Fibrinolysis is Essential for Allograft Integration
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Disclosures:

Introduction: Transplantation of allograft bone is frequently used in orthopedic procedures to augment fracture non-unions and critical-size skeletal defects during limb salvage procedures. Success of a grafts’ integration is dependent upon vascular invasion of the newly formed blood vessels into the transplanted bone. Following revasculatization, integration of the transplanted bone occurs through remodeling of bone matrices. However, the revascularization and integration of donor bone remains a significant challenge and many of these surgeries result in failed allograft incorporation (1, 2). A common finding at the graft-host interface in failed allograft integration is a fibrin matrix that separates the avascular donor bone and recipient’s vascularized bone(3). Based on these observations we hypothesized that an inability to clear fibrin would result in impairment of sterilized graft integration. To test our hypothesis we transplanted sterilized allografts into the femurs of wild type mice and mice which were deficient in plasminogen, the zymogen of the physiologic enzyme responsible for fibrin degradation.

Methods: All animal protocols were reviewed and approved by IACUC. 8 week mice had a 6mm sterilized allograft transplanted into their mid-shaft femurs (N= >6). To assess healing mice were followed for 4 and 6 weeks post operatively for sterilized allografts. Weekly x-rays were performed to assess callus formation and angiography was performed to assess vascular integration. µCT analysis was performed to determine graft integration followed by histologic sections to assess the composition of the integration site.

Results: Serial x-rays revealed plasminogen deficient mice that received a sterilized allograft had abnormal callus formation at the interface between the graft and femur as compared to wild type mice (figure 1). Additionally, µCT 3D reconstructions and 2D slices of femurs 6 weeks post operation demonstrate that plasminogen deficient mice fail to incorporate their allograft, as evident by a gap (yellow arrow) in mineralized bone (figure 1). Histological evaluation of the host graft interface in plasminogen deficient mice revealed the presence of fibrin interposed between the host and graft.

Discussion: These results demonstrate that a deficiency in fibrinolysis results in impaired sterilized graft integration. It has been demonstrated in vitro that an inhibition of plasminogen prevents endothelial cells invasion. As our results demonstrate that fibrin was interposed between the donor mouse and the allograft we postulate that fibrin accumulation is acting as a barrier to revascularization of the fracture callus.

Significance: These findings would suggest that resolving the accumulation of fibrin would enhance the integration of the transplanted bone. Specifically, that pharmaceutical methods targeting plasminogen, or other methods of depleting fibrinogen, at the local or systemic level may be used to improve allograft integration by removing the potential impediment of vascular and matrix in-growth.

Acknowledgments: