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Immunobiology of xenotransplantation

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Abstract The transplantation of organs between disparate species is hindered by severe immune responses of the recipient against the graft. These immune responses gives rise to hyperacute and acute vascular rejection and to cellular rejection. Research during the past decade has shed light on the elements of the immune system responsible for the rejection of xenografts and has provided novel and incisive therapies which might be applied to these problems.

Key words Xenotransplantation · Hyperacute rejection · Acute vascular rejection · Cellular rejection

Introduction

The successful engraftment of organs from animals into humans has been a goal in the field of transplantation since its inception in the first decade of this century [23]. Achieving this goal is prevented in part by physiologic limitations of the xenogeneic organ and by the potential for transmission of infectious disease from the transplant to the recipient. However, the main hurdle to transplanting organs between species remains the rapid and seemingly inexorable destruction of the transplant by the recipient's immune system. The past decade has brought much progress in understanding the mechanisms underlying immune-mediated injury of xenotransplants and new and incisive therapies for potentially overcoming the immunological hurdles [1, 16].

Biological responses to xenotransplantation

Organs transplanted between species undergo a series of biological responses summarized in Fig. 1. In unmodified recipients, an organ xenograft is subject to hyperacute rejection which destroys the organ within minutes to a few hours [15]. Hyperacute rejection is triggered by xenoreactive antibodies which bind to the endothelium lining donor blood vessels activating the complement system of the recipient [14]. Susceptibility to hyperacute rejection is heightened because the recipient's complement system is not compatible with complement regulatory proteins expressed in the donor organ. When hyperacute rejection is prevented, by either depletion of xenoreactive antibodies or by inhibition of the complement system of the recipient, the xenograft is next subject to acute vascular rejection which destroys the graft over a period of days to weeks [19]. Although a number of causes of acute vascular rejection have been postulated, recent studies suggest that acute vascular rejection is caused by the unremitting interaction of xenoreactive antibodies with donor endothelium perhaps in conjunction with the activation of small amounts of complement on the endothelium [11]. Prevention of acute vascular rejection for a period of days to weeks may allow a xenotransplant to undergo accommodation. Accommodation, first described in the transplantation of organs across ABO barriers [2], is an apparent resistance of the transplant to injury mediated by anti-donor antibodies and complement [17]. Xenografts are also subject to cell-mediated rejection. Cell–mediated rejection of xenotransplants may resemble cell-mediated rejection of allotransplants, although the former is accompanied by significant humoral injury. The sections that follow describe the susceptibility of organs to xenotransplant rejection.

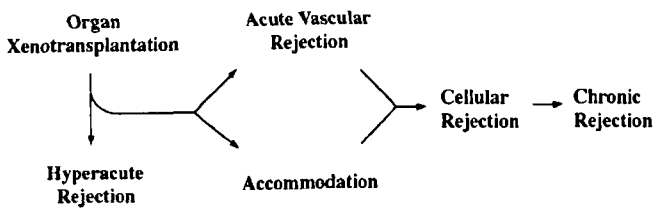

Fig. 1 The biological hurdles for xenotransplantation. Organ transplantation between unmodified disparate species leads to hyperacute rejection. If hyperacute rejection can be averted by depletion of xenoreactive natural antibodies or inhibition of complement system, the xenograft may be subject to acute vascular rejection or "accommodation" may occur. If acute vascular rejection is prevented, the graft will be subject to cellular rejection or chronic rejection

Xenoreactive antibodies and the antigens they recognize

Studies from several laboratories have demonstrated that the major fraction of xenoreactive antibodies in humans that would recognize the organs of lower animals are directed against Galα1–3Gal, a sugar expressed by lower mammals but not by humans and other higher primates. Depletion of anti-Galα1–3Gal antibodies prevents hyperacute rejection of pig organs transplanted into non-human primates [10, 21]. There is increasing evidence that anti-Galα1–3Gal antibodies may also be responsible for acute vascular rejection. Accordingly, therapeutic strategies aimed at the elimination of those antibodies through the induction of immunologic tolerance [3], or the reduction or elimination of the Galα1–3Gal saccharide in donor animals [22], or the prevention of graft injury through the induction of accommodation [17] would appear to be the most promising ways of dealing with acute vascular rejection for clinical purposes.

