Stem Cell Transplant is Effective in Preventing Aseptic Loosening

Vincentius Jeremy Suhardi, Xu Yang, Matthew B Greenblatt[1], Lionel B Ivashkiv[2], Anastasia Oktarina, Mathias P G Bostrom[3]
[1]Weill Cornell Medical College, [2]Hospital For Special Surgery, [3]Orthopedic Surgery, Hospital For Special Surgery

INTRODUCTION: Aseptic loosening is one of the leading cause of failures of total joint replacements (TJRs). Regardless of the etiology of loosening or the type of implants used (cementless or cemented), fibrotic tissue instead of bone ubiquitously forms at the bone-implant/cement interface. We have previously reported that Leptin receptor skeletal stem cells (LepR$^+$) are multipotent, and can differentiate into 1) osteoblasts to form bone, 2) myofibroblasts to form fibrotic tissue, or 3) adipose tissue. Here we aimed to evaluate whether transplantation of LepR$^+$ stem cells in peri-implant area of unstable implant can prevent formation of peri-implant fibrosis.

METHODS:

All experiments were approved by local IRB or IACUC. All identifying patient information was anonymized at the time of sample procurements.

Mouse LepR$^+$ cell isolation: Sixteen-week-old, female *Lepr*-Cre; tdTomato mice, in which *Lepr*-expressing cells are marked with tdTomato reporter, underwent implantation on their right tibiae to induce successful osseointegration (n=10). Briefly, a 3D printed titanium (Ti6Al4V) implant to mimic the tibial component of a cementless total knee replacement is press-fitted into the mouse's tibial medullary canal and its porous surface facilitates osseointegration. Peri-implant tissues were collected at 2 weeks post-implantation. Lin-(CD45, CD31, and Ter119 negative) *Lepr*-tdTomato+ cells were isolated using fluorescence-activated cell sorting (FACS) and pooled according to the implantation groups.

Transplantation of LepR$^+$ cells in peri-implant area: Immunodeficient mice (NOD-*scid* IL2Rgamma^{null}, n=10) underwent implantation on their right tibiae to induce peri-implant fibrosis. Briefly, to induce peri-implant fibrosis, the same implant as in the successful osseointegration model is used, except the intramedullary canal is over-drilled, resulting in implant micromotion and thus inducing formation of fibrotic tissue. After over-drilling the intramedullary canal, five mice received transplantation of approximately 10,000 LepR$^+$ cells to each mice into the intramedullary canal prior to insertion of the titanium implant. The remainder five mice received vehicle only into the intramedullary canal prior to insertion of the titanium implant. The tibias were collected 8 weeks later for histological analysis and immunofluorescence staining.

Statistical Analysis: Statistical analysis was performed using Student's t-test. $p<0.05$ was considered as significant.

RESULTS:

Mice receiving LepR+ cells had significantly less peri-implant fibrous tissue and more peri-implant osseous tissue than the vehicle only control (Figure 1). Transplanted LepR$^+$ cells (labelled with endogenously expressed Tdtomato fluorescent protein) forms bone, marrow cells, and small amount of myofibroblasts (Figure 2). Osteogenic LepR$^+$ cells from donor cells co-expresses bone gamma-carboxyglutamate protein (BGLAP) and Tdtomato, while fibrogenic LepR$^+$ cells from donor cells co-expresses alpha smooth muscle actin (αSMA) and Tdtomato (Figure 3).

DISCUSSION AND CONCLUSION:

This is the first study showing that transplantation of skeletal stem cells can drive formation of peri-implant bone despite initial implant instability. The transplanted skeletal stem cells not only differentiated into osteoblasts, but also can induced peri-implant host cells to also form bone instead of fibrous tissue. On the other hand, peri-implant fibrosis was formed in all the mice that receive vehicle only.

SIGNIFICANCE/CLINICAL RELEVANCE: Stem cell transplantation into peri-implant area may be a useful adjuvant to improve osseointegration. This is especially important as the prevalence of press-fitted total hip and total knee arthroplasty continues to increase in the United States.

REFERENCES: 1, Suhardi, V.J., et al. ORS Abstract. 2021.

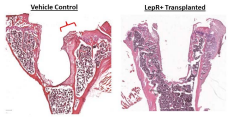

Figure 1. Representative histology of mice receiving LepR$^+$ cells in the peri-implant area vs vehicle only control. Red bracket marks the area of peri-implant fibrous tissue.

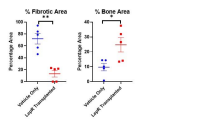

Figure 2. Quantification of peri-implant fibrous and osseous tissue. Mice receiving LepR cells in the peri-implant area has higher amount of peri-implant bone and lesser fibrosis than vehicle only control. *p<0.05, **p<0.01.

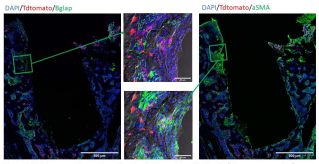

Figure 3. Multipotency of transplanted LepR cells. Transplanted LepR cells (Tdtomato expressing)can differentiate into osteoblast (expresses Bglap), myofibroblasts (expresses αSMA), and marrow cells. Dapi marks cell nuclei.