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Use of MHC Class I or II "Knock Out" Mice to Delineate the Role of These Molecules in Acceptance/Rejection of Xenografts

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IT has previously been reported that pretreatment of human islets with anti-MHC class I antibodies leads to their prolonged survival when subsequently transplanted into naive mice, suggesting that, as in allotransplantation, these molecules also play a role in the recognition and the initiation of effector responses to xenoantigens.[1] However, this protracted survival of cellular, unlike primary vascularized organ transplants, can also be ascribed partially to their inherent resistance to antibody-mediated injury; a feature largely attributed to the neovasculature, which is essentially of recipient origin. Of the vascularized organs, liver but not heart xenografts are an exception: they are relatively resistant to humoral rejection, thereby allowing for the development of cell-mediated responses.[2] This peculiar observation provides a unique opportunity to study the role of donor MHC class I and class II cell surface molecules in the acceptance or rejection of primary vascularized xenografts. To this end, we used MHC class I and class II "knock out" mice as donors of organs (liver and heart), which were transplanted into naive rat recipients. Furthermore, the influence of MHC disparity on xenograft survival in the reciprocal (rat to mouse) combination was also investigated.

MATERIALS AND METHODS

Rat to Mouse Experiments. Hearts obtained from 2- to 3-week-old ACI ($RT1^a$) or LEW ($RT1^l$) rats were heterotopically transplanted into adult B10 or C3H mice.

Mouse to Rat Experiments. Hearts (heterotopic) or livers (orthotopic) were transplanted from normal C3H ($H\text{-}2^k$), B10 ($H\text{-}2^h$), B6 ($H\text{-}2^b$), or MHC class I (B6: b2m) or class II (B6: CD2) deficient mice into naive 3- to 4-week-old LEW recipients.

RESULTS AND DISCUSSION

Rat to Mouse. C3H mice rejected LEW and ACI hearts in 5.6 ± 0.5 and 7.1 ± 0.8 days, respectively ($P < .0001$), whereas B10 mice rejected these grafts in 8.5 ± 0.7 and 7.7 ± 0.7 days, respectively ($P < .003$). Histopathological analysis of rejected cardiac xenografts revealed mononuclear cell infiltration with widespread thrombosis.

Mouse to Rat. Hearts obtained from B10, C3H, or B6 mice, when transplanted into LEW rats, were rejected in <3 days. Similar survival was also noted when hearts from MHC class I or class II knock out mice were transplanted into naive LEW recipients. The predominant effector mechanism appeared to be humoral, because histopathological analysis revealed widespread thrombosis and interstitial hemorrhage with mild cellular infiltration. Unlike hearts, mouse livers obtained from naive animals enjoyed prolonged survival (6 to 10 days) when transplanted into LEW rats. However, similar to our observations in hearts, the lack of expression of class I or class II antigens in the transplanted liver had no appreciable effect on prolonging its survival following transplantation. Interestingly, no discernible difference was noted in the titers of rat antimouse cytotoxic antibodies in the serum of LEW recipients of hearts or livers from b2m, CD2, or normal B6 mice.

Taken together, these observations suggest that the expression of donor MHC class I and class II cell-surface antigens may have an insignificant role in determining the tempo of rejection of xenografts transplanted from mouse to rat. It is therefore tempting to speculate that in this model, species-specific epitopes may play a more dominant role than MHC antigens in eliciting humoral or cellular responses.

REFERENCES

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