Endothelial Progenitor Cells: A Novel Cell-based Therapy in Orthopaedic Surgery

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Endothelial progenitor cells (EPCs) can be defined as bone marrow–derived precursor cells with the ability to differentiate into endothelial cells and to participate in the formation of new blood vessels. Bone marrow is the primary source of endothelial progenitors, which can be mobilized to the peripheral circulation and may seed in remote organs and tissues such as liver, spleen, heart, muscle, and adipose tissue. EPCs have been shown to express various endothelial surface markers, such as CD34, VEGFR2, and CD133, and to home to sites of ischemia[1] (Figure 1).

Vascular ingrowth at the fracture site has a cardinal role in the healing process and regeneration of the bone following fracture. However, segmental bone defects after severe trauma, infection, and surgical removal of tumors remain a major clinical problem. These facts, together with reports documenting the remarkable therapeutic potential of EPCs to improve neovascularization and tissue perfusion in other disciplines, have been the major drivers recently to investigate the effects of EPC therapy on fracture healing.

Matsumoto et al[2] investigated the therapeutic potential of systemically administered CD34+ cells on fracture healing in a rodent model. The authors transplanted human peripheral blood CD34+ cells, mononuclear cells, or saline into immunodeficient rats with a nonhealing femoral fracture. Fracture healing was significantly enhanced in the CD34+ group compared with the mononuclear cell and saline groups. Laser Doppler imaging demonstrated that fracture-induced ischemia was significantly reduced in the CD34+ cell–transplanted group compared with the other groups. The authors also noted that approximately 20% of human peripheral blood CD34+ cells expressed mRNA for osteocalcin after transplantation to a fracture site; this outcome may indicate the potential of CD34+ cells for osteogenic and endothelial differentiation.

Atesok et al[3] evaluated the effects of the local use of ex vivo–expanded EPCs on the stimulation of angiogenesis and the promotion of bone healing at a fracture site in a rat femur osteotomy model. Based on the results of radiographic, histologic, and micro-CT comparisons of the EPC-treated group with a control group, the authors stated that "local EPC therapy significantly enhanced bone regeneration in a segmental bone defect in rat femur." In a similar study, the same research group reported that local EPC therapy favorably affects biomechanical stability.[4]

Recent reports also suggest that EPCs derived from peripheral blood contribute to osteogenic differentiation by mesenchymal stem cells (MSCs) in vitro and that MSCs support the proliferation of EPCs.[5] Aguirre et al[6] investigated the interactions between bone marrow EPCs (BM-EPCs) and MSCs in an in vitro co-culture system. Their data suggested that cross-talk occurs between BM-EPCs and MSCs through paracrine and direct cell contact mechanisms, leading to

Topics from the frontiers of basic research presented by the Orthopaedic Research Society.

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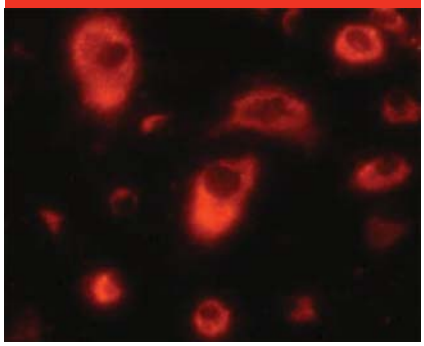
J Am Acad Orthop Surg 2012;20:672-674

http://dx.doi.org/10.5435/JAAOS-20-10-672

Figure 1



Phenotype of cultured endothelial progenitor cells (EPCs) can be characterized according to their ability to uptake DiI-labeled acetylated low-density lipoprotein (DiI-Ac-LDL) to confirm their endothelial lineage. Image demonstrates DiI-Ac-LDL–stained EPCs under fluorescent microscope (×40).

modulation of the angiogenic response. In a rat model study, Seebach et al[7] observed a synergistic effect between EPCs and MSCs and suggested that the initial stage of neovascularization by EPCs be considered crucial for complete bone regeneration.

Positive effects of EPC therapy have been demonstrated in ligament tissue regeneration, as well. Matsumoto et al[8] recently demonstrated that CD34- and CD146-expressing vascular cells exist in human anterior cruciate ligament tissues, have a potential for multilineage differentiation, and are recruited to the rupture site to participate in the intrinsic healing of injured anterior cruciate ligament. In a rodent model, Tei et al[9] studied the effects of locally transplanted human peripheral blood CD34+ cells on the healing of medial collateral ligament injury. Macroscopic, histologic, and biomechanical assessments showed significantly enhanced ligament healing in a CD34+ cell transplantation group compared with a control group. The authors suggested that "local transplantation of circulating human CD34+ cells may augment the ligament healing process by promoting a favorable environment through neovascularization."

Based on the promising results from ex vivo and animal model EPC studies, clinical trials have been started. As a pilot case from a clinical trial, Kuroda et al[10] reported the results of transplantation of autologous peripheral blood CD34+ cells—the hematopoietic/EPC-enriched population—into a patient with nonunion of a tibia fracture. Clinical and radiologic healing of the fracture was achieved at 12 weeks after the cell therapy with bone grafting, and no serious short-term complications were encountered.

EPCs, with their unique features, such as the ability to differentiate into endothelial cells and to participate in the establishment of neovasculature, in addition to their high plasticity, may offer therapeutic alternatives for both bone and ligament tissue engineering. It is likely that more investigators will be attracted in the near future to exploring the potential of these cells in orthopaedic surgery.[11]

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