Transplants and Grafts

Augmentation of Vascularized Composite Allotransplantation Preservation Solution with a Targeted Complement Inhibitor Prolongs Graft Survival

Recipients of vascularized composite allografts require aggressive and lifelong immunosuppression to manage allograft rejection. The development of strategies to minimize immunosuppression exposure is pertinent for this procedure due to the adverse effects that immunosuppression can produce over time. Vascularized composite allografts are procured entirely from brain dead (BD) donors. In solid organ transplantation, the onset of BD has been shown to promote immunogenicity and poorer post-transplant outcomes. The complement system participates in the provision of a pro-inflammatory environment and BD increases complement-mediated mechanisms of graft injury, which can lead to a heightened rejection response post-transplant.

Researchers from the Medical University of South Carolina (Charleston, South Carolina) are investigating the feasibility of pre-coating vascularized composite allografts prior to transplantation with a targeted complement inhibitor, CR2-Crry. This work aims to determine how donor complement affects acute allograft injury and rejection using preclinical models of donor BD, tissue preservation, and vascularized composite allotransplantation (VCA). BD was induced in donor mice and the animals were maintained for three hours. Donor VCA were perfused in-situ prior to harvest with University of Wisconsin (UW) solution or UW solution augmented with CR2-Crry followed by storage at 4 degrees Celsius for two or six hours. Allografts were analyzed for acute inflammation, ischemia reperfusion injury, and survival following transplantation to recipient mice. Results demonstrated that vascularized composite allografts perfused in-situ with CR2-Crry augmented UW solution were significantly protected from skin and muscle ischemia-reperfusion injury, complement deposition, and infiltration of neutrophils and macrophages, as compared to allografts perfused with UW solution alone. Donor perfusion with CR2-Crry augmented UW solution followed by two or six hours of cold storage was also associated with a significant increase in allograft survival compared to perfusion with UW solution alone (Figure 1). These findings indicate that in-situ perfusion of a site specific complement inhibitor prior to donor allograft harvest significantly ameliorates ischemia reperfusion injury, decreases alloimmune priming, and allows for prolonged vascularized composite allograft survival (*Zhu, Bailey, et al. 2017*).

In conclusion, reducing graft injury during tissue preservation is a promising approach to improving post-transplantation outcomes, while extending graft storage may facilitate the availability of VCA procedures to Service members over wider geographical distances.

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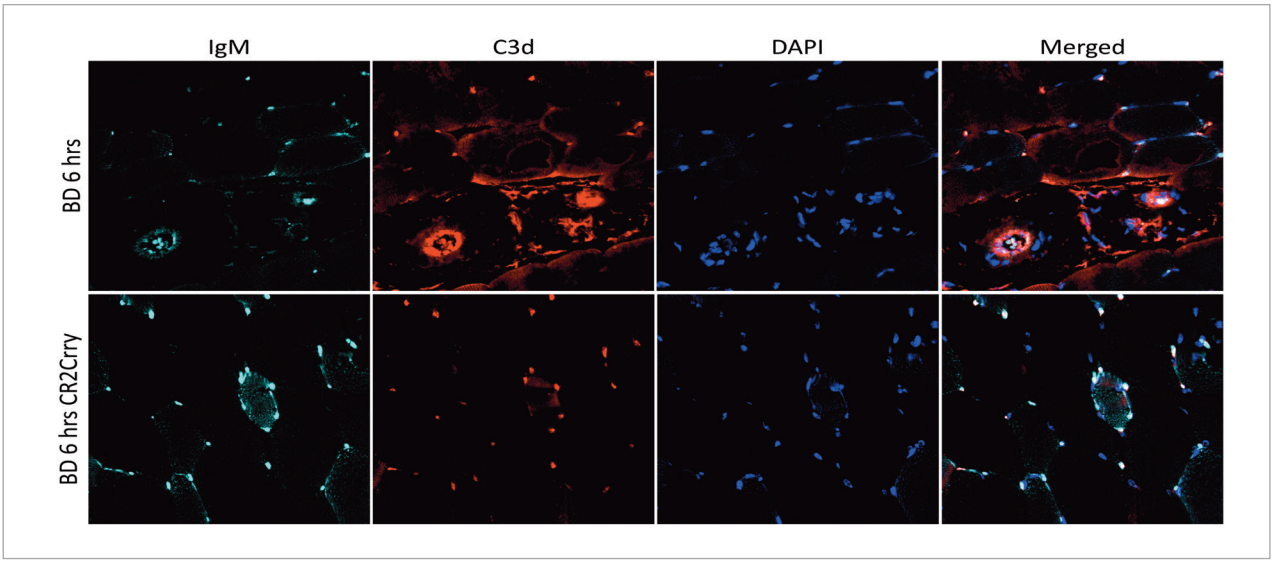

FIGURE 1: Perfusion of vascularized composite allografts in-situ in the BD donor with UW solution augmented with the site targeted C3 complement inhibitor, CR2-Crry, reduces C3 deposition in the muscle of vascularized composite allograft following 6 hours of cold storage. (Figure used with permission from the authors)

REFERENCES:

Zhu, P., Bailey, S. R., Lei, B., Paulos, C. M., Atkinson, C., and Tomlinson, S. 2017. "Targeted Complement Inhibition Protects Vascularized Composite Allografts from Acute Graft Injury and Prolongs Graft Survival When Combined with Subtherapeutic Cyclosporine a Therapy." Transplantation 101 (4):e75-e85. doi: 10.1097/TP.0000000000001625.