**MFG-E8 decreases intimal proliferation in a murine model of transplant vasculopathy**

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**Introduction**

Milk Fat Globule Epidermal growth factor-8 (MFG-E8), released by apoptotic cells, can reprogram macrophages from a pro- to anti-inflammatory phenotype1. We aimed to study its role in a model of chronic transplant vasculopathy, the major cause of long-term allograft dysfunction in renal and heart transplantation2.

**Hypothesis**

Intragraft MFG-E8 is crucial to dampen local and systemic inflammation.

**Material & Methods**

Aortic transplantation and MFG-E8 injection procedures (30 µg/kg, intraperitoneally, twice a week). Isograft served as control (Balb/C aorta in Balb/C). n = 8-10 per group.

**Results**

All data are shown as mean ± SEM.

Figure 1 – Aortic transplantation and MFG-E8 injection procedures (30 µg/kg, intraperitoneally, twice a week). Isograft served as control (Balb/C aorta in Balb/C). n = 8-10 per group.

Figure 2 – MFG-E8 decreased intimal proliferation (intima/media ratio) of the allograft, evaluated at week 9 by Hematoxylin & Eosin stain (* p < 0.05 ; ** p < 0.01 ; ANOVA + Tukey post-test). No rejection occurred in isograft group (intima/media ratio = 0.18, dotted line).

**MFG-E8 decreased local inflammation**

Figure 3 – (A) Macrophage infiltration (Mac-2+ cells) of the allograft, by immunofluorescence, at week 9, seemed to decrease with MFG-E8 injection (B). (C) Anti-inflammatory macrophages (Mac-2+ CD206+ cells, arrow head). Proportion of anti-inflammatory macrophage infiltration increased with MFG-E8 (D) and negatively correlated with rejection (E) (Pearson test).

**MFG-E8 decreased systemic inflammation**

Figure 5 – T cells. In blood, by flow cytometry, (A) activated CD8+ T cells at week 1 vs. before graft was higher in KO groups. T test, * : p< 0.05. (B) Activated CD4+ T cells overtime, using linear mixed model, was modulated by MFG-E8.

Figure 6 – B cells. (A) Total immunoglobulin G (IgG) levels, by ELISA, seemed to decrease in WT groups. (B) No difference in Donor Specific Antibodies (DSA) by flow cytometry.

**Conclusion**

Absence of MFG-E8 promotes increased intimal proliferation in the transplant. MFG-E8 decreases macrophage infiltration and increases anti-inflammatory macrophage proliferation. MFG-E8 also modulates activation of T cells. Thus, MFG-E8 improves transplant outcome by acting as an "analarmine"3, reducing the pro-inflammatory allograft microenvironment.

**References**