

## Paracrine effect of transplanted rib chondrocyte spheroids on bone marrow derived stem cells

K. Gelse ([kolja.gelse@web.de](mailto:kolja.gelse@web.de))<sup>1,2</sup>, M. Brem<sup>1</sup>, A. Olk<sup>1</sup>, F. Hennig<sup>1</sup>, B. Swoboda<sup>2</sup>

<sup>1</sup>Department of Orthopaedic Trauma Surgery, <sup>2</sup>Department of Orthopaedic Rheumatology, University Hospital Erlangen, Germany

### INTRODUCTION:

Mesenchymal stem cells represent a cell population which is considered suitable for cartilage repair. However, certain stimuli, e.g. specific growth factors, are required to induce their chondrogenic differentiation<sup>1</sup>. Growth factors may not only be provided in form of recombinant proteins, but the appropriate factors may also be endogenously secreted by chondrocytes<sup>2,3</sup>. The study's objective was to investigate if transplanted chondrocyte- or periosteal cell spheroids have a chondroinductive paracrine influence on ingrowing bone marrow-derived stem cells (BMSCs) in a novel cartilage repair approach in miniature pigs.

### METHODS:

Autologous rib chondrocytes or periosteal cells were cultured as spheroids and press-fitted into cavities that were milled into large, superficial chondral lesions of the patellar joint surface of miniature pigs. Within the milled cavities, the subchondral bone plate was either left intact (partial-thickness cavities) or was penetrated (full-thickness cavities) which allowed stem cells from the underlying bone marrow to invade into the lesions. Tracking of the transplanted cells was performed by cell-labelling with iron-oxide nanoparticles. After 3 and 12 weeks, the repair tissues were assessed (immuno-)histologically.

*In vitro* experiments investigated the paracrine effect of chondrocytes on the gene expression profile of BMSCs. The secretion of growth factors, including Bone Morphogenetic Protein-2 (BMP-2) and Platelet derived Growth Factor (PDGF), by chondrocytes or periosteal cells were determined by ELISA.

### RESULTS:

The transplantation of chondrocyte spheroids into full-thickness cavities induced the formation of additional secondary repair cartilage that exceeded the original volume of the transplanted spheroids. The resulting continuous tissue was rich in proteoglycans and

stained positive for type II collagen. Cell labelling revealed that secondarily invading repair cells did not originate from transplanted spheroids, but rather from arroded bone marrow. However, secondary invasion of repair cells was less pronounced following transplantation of periosteal cells and absent in partial-thickness cavities<sup>4</sup>.

According to *in vitro* analyses, these observations could be ascribed to the ability of chondrocyte spheroids to secrete relevant amounts of BMP-2, which was not detected for periosteal cells. Neither cell type secreted relevant amounts of PDGF.

*In vitro*, BMSCs failed to spontaneously undergo chondrogenic differentiation, even if cultured in high cell-density in form of spheroids. However, coculture with chondrocytes significantly induced the expression of the cartilage-specific gene Sox-9 in BMSCs.

### DISCUSSION & CONCLUSIONS:

Transplanted chondrocyte spheroids exert a dual function: they provide cells for the repair tissue and have a stimulatory paracrine activity, which promotes ingrowth and chondrogenesis of BMSCs.

The chondrogenic differentiation of BMSCs is susceptible to growth factors released by chondrocytes. BMP-2 could represent one potential candidate factor in this respect.

### REFERENCES:

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