Aaron Nauth, MD, MSc
Arthroscopy and Orthopaedic Trauma Surgery
Assistant Professor, University of Toronto
Division of Orthopaedic Surgery

St. Michael's
Inspired Care. Inspiring Science.

Stem Cell Populations for Fracture Healing: Which Ones are Most Useful?

Stem Cell Symposium, Orthopaedic Trauma Association Basic Science Focus Forum 2013

STEM CELL POPULATIONS IN FRACTURE REPAIR

- Mesenchymal Stem Cells (MSCs)
- Endothelial Progenitor Cells (EPCs)
- Muscle Derived Stem Cells
- Adipose-Derived Stem Cells
- Perivascular Stem Cells

MESENCHYMAL STEM CELLS (MSCs)

- Traditional stem cell population used in fracture repair
- Due to their known ability to differentiate into cartilage and bone *in vitro*
- Universal Definition (International Society for Cellular Therapy)
    - Plastic Adherent
    - Express CD105, CD73, CD90
    - Lack expression CD45, CD34, CD14, CD11b, CD79a, CD19, HLA-DR
    - Differentiate into osteoblasts, adipocytes, chondroblasts
- Multiple preclinical investigations have demonstrated the ability of ex vivo cultured MSCs to accelerate fracture healing[1], and heal bone defects when combined with osteoconductive scaffolds[2] or osteoinductive proteins[3]
- Some authors have reported ineffectiveness when using MSCs to heal bone defects in preclinical models[4]
- There have been several case series reported in the literature of MSC therapy in humans but no comparative studies with AICBG[5,6]

ENDOTHELIAL PROGENITOR CELLS (EPCs)

- Precursor cells which reside in the bone marrow and peripheral blood
- Form vascular networks in vitro
- Mobilize and home to areas of tissue ischemia
- Contribute to post natal neovascularization
- Highly effective angiogenesis in animal models of MI, limb ischemia, and stroke
- Accepted Markers:
    - CD133, CD34, VEGFR-2
    - Uptake of AcLDL and Leptin
    - Tube formation on Matrigel
- Multiple authors have demonstrated effectiveness with EPC therapy for healing bone defects in preclinical models[7-9]

Division of Orthopaedic Surgery
Suite 800, 55 Queen Street East
Toronto, ON, M5C 1R6
tel: 416-864-6017
fax: 416-359-1601

UNIVERSITY OF TORONTO

Aaron Nauth, MD, MSc
Arthroscopy and Orthopaedic Trauma Surgery
Assistant Professor, University of Toronto
Division of Orthopaedic Surgery

St. Michael's
Inspired Care. Inspiring Science.

Stem Cell Populations for Fracture Healing: Which Ones are Most Useful?

Stem Cell Symposium, Orthopaedic Trauma Association Basic Science Focus Forum 2013

EPCs VERSUS MSCs

- Recent preclinical investigation has demonstrated increased effectiveness of EPC therapy over MSC therapy in a bone defect model[10]
- Other authors have reported synergistic effects on angiogenesis and osteogenesis when EPCs and MSCs are combined in preclinical models[11]
- Recent basic science investigation has demonstrated that both AICBG and RIA contain viable populations of MSCs and EPCs[12]

CONCLUSIONS

- Both MSCs and EPCs have demonstrated effectiveness in preclinical models of fracture healing
- There is emerging evidence to suggest that EPCs may be superior to MSCs, due to their combined effects on osteogenesis and angiogenesis
- The best strategy may be combined administration of both cell populations

REFERENCES

1. Granero-Molto F, Weis JA, Miga MI, et al. Regenerative effects of transplanted mesenchymal stem cells in fracture healing. *Stem cells.* Aug 2009;27(8):1887-1898.
2. Arinzeh TL, Peter SJ, Archambault MP, et al. Allogeneic mesenchymal stem cells regenerate bone in a critical-sized canine segmental defect. *J Bone Joint Surg Am.* Oct 2003;85-A(10):1927-1935.
3. Burastero G, Scarfi S, Ferraris C, et al. The association of human mesenchymal stem cells with BMP-7 improves bone regeneration of critical-size segmental bone defects in athymic rats. *Bone.* Jul 2010;47(1):117-126.
4. Cuomo AV, Virk M, Petrigliano F, Morgan EF, Lieberman JR. Mesenchymal stem cell concentration and bone repair: potential pitfalls from bench to bedside. *J Bone Joint Surg Am.* May 2009;91(5):1073-1083.
5. Giannotti S, Trombi L, Bottai V, et al. Use of Autologous Human mesenchymal Stromal Cell/Fibrin Clot Constructs in Upper Limb Non-Unions: Long-Term Assessment. *PLoS One.* 2013;8(8):e73893.
6. Marcacci M, Kon E, Moukhachev V, et al. Stem cells associated with macroporous bioceramics for long bone repair: 6- to 7-year outcome of a pilot clinical study. *Tissue engineering.* May 2007;13(5):947-955.
7. Mifune Y, Matsumoto T, Kawamoto A, et al. Local delivery of granulocyte colony stimulating factor-mobilized CD34-positive progenitor cells using bioscaffold for modality of unhealing bone fracture. *Stem cells.* Jun 2008;26(6):1395-1405.
8. Rozen N, Bick T, Bajayo A, et al. Transplanted blood-derived endothelial progenitor cells (EPC) enhance bridging of sheep tibia critical size defects. *Bone.* Nov 2009;45(5):918-924.
9. Li R, Atesok K, Nauth A, et al. Endothelial progenitor cells for fracture healing: a microcomputed tomography and biomechanical analysis. *J Orthop Trauma.* Aug 2011;25(8):467-471.
10. Nauth A, Li R, Schemitsch EH. Endothelial progenitor cells for fracture healing and angiogenesis: A comparison with Mesenchymal Stem Cells. Annual Meeting of the American Academy of Orthopaedic Surgeons; 2010; Las Vegas, NV.
11. Seebach C, Henrich D, Kahling C, et al. Endothelial progenitor cells and mesenchymal stem cells seeded onto beta-TCP granules enhance early vascularization and bone healing in a critical-sized bone defect in rats. *Tissue Eng Part A.* Jun 2010;16(6):1961-1970.
12. Henrich D, Seebach C, Sterlepper E, Tauchmann C, Marzi I, Frank J. RIA reamings and hip aspirate: a comparative evaluation of osteoprogenitor and endothelial progenitor cells. *Injury.* Nov 2010;41 Suppl 2:S62-68.

Division of Orthopaedic Surgery
Suite 800, 55 Queen Street East
Toronto, ON, M5C 1R6
tel: 416-864-6017
fax: 416-359-1601

UNIVERSITY OF TORONTO