The complement system

For nearly 35 years the major hurdle to xenotransplantation has been known to be the activation of recipient complement in the donor organ [8]. Complement activation in pig organs transplanted into non-human primates is mediated almost entirely by the binding of complement-fixing xenoreactive antibodies [18]. In addition, pig organs are subject to complement-mediated injury owing to the failure of complement regulatory proteins, such as decay accelerating factor, membrane co-factor protein, or CD59, in those organs to control activation of the recipient's complement system [6]. The problem of incompatibility of complement regulatory proteins has been recently addressed by the generation of transgenic pigs expressing human complement regulatory proteins, especially decay accelerating factor, with or without CD59 [5, 13]. This manipulation alone prevents hyperacute rejection even when the complement regulatory proteins are expressed at low levels.

Humoral response to xenotransplantation

As might be expected, individuals exposed to foreign organs or tissues mount a substantial humoral response [4, 20]. This response is most easily seen if the exposure to foreign tissue is transient since a functioning organ xenograft will absorb anti-donor antibodies from the blood [12]. The xenoreactive natural antibodies made by humans after exposure to pig tissue recognize predominantly Galα1–3Gal. The levels of these antibodies in non-human primates also increase rapidly following xenotransplantation and their occurrence is linked with acute vascular rejection [12]. In addition to anti-Galα1–3Gal antibodies, however, it is likely that antibodies against other pig antigens, particularly pig proteins, are elicited. Only a fragmentary knowledge of the specificity and function of elicited xenoreactive antibodies has been established; however, it is highly likely that these antibodies will be found to cause acute vascular rejection at later times and to be a major hurdle to the clinical application of xenotransplantation.

Cell-mediated immune responses

Cell-mediated immunity to xenotransplantation leading to cellular rejection is likely to be an important impediment to xenotransplantation [1]. Work in the past decade has shown that some aspects of this response, particularly the ability of T cells in humans to recognize pig histocompatibility antigens expressed on pig cells, can resemble cell-mediated responses to allotransplants. However, some aspects of the cell-mediated immune response to xenotransplantation are likely to be more severe than the cell-mediated immune respone to allotransplantation and may warrant unique therapeutic approaches. One important aspect of the cellular immune response in xenotransplantation is likely to be the vast diversity of proteins which can give rise to T cell responses. So diverse is the repertoire of peptides generated across species, that primary T cell responses can be detected in vitro by indirect antigen presentation. Whether the diversity of the indirect T cell response will require new approaches to immunotherapy is as yet unclear. A second important aspect of the cell-mediated response to xenotransplantation is the impact of humoral immunity. The presence of anti-donor antibodies portends and probably causes severe cellular immune responses. A third and as yet incompletely under-

stood hurdle will be the possibility that immunoregulatory T cells, that is T cells which would dampen cellular immune-mediated responses, will be less active across species than they are in the allotransplant setting [16]. A fourth issue relates to the possibility that natural killer cells of the recipient might be highly reactive with the graft. Clearly selecting the appropriate means of immunomodulation or immunosuppression or tolerance will be an important challenge in the field of xenotransplantation.

Concluding remarks

The past decade has brought a much fuller understanding of the molecular basis of the immune response to xenotransplantation and has provided some incisive strategies, such as the genetic engineering of source animals and the development of specific immunodepleting techniques. These therapeutic advances may prove to be sufficient to allow xenotransplantation to enter the clinical arena. The major importance of these advances, however, may be that they underscore the acceleration of research in this field and point to a brighter future where the identification of a hurdle at a molecular level can give rise very rapidly to the application of technology to overcoming that hurdle. Thus, for the first time there is increasing optimism that the immunological hurdles to xenotransplantation may be truly assailable. Consistent with this view, there already are clinical trials and promising experimental results involving the transplantation of non-vascular grafts between species [7, 9].

