

DOSE-EFFECT OF TRANSFORMING GROWTH FACTOR BETA3 ON DEGRADATION OF TRICALCIUM PHOSPHATE CERAMIC

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INTRODUCTION: Transforming growth factor (TGF) beta3 is a polyfunctional regulatory cytokine out of the TGF beta superfamily. It has been shown to have roles in embryogenesis, soft tissue healing, tumor genesis as well as tumor suppression angiogenesis and osteogenesis. A clear effect of TGF-beta3 on cranial bone regeneration has been observed in a preceding study in the rabbit using polylactic acid (PLA) as carrier.

Scaffolding matrices for bone repair should be of porous nature with interconnecting pores in dimensions similar to trabecular bone. Their components mimic mineralised bone and their degradation ideally goes hand in hand with replacement by newly formed bone. Even though many studies have been performed, the ideal material has not been found yet.

The purpose of this study was to determine an eventual dose related action of the growth factor on bone formation as well as carrier degradation.

METHODS: A paired cranial defect design was used in the rabbit. Dose effects of 10 $\mu\text{g}/\text{cm}^3$, 50 $\mu\text{g}/\text{cm}^3$ and 250 $\mu\text{g}/\text{cm}^3$ were compared, using particulate Tricalcium phosphate (TCP) as a carrier. The observation time was 8 weeks. All animals received intravital labeling with bone seeking fluochromes in order to gain information on the timing of bone formation. The specimens were analysed using quantitative computed tomography, quantitative radiology and histomorphometry. For data analysis a „within animal“ comparison was performed using a paired t-test for parametric data, and a Wilcoxon test for non-parametric data. „Between animals“ comparisons were done in two-sample t-tests for parametric data, and a Mann-Witney U-test for non-parametric data.

RESULTS: The evaluation of the radiographs as well as of the histological sections showed clear dose effects on the carrier: While the non-loaded control carriers within the same animals were not affected in all three dose groups, the tricalcium phosphate carrier loaded with the growth factor disappeared significantly faster with increasing dose. In the low dose group bone formation and carrier degradation were not significantly different to the non-loaded sites. Bone formation was

enhanced, but not significantly different between the two groups with a higher dose in spite of the fact that more space for the regenerate became available with increasing degradation.

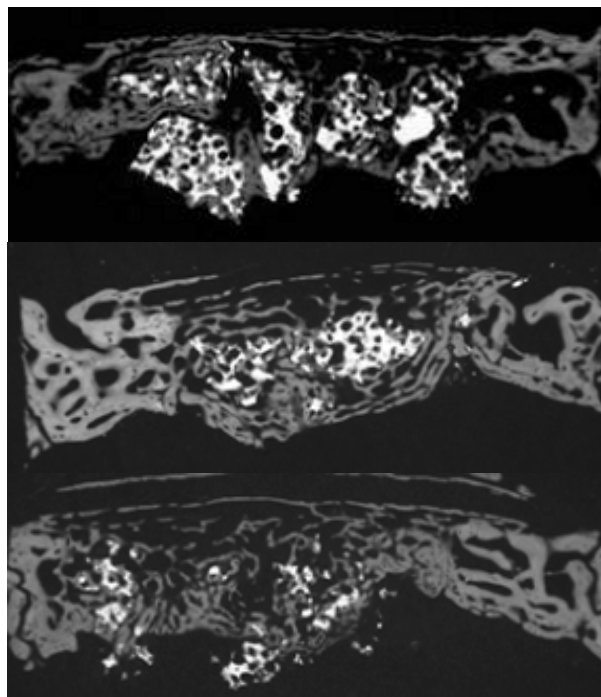


Fig. 1: Increasing influence of TGFbeta3 dose on the degradation of the ceramic carrier. Bony replacement of the carrier does not follow the speed of degradation. Top: low dose, middle: medium dose, bottom: high dose.

DISCUSSION & CONCLUSIONS: TGF- β 3 has a significant, dose related effect on degradation of the TCP-carrier onto which it is loaded. A systemic action on carrier degradation at remote sites could not be shown. Additionally, this growth factor has a clear effect on bone regeneration. There are indications that there might be something like a therapeutic window near a dose of 50 $\mu\text{g}/\text{cm}^3$ in the early phase, and a direct dose / effect relationship at a later stage of bone regeneration. The exact mechanisms of dose dependence as well as the signaling pathway responsible for the time pattern of enhancement of bone regeneration remain unclear.

ACKNOWLEDGEMENTS: The authors thank R.Wieling, I.Keller and D.Pfluger for help in surgery, histology and statistics.