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Orthopaedic Research Society

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POSTER SESSION #: PS2-111
POSTER SESSION TITLE: Cartilage, Synovium and Osteoarthritis - Progenitors and Stem Cells
POSTER #: 1319
POSTER TITLE: Reconstruction Of Osteochondral Defects Using A Microenvironment Created From Autologous Endothelial Progenitor Cells And Porous Plga Scaffolds In A Rabbit Model.
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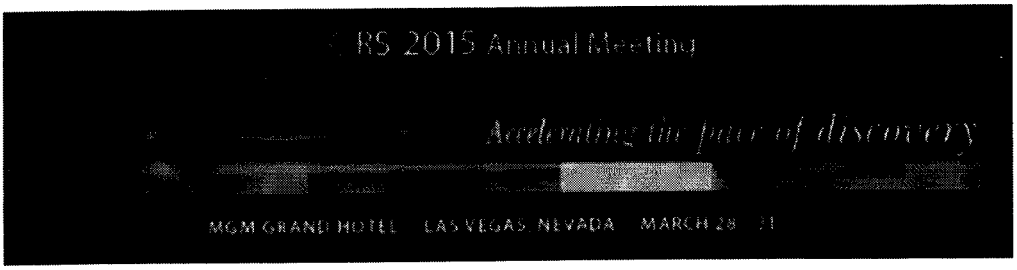

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Reconstruction Of Osteochondral Defects Using A Microenvironment Created From Autologous Endothelial Progenitor Cells And Porous Plga Scaffolds In A Rabbit Model.

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Abstract:
Introduction: Osteochondritis dissecans (OCD) is a pathological disorder in which the articular cartilage is detached from the subchondral bone. Poly(lactide-co-glycolide) (PLGA) has been used as a biomaterial in FDA-approved medical devices, in orthopedic applications and extensively in pre-clinical trials [1]. Previous study demonstrated that a degradable porous PLGA created a temporary space for neo-tissue development and facilitated the regeneration process of cartilage defects [2]. Endothelial progenitor cells (EPC) provide a high capacity for regeneration and vasculogenesis in different tissues. EPC are often adopted and cultured in medium, in which isolation could dispel donor site morbidity risks and provide an ideal autologous cell source. The applications for EPC have been reported for cardiovascular diseases [3] and bone regeneration [4]. However, no previous studies have evaluated the effect of EPC in cartilage repair. Accordingly, we hypothesized that a degradable porous PLGA can provide a topographical cue to promote cell migration, attachment, proliferation, and tissue regeneration. Meanwhile, EPC will offer a biological cue and change in situ the microenvironment or niche, which will trigger the surrounding stem cells to commence self-renewal, proliferation, differentiation, and mobilization, and aid chondrogenesis, osteogenesis [5] and angiogenesis [6], thereby remedying osteochondral defects.
Methods: EPC obtained by purifying a small amount of peripheral blood from rabbits were seeded into a highly porous, biocompatible PLGA scaffold. Adult New Zealand white rabbits used in this study as animal model. We created a 3 mm in diameter and 3 mm in depth cylindrical defect on both the weight-bearing area of medial femoral condyles of the knee. Animals were randomly assigned into one of the three groups: EPCs seeded PLGA scaffold (EPC-PLGA group)(n=16), PLGA scaffold (PLGA group)(n=12), and empty defect (ED group)(n=12). All the groups were implanted into osteochondral defects for 4 and 12 weeks, respectively. The defect sites were evaluated by gross appearance, micro-CT and Histology analysis.
Results: The macroscopic appearance (Fig 1) shows that by the 12 weeks, in ED group, the margin was irregular and the defect was partially filled with regenerative tissue. In PLGA group, the defect was fully filled and slightly convex in the central area which was close to opaque. The edge of regenerated tissue was well integrated with adjacent articular cartilage. In EPC-PLGA group, the defect area was fully filled with lucid regenerative tissue smoothly of which the margin

