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Organs transplanted between disparate species are susceptible to hyperacute rejection (HAR).[1] Characterized by the nearly immediate loss of graft function, formation in the graft of platelet thrombi, and the presence of interstitial hemorrhage, HAR is arguably the most severe of all immune responses known.

HAR is triggered by the binding to the graft of anti-Galα1-3Gal antibodies,[2-4] which are present at some level in all immunocompetent humans, much as are antibodies directed against the blood group A and B antigens in those humans who do not express the blood group antigens.[5] Antibody binding to the xenograft triggers the activation of complement,[6] and it is complement activation, particularly the formation of terminal complement complexes, which allows HAR to proceed.[7]

The pathogenic mechanisms giving rise to HAR have not been demonstrated definitively; however, in vitro studies suggest that those mechanisms may well include a distortion in endothelial shape caused by the rapid insertion of terminal complement complexes in endothelium.[8] A change in endothelial shape allows the immediate interaction of circulating platelets with the matrix underlying endothelial cells, potentially accounting for the platelet aggregation as the first demonstrable change in xenografts. An alternative mechanism may involve the shedding of von Willebrand factor and other porcine proteins from endothelium, leading to formation of immune complexes and the consumption of platelets in a like manner.[9]

Although susceptibility to HAR is considered to be a property of species, and, thus, species are referred to as discordant or concordant depending on this property,[10] some investigators have found that porcine organs do not invariably undergo HAR upon transplantation into nonhuman primates.[11] The author has considered, in detail, some of the factors that may underlie varying responses to xenotransplantation with regard to the occurrence of HAR.[12] Regardless of whether HAR occurs in every instance or only on some occasions, the risk of that process poses such a severe hurdle to the clinical application of xenotransplantation that efforts must be undertaken to prevent it with certainty or near-certainty.

Has Hyperacute Rejection Been Overcome?

If HAR is defined as rejection occurring within 24 hours of reperfusion of an organ graft with the characteristics as previously described, then HAR has indeed been overcome by preventive measures. The most reliable approach to preventing HAR is inhibiting complement activation. At the present time, effective inhibition of complement has prevented HAR. It would seem the standard approach for preventing HAR is expressing human complement regulatory proteins, such as decay accelerating factor (DAF), or membrane cofactor protein in the graft.[13,14] This approach, which is accomplished by transgenic techniques, is preferred because it leaves the complement system intact to defend the recipient against infectious organisms. Alternative approaches, such as the administration of soluble complement receptor 1 or anti-C5 antibodies, inevitably compromise some measure of host defense.

Acute Vascular Rejection—A Delayed Form of Hyperacute Rejection?

When cobra venom factor or other complement inhibitors are given to the recipients of xenografts,

Jeffrey L. Platt, M.D.
Transplantation Biology
Medical Sciences
Building 2-66
Mayo Clinic
200 1st Street S.W.
Rochester, Minnesota, USA 55905
Tel.: 507.538.0313
Fax: 507.284.4957
email: platt.jeffrey@mayo.edu

and when the xenografts do not undergo rejection within the first 24 hours, they may still succumb to a severe type of vascular rejection over a period of days to weeks.[15] This type of rejection, which is referred to as acute vascular rejection (AVR), was once thought to be a delayed manifestation of HAR. The mistaken understanding about the identity of this type of rejection is owed, in part, to certain similarities in the histologic picture which, in turn, reflect manifestations of ischemia, such as interstitial hemorrhage and the presence of fibrin at certain places in the graft. However, certain aspects of the pathogenesis and manifestations of AVR depart fundamentally from the corresponding aspects of HAR, and remove any clinical or scientific value from combining these processes under one heading.

Seminal events in HAR appear to be the rapid assembly of terminal complement complexes on xenograft endothelium and aggregation of platelets at frequent points in the vasculature of the transplant. In contrast, the earliest events in the development of AVR are a thickening of endothelial cells and deposition of fibrin on those cells.[16] In contrast to HAR, AVR is not generally characterized by the presence of abundant amounts of terminal complement complexes on graft vasculature and, in fact, some such complexes may not be found at all. These aspects are of import if AVR and HAR are to be treated by definitive and incisive approaches.

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For example, anti-C5a antibodies, transgenic expression of DAF, membrane cofactor protein, and CD59 definitively prevent HAR but have no impact on the occurrence of AVR. On the other hand, measures that can prevent AVR, such as the removal of xenoreactive antibodies by immunoabsorption,[17] may have little effect on HAR in experimental models in which complement can be activated by other means, particularly the alternative complement pathway.[18,19]

So, in answer to the question "Has hyperacute rejection been overcome?", the simple answer is "Yes".

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