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Bone healing by non-viral BMP-2 gene transfer – a novel vector release out of a mechanically stable PDLLA-coating of metallic surfaces

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Gene transfer of growth factors is a promising technique to improve healing of bony defects. Animal studies have shown the use viral BMP-2 gene transfer, but this application is not transferable to humans due to the high risks related to viral vectors. In contrast, non-viral gene transfer of BMP-2, not related to such risks, has not been performed in vivo up to date. Among other reasons no suitable carrier system has been found allowing continuous vector release and stable adherence to metallic surfaces without negative influence on the non-viral gene transfer.

For non-viral gene transfer BMP-2 cDNA was cloned in an expression plasmid. This plasmid was complexed with polyethylenimine followed by incubation with protective copolymers (copolymer protected gene vectors, COPROGs). These were integrated in a biodegradable polylactid carrier (Poly-D, L-Lactid, mw 30000 Dalton). Different metallic surfaces were coated with the COPROGs/PDLLA in different concentrations and the effect of the non-viral gene transfer was analysed both in vitro (ELISA) and in vivo (histology, microCT). To analyse bone regeneration in vivo critical size were set in the mandibular angle of 6 month old male Sprague Dawley rats and covered with titanium foils coated with either COPROG/PDLLA or PDLLA alone. The PDLLA coating revealed mechanically stable adherence to the metal surface. Even in fracture experiments near the fracture gap this coating kept intact. Further, the PDLLA coating provided a continuous vector release in vitro. The BMP-2 expression in vitro was dependent on the COPROGs/PDLLA concentration and persisted over a period of at least 28 days. In vivo, the gene transfer led to a complete bony consolidation within 56 days, while the control group presented just a partial bony regeneration at the critical size defect border.

This is the first presentation of a non-viral gene transfer of BMP-2 out of a biodegradable carrier exhibiting mechanically stable adherence to metallic surfaces successful in vivo and in vitro. Furthermore, we addressed the problem of a continuous vector release directly into a bony defect.