was barely observed. The surrounding articular surface presented the same color as normal cartilage. The gross appearance and histological assessment of each medial femoral condyle was evaluated according to the modified Wayne's grading scale[7] which was developed by Wayne et al according to the Visual Histological Assessment Scale of the International Cartilage Repair Society (ICRS)[8]. Following this method, the quantitative scores are shown in Fig 2. The score of EPC-PLGA group is significantly higher than PLGA group and ED group. In addition, the score of PLGA group at 4 weeks is similar to ED group at 12 weeks. We used micro-CT to examine the repair situation (Fig 3). More reconstituted bone tissues were observed in all groups at 12 weeks than at 4 weeks. In ED group, the defect was still not filled and the regenerated tissue grew toward inside the defect. In PLGA and EPC-PLGA groups, the defect areas were fully filled with mineralized tissue. For Bone Volume/Tissue Volume (BV/TV) scores (Fig 4) at 12 weeks, the EPC-PLGA group is similar to the sham group and significantly higher than PLGA group and ED group. Furthermore, in EPC-PLGA groups were obviously raise from 4 to12 weeks. The defect surfaces were still remained in concave shape in both ED and PLGA groups; However, in EPC-PLGA group is almost recovered into smooth appearance. At 12 weeks, the ED group exhibited disordered collagen alignment and rough surface was covered the fibrous tissue. The PLGA group presented a rather smoother surface with chondroblasts observed in the cartilage layer, and the collagen fibers were thinner and more disorganized than those in EPC-PLGA group. EPC-PLGA group exhibited nearly normal collagen alignment as normal cartilage and the chondrocytes presented as lacuna morphology without the invasion of blood vessels in the cartilage layer(Fig 5, 6). At 4 weeks, the defect surface of ED and PLGA groups lacked of sulfated glycosaminoglycans (GAGs); In EPC-PLGA group, GAGs presented stronger on the defect surface. At 12 weeks, little amount of GAGs were observed in ED group. In PLGA group, the GAGs presented from the adjacent host toward defect surface, however, no GAGs expression in middle area of the defect surface. For EPC-PLGA group, GAGs expressed on the surface of cartilage and no gap was found in the conjunction area(Fig 7). To further examine the expression of collagen type I, II and MMP13 by immunohistological stainings. The expression of collagen type I is relatively strong at 4 weeks especially in EPC-PLGA group, but to disappear at 12 weeks. The surface of defect area presents certain amount of collagen type I in ED group. A apparent collagen type II expression was observed in EPC-PLGA group than in others (Fig 8). For MMP13 expression, all groups were strong at 4 weeks. After 12 weeks treatment, ED and PLGA group present strong expression of MMP-13 while weak expression in EPC-PLGA group(Fig 9). In this study, we demonstrated that the combination of EPCs and 3-D porous PLGA scaffold does greatly promote osteochondral regeneration in the rabbit model; for instance, neocartilage in EPC-PLGA group presented similar cell composition and collagen alignment with normal articular cartilage as hyaline cartilage formation after 12 weeks.

Discussion: PLGA scaffolds with proper pore sizes not only provides an biocompatible environment for EPC and a mechanical support for stem cells but also serves as a 3D topographical cue for stem cell migration, attachment and homing at the site of the defect. In this study, we did not provide direct evidence for the final fate of the transplanted EPC, as these endothelial progenitors may transdifferentiate into other mesenchymal cells, i.e., chondrocytes. Our delivery system incorporating EPC with PLGA scaffolds theoretically provides a biological cue to recruit surrounding cells and offers a vessel-rich microenvironment for nutrition support in the regenerating joint tissue. We first demonstrated that the transplantation of EPC seeded in 3D PLGA grafts enhances the formation of hyaline cartilage and the neovascularization in the subchondral bone of osteochondral defects without the supplement of exogenous growth factors.

Significance: We demonstrated that pre-seeding EPC onto highly porous, biocompatible PLGA scaffolds creates a favorable in situ microenvironment for the regeneration of osteochondral regions by facilitating chondrocyte growth and hyaline cartilage synthesis and providing sound, complete osteochondral integration and a vascularized bone matrix.

