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Craniofacial bone tissue engineering with biomimetic constructs

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ABSTRACT

The repair of bone defects and nonunions remains a significant clinical problem in orthopedic and maxillofacial reconstructive surgery. Tissue engineering offers a potential approach to overcome existing limitations related to auto- and allograft tissues. Novel biomimetic engineering strategies enable us to model the desirable physiological signaling in the bioengineered devices and to study tissue repair and regeneration under conditions resembling the human *in vivo* context. In the current thesis we aimed to better understand how a biomimetic approach in tissue engineering can be applied toward the repair and regeneration of the bone tissue in craniofacial area. In our first study we designed a biomimetic construct composed of ceramic scaffold modified with *in vitro*-derived extracellular matrix (HA-ECM), and assessed the osteogenic properties of the generated HA-ECM *in vivo*. Cell-derived matrix enhanced the osteogenic properties of ceramic scaffold, and the construct modulated the local inflammatory response in a bone repair-favorable way. We then continued to investigate the osteogenic properties of bone marrow stromal cell (BMSC)-loaded constructs and assessed the cellular components of the elicited foreign body reaction following implantation. The implications of BMSCs in the regulation of the foreign body reaction triggered by the tissue-engineered constructs were highlighted, demonstrating higher efficiency for the BMSC combination therapy. Furthermore, we investigated the effect of HA-ECM on the osteogenic differentiation of periodontal ligament progenitor cells (PDLC) and assessed the effect of PDLC-seeded HA-ECM on the bone repair. The HA-ECM enhanced the osteogenic differentiation of PDLC and the treatment with PDLC-seeded HA-ECM significantly improved calvarial bone repair. In the final study we have been able to implement a GMP-grade methodology for the biomimetic construct production under complete xeno-free conditions. The resulted tissue-engineered construct has promoted osteogenic differentiation of human MSCs *in vitro* and displayed biological safety and high biocompatibility *in vivo*. In conclusion, the work presented in this thesis highlights the functional *in vitro*-generated biomimetic tissue-engineered constructs with enhanced osteogenicity, biocompatibility and suitable handling properties, as a promising tool for craniofacial bone regeneration.

Key words: bone regeneration, tissue engineering, extracellular matrix, biomimetic scaffold, foreign body reaction, mesenchymal stem cells, bioceramics.

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