Busulfan depletes neutrophils and delays accelerated acute rejection of discordant xenografts in the guinea pig-to-rat model.

Abstract:
Complement factor C6 plays a critical role in mediating hyperacute rejection of discordant xenografts. In order to explore the mechanism of discordant xenograft rejection, we investigated kinetics and phenotypes of the cellular infiltrate in xenografts in untreated and leukocyte-depleted recipients, in relation to graft survival. Guinea pig cardiac xenografts were heterotopically transplanted to totally C6-deficient PVG (C-) rats. Grafts were removed after 0, 6, 12, and 24 h (n = 6). Histological evaluation was performed with hematoxylin and eosin (H& E) and immunoperoxidase staining. The agents fucoidin and busulfan were applied to delay xenograft rejection further. Within 6 h, minimal perivascular edema with isolated infiltrating CD11b/c- and ED1-positive cells were found. An intense infiltration of CD11b/c- and ED1-positive cells with interstitial hemorrhage was present after 24 h, though with little CD161 and CD3 cell infiltration. Inhibition of cell adhesion by fucoidin did not prolong xenograft survival (34 +/- 15 h, n = 4, P<0.47), but the depletion of granulocytes by injection of busulfan did prolong survival of the discordant xenografts, to 62 +/- 22 h (n = 7, P< or = 0.0039). These results demonstrate a significant effect of specific depletion of granulocytes and macrophages by busulfan therapy on guinea pig cardiac xenograft survival in PVG (C-) rats, suggesting the participation of these infiltrating cells in the
xenoreactive rejection process.

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