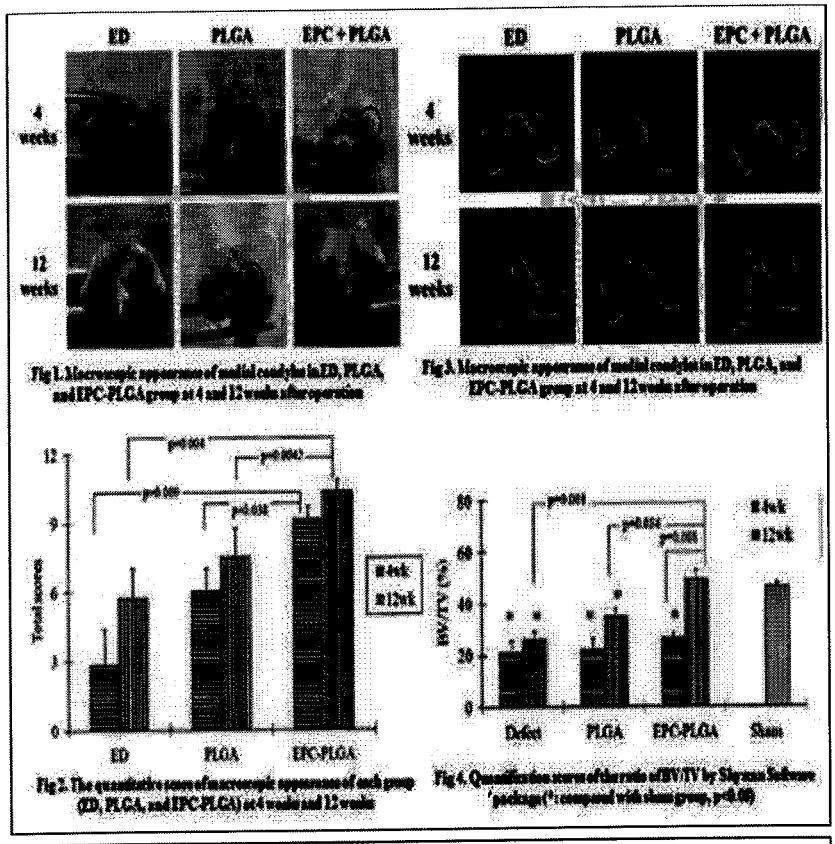

Fig 1. Macroscopic appearance of medial condyle in ED, PLGA, and EPC-PLGA group at 4 and 12 weeks after operation

Fig 3. Macroscopic appearance of medial condyle in ED, PLGA, and EPC-PLGA group at 4 and 12 weeks after operation

Fig 2. The quantitative score of macroscopic appearance of each group (ED, PLGA, and EPC-PLGA) at 4 weeks and 12 weeks

Fig 4. Quantification score of the ratio of BV/TV by Sigmas Software package (* compared with sham group, $p<0.05$)

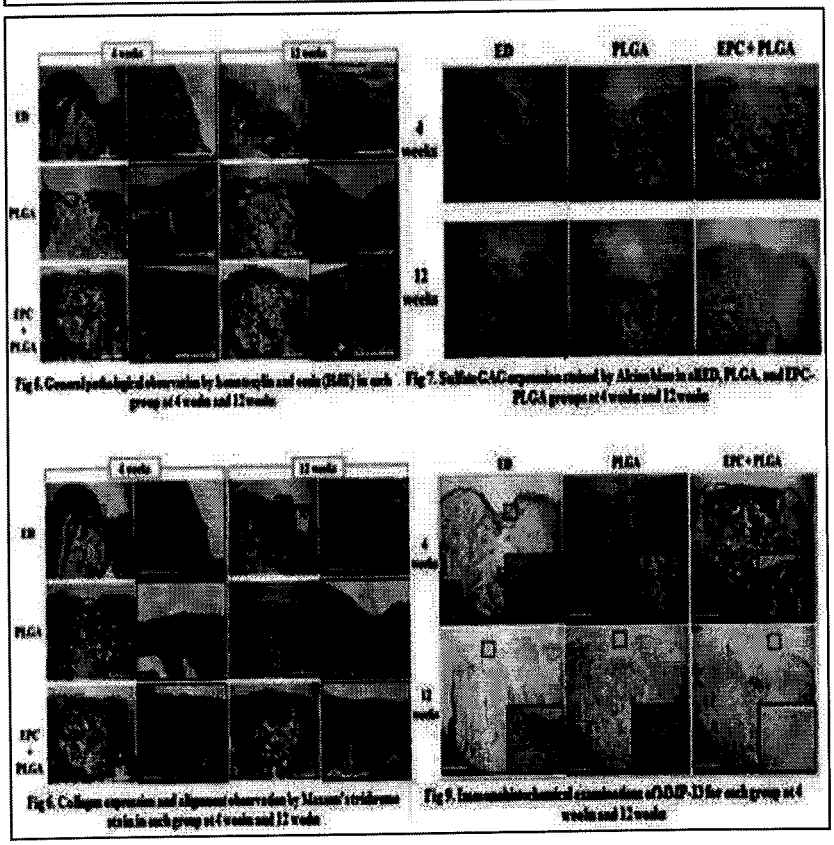

Fig 6. Cranial pathological observation by hematoxylin and eosin (H&E) in each group at 4 weeks and 12 weeks

Fig 7. Sulfate GAG expression evaluated by Alcian blue in sEED, PLGA, and EPC-PLGA groups at 4 weeks and 12 weeks

Fig 8. Collagen expression and alignment observation by Masson's trichrome stain in each group at 4 weeks and 12 weeks

Fig 9. Immunohistochemical examination of OCIP-1) for each group at 4 weeks and 12 weeks

