

PDGFAA Induces LEPR-expressing Stromal Cells to mediate peri-implant fibrosis

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INTRODUCTION: Impaired osteointegration is the leading cause of implant loosening after total joint replacements (TJRs). Advanced age is associated with higher risk of complications after TJR. Our recent study has identified that leptin receptor (LEPR) expressing stromal cells contribute to peri-implant fibrosis¹. Platelet-derived growth factor receptor alpha (PDGFR α) is a member of the PDGF family. Its expression in LEPR+ cells contributes to fibroblast generation in lung fibrosis and myelofibrosis^{2,3}. Using our established mouse model, we aimed to investigate whether PDGFR α or one of its ligands, PDGFAA, affect the fate of peri-implant LepR+ stromal cells and contribute to peri implant fibrosis and poor osseointegration associated with aging.

METHODS: All experiments were approved by a local IACUC. We used six 60-week-old *Lepr-CreER; Pdgfra*^{fl/fl}; Ai6 mice, in which *Pdgfra* was deleted in LEPR+ cells upon tamoxifen administration. Equal numbers of young (13-weeks old) and old (80 weeks old) *Lepr-CreER; Pdgfra*^{fl/+}; Ai6 mice were used as controls. Deletion of one allele of *Pdgfra* was reported not to result in observable phenotypes³. Three doses of tamoxifen (2mg, I.P) were given 3, 2, and 1 day before surgery. All mice received a 3-D printed titanium implants with a porous stem surface. Implants were inserted into an over drilled tibial medullary canal to induce fibrous-integration. Tibiae were collected 2 weeks post-implantation. The peri-implant bone volume fraction (BV/TV) was measured by Micro-CT. Bone and fibrotic tissue percentages of peri-implant tissue were determined by histology analysis. PDGFR α and PDGFAA expression was detected by immunofluorescence. Bulk RNA transcriptome analysis was based on our previously published data⁴. Differences between three groups were assessed using one-way ANOVA followed by Tukey's multiple comparisons test, with $p < 0.05$ as significance.

RESULTS: PDGFAA protein and RNA expression was significantly higher in the peri-implant tissue in old mice relative to young mice. No significant difference was seen in PDGFR α expression (Fig. 1). Deletion of *Pdgfra* in LEPR-lineage cells increased osseointegration as shown by peri-implant BV/TV. This result was supported by histology showing quantitative increases in areal measurements of bone and decreased areal measurements of fibrosis in the peri-implant region (Fig. 2).

DISCUSSION: Aging results in increased production of PDGFAA in the peri-implant region and PDGFAA acts on LepR+ stromal cells to promote peri-implant fibrosis, resulting in impaired osteointegration. Deletion of *Pdgfra* in LepR+ cells reduces fibrosis and improves bone formation, suggesting that osteogenic LepR+ cells divert to a fibrotic phenotype after PDGFAA stimulation. Further studies are needed to determine the cellular origin of PDGFAA in the peri-implant microenvironment.

SIGNIFICANCE/CLINICAL RELEVANCE: Increased levels of PDGFAA are produced in the peri-implant region in aged mice. This in turn activates the *Pdgfra* pathway in LEPR+ cells, leading to their fibrogenic differentiation, peri-implant fibrosis and, ultimately, osteointegration failure and implant loosening. Targeting PDGFAA signaling or modulating PDGFR α activity in LepR+ cells may offer therapeutic strategies to mitigate fibrosis and enhance osteointegration in elder patients receiving TJRs.

REFERENCE:

1. Suhardi, Vincentius Jeremy et al. Prevention and Treatment of Peri-Implant Fibrosis by Functionally Inhibiting Skeletal Cells Expressing the Leptin Receptor. *Nature Biomedical Engineering* 8 (2024): 1285–1307.
2. Matthew Decker et al. Leptin-receptor-expressing bone marrow stromal cells are myofibroblasts in primary myelofibrosis. *Nature Cell Biology*. 19 (2017): 677-688.
3. Dvir Aran et al. Reference-based analysis of lung single-cell sequencing reveals a transitional profibrotic macrophage. *Nature Immunology*. 20 (2019): 163-172.
4. Kathleen Turajane et al. RNA-seq Analysis of Peri-Implant Tissue Shows Differences in Immune, Notch, Wnt, and Angiogenesis Pathways in Aged Versus Young Mice. *JBMR Plus*, 5. 11 (2021), e10535.

IMAGES AND TABLES:

