Leukocyte adhesion and activation in xenografts

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Introduction

Over the decade, substantial increases in transplant organ and recipient survival have been accompanied by a significant increase in the quality of life for patients with end stage organ failure. However, the increasing access to organ transplant lists, coupled with static or even falling organ donation rates, have resulted in a doubling of the waiting time for patients receiving a cadaveric kidney to around three years at many major centers. In addition, many patients waiting for a suitable heart or liver die while waiting because of the lack of effective life support systems. While living related kidney transplantation has the potential to alleviate kidney organ shortages, grafting of liver or lung from living donors has been performed in only a few specialised centres to date.

The proposed use of an unlimited supply of animal organs in clinical practice, i.e. xenotransplantation, could provide a bridge to a successful allograft, or more optimistically may even substitute for allografts and provide for long term graft survival [1–3]. Unfortunately, the clinical application of xenotransplantation, to date, has resulted in universal suboptimal results with failure when measured against the routine and effective use of allografts. This form of clinical intervention will only be feasible once the mechanisms of xenograft loss have been better determined and effective therapies tested in appropriate animal models [2, 4–6]. Indeed, recent developments in the field of xenotransplantation biology have greatly expanded our understanding of the mechanisms by which xenografts are rejected [7–10]. Novel molecular biological techniques have allowed the production of donor animals (pigs) with human transgenes directed toward amelioration of the complement (C) activation [11] and antibody interactions [12, 13] shown to be of great immediate importance in xenograft rejection. However, with these advances, it has become apparent that the rejection response directed at a discordant xenograft is composed of many separate elements that appear to have different kinetics and result in various manifestations of xenograft rejection [3, 5, 7].
Discordant porcine organs can function for several days in primates following the inhibition of C and/or removal of xenoreactive natural antibodies (XNA) that are associated with hyperacute rejection (HAR) [3, 14, 15]. However, a xenograft rejection process, characterized by humoral and cell-mediated vascular and parenchymal injury, then ensues. This acute vascular-type or delayed xenograft rejection process (AVR/DXR) and the associated antibody/cellular mediated responses in primates to porcine antigens are considered the major barrier to xenograft acceptance at this time [4, 5, 7]. This response may be initiated by natural killer (NK) cell-mediated endothelial cell (EC) activation, associated with secondary xenoreactive antibody and T cell responses [16]. Currently, the mechanisms whereby NK cells, T cells and monocytes interact with porcine endothelium and the role of co-stimulatory pathways remain undetermined but available data will be addressed in this chapter.

The scientific uncertainty regarding the mechanisms of these immune reactions has been recently coupled with public health questions regarding the importance of potential zoonoses such as porcine endogenous retroviruses (PERV) and how interspecies molecular barriers may compromise control of certain infections [17, 18] or even any associated lymphoproliferative disorders. These unresolved scientific issues, in addition to many social and potential ethical issues surrounding xenotransplantation, will require extensive debate between the appropriate regulatory bodies prior to the commencement of clinical trials in xenotransplantation. These issues are beyond the scope of this chapter but have recently been reviewed [19].

Mechanisms of discordant xenograft rejection

Hyperacute rejection (HAR)

Following transplantation of a vascularized discordant xenograft (pig to primate), pre-formed XNA are bound to the endothelial cells (EC) resulting in C activation, vascular damage, intravascular thrombosis and finally ischaemic necrosis. Depending on the species combination, HAR is either initiated by the rapid deposition of XNA from recipients within the graft and the subsequent activation of the classical pathway of C activation (e.g. pig to primate) [20], or is mediated by direct activation of host C through the graft endothelium (e.g. guinea pig to rat combination) [21]. In addition to the activation of C, neutrophil adherence and vasoconstriction may contribute to the pathogenesis of HAR in various models of xenograft rejection [8, 22, 23]. One of the major complications that accompanies HAR relates to thrombosis of the graft microvasculature with platelet sequestration [8]. This development may be associated with ongoing inflammatory responses linked to C-activation [24, 25] or to other inflammatory mediators in certain vascular beds, such as that of the lung [26].