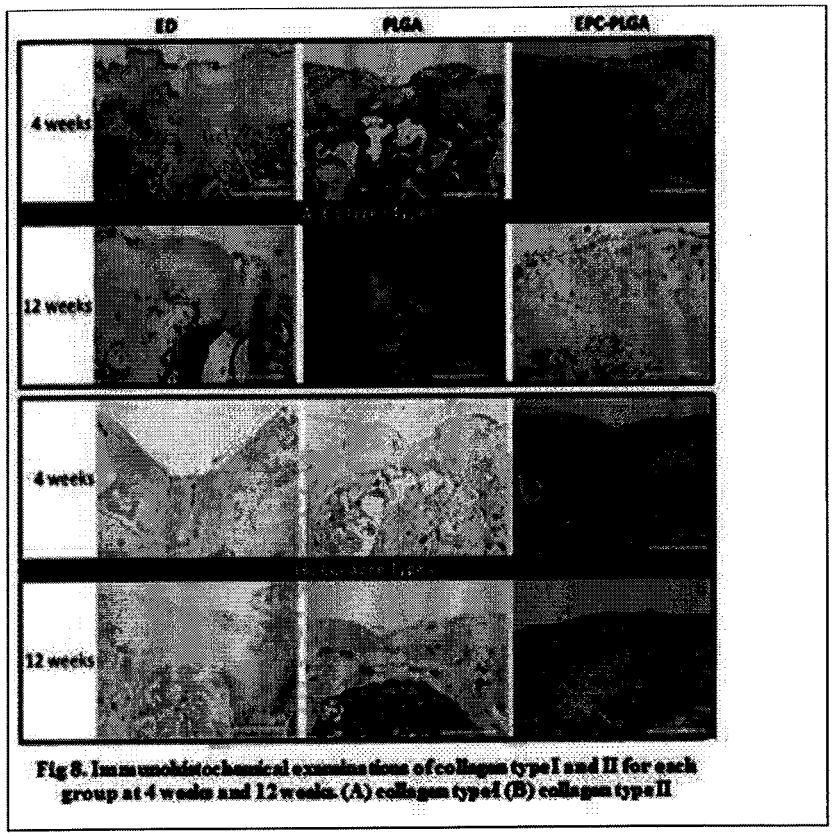

Fig 8. Immunohistochemical examinations of collagen type I and II for each group at 4 weeks and 12 weeks. (A) collagen type I (B) collagen type II

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Author Disclosure Information: **T. Lin:** None. **N. Chang:** None. **H. Hsu:** None. **M. Yeh:** None.
Additional Questions (Complete):

*** Is there any commercial support for this abstract?**: No

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: Chang NJ, Lam CF, Lin CC, Chen WL, Li CF, Lin YT, et al. Transplantation of Autologous Endothelial Progenitor Cells in Porous Plga Scaffolds Create a Microenvironment for the Regeneration of Hyaline Cartilage in Rabbits. Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society. 2013

*** Abstract Description:** Basic Science

*** Were issues of sex and/or gender differences considered in this research study?**: No

If no, please provide an explanation for why it was not considered pertinent or, if it was pertinent, why it was not studied. : Because the endothelial progenitor cells and PLGA scaffold were not influenced by rabbit's sex and/or gender.

*** Abstract references:** : [1] Munirah S, Kim SH, Ruszymah BH, Khang G. The use of fibrin and poly(lactic-co-glycolic acid) hybrid scaffold for articular cartilage tissue engineering: an in vivo analysis. Eur Cell Mater 2008;15:41-52.[2] Chang NJ, Jhung YR, Issariyakul N, Yao CK, Yeh ML. Synergistic stimuli by hydrodynamic pressure and hydrophilic coating on PLGA scaffolds for extracellular matrix synthesis of engineered cartilage. J Biomater Sci Polym Ed 2012;23:2133-51.[3] Lam CF, Roan JN, Lee CH, Chang PJ, Huang CC, Liu YC, et al. Transplantation of endothelial progenitor cells improves pulmonary endothelial function and gas exchange in rabbits with endotoxin-induced acute lung injury. Anesth Analg 2011;112: 620-7.[4] Sun Y, Feng Y, Zhang C, Cheng X, Chen S, Ai Z, et al. Beneficial effect of autologous transplantation of endothelial progenitor cells on steroid-induced femoral head osteonecrosis in rabbits. Cell Transplant 2011;20:233-43. [5] Yu H, Vandevord PJ, Gong W, Wu B, Song Z, Matthew HW, et al. Promotion of osteogenesis in tissue-engineered bone by preseeding endothelial progenitor cells-derived endothelial cells. J Orthop Res 2008;26:1147-52.[6] Bautch VL. Stem cells and the vasculature. Nat Med 2011;17:1437-43.[7] Wayne JS, McDowell CL, Shields KJ, Tuan RS. In vivo response of polylactic acid-alginate scaffolds and bone marrow-derived cells for cartilage tissue engineering. Tissue Eng

2005;11:953-63.[8] Mainil-Varlet P, Aigner T, Brittberg M, Bullough P, Hollander A, Hunziker E, et al. Histological assessment of cartilage repair: a report by the histology endpoint committee of the international cartilage repair society (ICRS). J Bone Jt Surg Am 2003;85:45-57.

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