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Age-Dependent Healing Potential of Anterior Cruciate Ligament Remnant-Derived Cells

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Summary:
Anterior cruciate ligament (ACL) remnant-derived cells from young patients enhance angiogenesis, vasculogenesis and osteogenesis, and have a greater effect on the maturation of bone-tendon healing in an immunodeficient rat ACL reconstruction model, compared to cells collected from older patients

Abstract:
INTRODUCTION
The anterior cruciate ligament (ACL) does not heal spontaneously after injury, and ACL patients of different ages respond differently to treatment. Although it was reported that the healing potential of ruptured ACL remnants decreases with age as CD34+ cells were more prevalent in ACL remnants in young patients, whether the healing potential of ACL-derived cells on the maturation of bone-tendon healing depends on the patient's age has remained unclear.

METHODS
Sixty 10-week-old female immunodeficient rats underwent ACL reconstruction using autologous flexor digitorum longus tendon as a graft followed by intracapsular administration of ACL-derived cells from patients in their 10s (Group 10s) or patients in their thirties (Group 30s), or of PBS only (Group PBS). Histological examination (Hematoxylin & Eosin stain and Movat pentachrome stain), immunohistological assessment (intrinsic and human cell-derived vasculogenesis/angiogenesis and osteogenesis), radiographic examination (evaluation by micro-CT to assess the areas of tibial bone tunnel) and biomechanical examination (tensile test to record the ultimate load to failure of the tendon grafts) were performed.

RESULTS
Histological examination: Early healing inducing endochondral ossification-like integration was observed at week 4 only in Group 10s around the tibial tunnel. At week 8, mature bone ingrowth was found only in Group 10s. Immunohistological assessment: The number of differentiated human endothelial cells (ECs) at the vascular sites and differentiated human osteoblasts (OBs) in the area around the bone-tendon junction were significantly greater in Group 10s. In addition, vascular staining with isolectin B4 demonstrated greater intrinsic neovascularization around the bone tunnel and OB staining with rat osteocalcin (OC) antigen demonstrated greater enhancement of intrinsic osteogenesis at the perigraft sites in group 10s. Radiographic examination: In Group 10s, the reduction rates of the

areas of the tibial bone tunnel at a 3 mm depth from the tibial joint surface at week 4 and week 8 to week 0 were higher than those of the other groups. Biomechanical examination: Failure load of tensile test demonstrated that biomechanical strength was significantly higher in Group 10s compared to the other groups.

DISCUSSION

From these results, it was demonstrated that ACL-derived cells from young patients were highly effective in accelerating the healing of the bone-tendon junction. Recently, it was demonstrated that CD34+ vascular cells could migrate to a ruptured ACL site and support healing with the potential for multilineage differentiation in ACL tissues and that ACL-derived CD34+ cells contributed to bone-tendon healing via angiogenesis/vasculogenesis and osteogenesis. In the present study, CD34+ cells in the ACL-derived cells of young patients may have enhanced angiogenesis and osteogenesis, leading to early bone-tendon healing in Group 10s. All things considered, the results of the previous study that ACL remnants of young patients had more CD34+ cells compared to ACL remnants of older patients, and that these CD34+ cells had a higher potential for proliferation and multilineage differentiation in vitro explains the results of this current study. We suggests that surgeons should consider the patient's age in the use of ruptured ACL remnant tissue to accelerate the bone-tendon healing in ACL reconstruction.