Immune Response and Revascularization of Acellular Nerve Allografts Following Mesenchymal Stem Cell Seeding and Surgical Angiogenesis

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Background
• Increasing evidence demonstrates an interplay between neovascularization and immune cells (1-3).
• An optimal immunotolerant local environment is of importance to enhance revascularization (4).
• We investigated the early immune response and subsequent revascularization of acellular nerve allografts (ANA) at longer follow-up after combined stem cell delivery and surgical angiogenesis in a rat sciatic nerve defect model.

Methods
• The study was approved by the Institutional Animal Care and Use Committee (IACUC A3348-18).
• Nerve allografts were harvested from Sprague Dawley rats and decellularized. Isogenic MSCs were isolated from the inguinal fat pad of Lewis rats.
• Helper T cells (CD4+) were significantly increased in groups III and IV compared to group II on day 14.
• Regulatory T cells (CD4+CD25+) were significantly higher in groups III-IV compared to group II on day 7.
• Cytotoxic T cells (CD8+) were significantly reduced in groups IV and V compared to group II on day 7.
• Group II demonstrated the highest levels of natural killer cells (CD161+) compared to groups III-V.
• Vascular volume was significantly higher in groups III-V compared to group II at 12 weeks.
• The CD4/CD8 ratio at day 7 and 14 demonstrated a positive correlation to the vascular volume at 12 weeks (r=0.508, CI: 0.1814-0.7342, r^2 = 0.2585, p = 0.004 and r = 0.735, CI: 0.5097-0.8660, r^2 = 0.5402, p < 0.001, respectively)

Results
• Peripheral blood immune cell phenotyping at day 7 and 14.
• Regulatory T cells (CD4+CD25+) were significantly higher in groups III-V compared to group II on day 7.
• Cytotoxic T cells (CD8+) were significantly reduced in groups IV and V compared to group II on day 7.
• Group III demonstrated the highest levels of natural killer cells (CD161+) compared to groups II-V.
• Vascular volume was significantly higher in groups III-V compared to group II at 12 weeks.

Conclusions
Early favorable immune responses were observed in ANAs treated with surgical angiogenesis with or without stem cell delivery and demonstrated improved vascularity at longer follow-up.

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