Repair of articular cartilage with anti-VEGF antibody bevacizumab

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INTRODUCTION
Mature articular cartilage has a limited capacity to regenerate after degeneration or injury. For this reason, various treatments have been developed to induce restoration by regenerative medicine. At present, techniques using penetration of subchondral bone, mosaicplasty, cell transplantation, and implantation of tissue-engineered cartilage with various scaffold materials or without scaffold have been developed to overcome this obstacle. Generally, osteochondral defects are repaired by endochondral ossification. Since the defect filled with reparative cells derived from bone marrow and shows many vascular invasions, it is eventually replaced by bone. We have previously constructed and transplanted scaffold-free tissue-engineered cartilage into an osteochondral defect (1), and good restorative effects have been reported in a long-term study (2). We confirmed that, in the early stage of transplantation, reparative cells derived from bone marrow-acquired properties of angiogenesis achieve good restorative effects of articular cartilage (3). We thus hypothesized that better cartilage repair may be attained by inhibiting the bioactivity of vascular endothelial growth factor (VEGF) in the osteochondral defect. The objective of this study was to investigate the efficacy of repair in an osteochondral defect model of the rabbit knee joint following administration of bevacizumab, a humanized monoclonal anti-VEGF antibody, without using cultured cells or artificial scaffolds.

METHODS
Japanese white rabbits (n=54; weight, 3 kg) were used in this study. An osteochondral defect (diameter, 5 mm; depth, 3 mm) was created on the patellar groove of the femur. Rabbits were classified into two recipient groups: Group B, administration of bevacizumab (n=28; 100 mg intravenous injection administered on the day of surgery and 2 weeks later); and the Controls (n=26; defect only). Rabbits were sacrificed 1, 3 and 6 months postoperatively. Sections were stained with safranin O. Repairing sites were evaluated using the modified O’Driscoll ICRS grading system. Sections were evaluated for type I and II collagen, chondromodulin (ChM)-I, VEGF and superficial zone protein (SZP) by immunohistochemistry. Differences in histological scores were assessed using the Mann-Whitney U test. Values of P<0.01 were accepted as statistically significant.

RESULTS
At 1 month after surgery, in Group B, the repair site appeared to be filled with cartilaginous tissues (Fig. 1A, 1B). At 3 and 6 months, the repair site maintained the cartilage phenotype (Fig. 2A, 2B, 3A and 3B). At 1 month in the Controls, defects were filled with mainly fibrous tissue (Fig. 1C, 1D). At 3 and 6 months, the defect was replaced by fibrous tissue and bone (Fig. 2C, 2D, 3C and 3D). At 6 months, in Group B, the repair site was recognized by the expression of type II collagen (Fig. 4A), but type I collagen was not apparent (Fig. 4B). Expression of SZP, which contributes to the lubrication of articular cartilage, was recognized at the surface of the repair tissue in Group B at 6 months postoperatively (Fig. 4C). Over the 6 months, histological scores were significantly higher in Group B than in the Controls (Fig. 7). At 1 month, Group B showed intense positive results for ChM-I in the bottom of the repair tissue (Fig. 5A, 5B). VEGF was also identified in the same area (Fig. 5C). Conversely, the remodeling hypertrophic chondrocyte layer was intensely positive for VEGF (Fig. 6B).

DISCUSSION
VEGF is overexpressed in numerous solid angiogenic tumors and hematological malignancies. Interrupting the VEGF pathway has thus become a major focus of oncological research (4). The most successful antiangiogenic approach is bevacizumab, a humanized monoclonal anti-VEGF antibody. Bevacizumab broadly represents a major advance in antiangiogenic therapy (5). We report herein cartilage repair effects following intravenous administration of bevacizumab as an anti-VEGF antibody for osteochondral defects. As a result, a good process of cartilage repair was confirmed within 6 months postoperatively. Furthermore, SZP was expressed at the surface of the repair site. Interestingly, expression of ChM-I was acquired in the early stage of the repaired tissue after bevacizumab administration. Expression of ChM-I in this study inhibited vascular invasion from subchondral bone, indicating that ChM-I facilitated the expression of the factors required for articular cartilage.

CONCLUSION
Intravenous administration of bevacizumab contributes to the repair of articular cartilage in an osteochondral defect model.

REFERENCES