial cell concentration and vascular matrix density were defined as additional variables, and were related to processes (by modulating and/or adding terms to the equations), like chemotaxis, osteogenic differentiation and chondrocyte hypertrophy. Model equations were implemented in a customised finite volume code [2]. A simplified geometrical domain of a fracture callus, based on [3], was constructed (fig. 1).

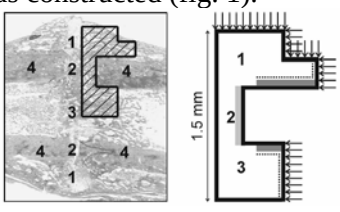

Fig. 1: Standardised rodent fracture model and simplified callus geometry at post fracture week 3: periosteal (1), intercortical (2) and endosteal (3) callus; cortical bone (4).

Apart from normal fracture healing, a pathological case was considered as well, based on an atrophic non-union model [4]. Possible tissue engineering strategies to treat non-union were modeled as well, including the administration of mesenchymal stem cells, osteogenic and/or angiogenic growth factors at various locations and time points.

RESULTS: The model was able to correctly predict the sequence of events during normal healing. For the case of atrophic non-union no cartilage or bone formation was predicted in the callus over a period of 12 weeks after fracture, while vascularisation of the callus continued progressively during this period, as experimentally observed in [4]. Administration of only mesenchymal stem cells restored healing if administered in the callus area at fracture initiation, and if applied at a sufficiently high concentration ($2x10^4$ cells/ml). When administered at post fracture day 20, healing could only be resumed if osteogenic and angiogenic growth factors were administered simultaneously and their effect on healing rate strongly depended on the location of administration.

DISCUSSION & CONCLUSIONS: A mathematical model of bone regeneration, including angiogenesis, was developed and applied to study normal fracture healing and the effect of different tissue engineering strategies for the treatment of atrophic non-union. It may be used as a computational tool to help define additional experiments on the effect of different treatment modalities.

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