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References

1. Auchincloss H Jr, Sachs DH (1998) Xenogeneic transplantation. Annu Rev Immunol 16: 433–470
2. Bannett AD, McAlack RF, Raja R, Baquero A, Morris M (1987) Experiences with known ABO-mismatched renal transplants. Transpl Proc 19: 4543–4546
3. Bracy JL, Sachs DH, Iacomini J (1998) Inhibition of xenoreactive natural antibody production by retroviral gene therapy. Science 281: 1845–1847
4. Cotterell AH, Collins BH, Parker W, Harland RC, Platt JL (1995) The humoral immune response in humans following cross-perfusion of porcine organs. Transplantation 60: 861–868
5. Cozzi E, Yannoutsos N, Langford GA, Pino-Chavez G, Wallwork J, White DJG (1997) Effect of transgenic expression of human decay-accelerating factor on the inhibition of hyperacute rejection of pig organs. In: Cooper DKC, Kemp E, Platt JL, White DJG (eds) Xenotransplantation: the transplantation of organs and tissues between species. Springer, Berlin Heidelberg New York, pp 665–682
6. Dalmasso AP, Vercellotti GM, Platt JL, Bach FH (1991) Inhibition of complement-mediated endothelial cell cytotoxicity by decay accelerating factor: potential for prevention of xenograft hyperacute rejection. Transplantation 52: 530–533
7. Deacon T, Schumacher J, Dinsmore J, Thomas C, Palmer P, Kott S, Edge A, Penney D, Kassissieh S, Dempsey P, Isacson O (1997) Histological evidence of fetal pig neural cell survival after transplantation into a patient with Parkinson's disease. Nat Med 3: 350–353
8. Gewurz H, Clark DS, Cooper MD, Varco RL, Good RA (1967) Effect of cobra venom-induced inhibition of complement activity on allograft and xenograft rejection reactions. Transplantation 5: 1296–1303
9. Groth CG, Korsgren O, Tibell A, Tollemar J, Moller E, Bolinder J, Ostman J, Reinholt FP, Hellerstrom C, Andersson A (1994) Transplantation of porcine fetal pancreas to diabetic patients. Lancet 344: 1402–1404
10. Lin SS, Kooyman DL, Daniels LJ, Daggett CW, Parker W, Lawson JH, Hoopes CW, Gullotto C, Li L, Birch P, Davis RD, Diamond LE, Logan JS, Platt JL (1997) The role of natural anti-Gala1–3Gal antibodies in hyperacute rejection of pig-to-baboon cardiac xenotransplants. Transplant Immunol 5: 212–218
11. Lin SS, Weidner BC, Byrne GW, Diamond LE, Lawson JH, Hoopes CW, Daniels LJ, Daggett CW, Parker W, Harland RC, Davis RD, Bollinger RR, Logan JS, Platt JL (1998) The role of antibodies in acute vascular rejection of pig-to-baboon cardiac transplants. J Clin Invest 101: 1745–1756
12. McCurry KR, Parker W, Cotterell AH, Weidner BC, Lin SS, Daniels LJ, Holzknecht ZE, Byrne GW, Diamond LE, Logan JS, Platt JL (1997) Humoral responses in pig-to-baboon cardiac transplantation: implications for the pathogenesis and treatment of acute vascular rejection and for accommodation. Hum Immunol 58: 91–105
13. Parker W, Saadi S, Lin SS, Holzknecht ZE, Bustos M, Platt JL (1996) Transplantation of discordant xenografts: a challenge revisited. Immunol Today 17: 373–378
14. Perper RJ, Najarian JS (1966) Experimental renal heterotransplantation. I. In widely divergent species. Transplantation 4: 377–388
15. Platt JL (1995) Hyperacute xenograft rejection. Landes, New York
16. Platt JL (1998) New directions for organ transplantation. Nature (suppl) 392: 11–17
17. Platt JL, Vercellotti GM, Dalmasso AP, Matas AJ, Bolman RM, Najarian JS, Bach FH (1990) Transplantation of discordant xenografts: a review of progress. Immunol Today 11: 450–456
18. Platt JL, Fischel RJ, Matas AJ, Reif SA, Bolman RM, Bach FH (1991) Immunopathology of hyperacute xenograft rejection in a swine-to-primate model. Transplantation 52: 214–220
19. Platt JL, Lin SS, McGregor CGA (1998) Acute vascular rejection. Xenotransplantation 5: 169–175

20. Rydberg L, Cairns TD, Groth CG, Gustavsson ML, Karlsson EC, Moller E, Satake M, Tibell A, Samuelsson BE (1994) Specificities of human IgM and IgG anticarbohydrate xenoantibodies found in the sera of diabetic patients grafted with fetal pig islets. Xenotransplantation 1: 69–79
21. Sachs DH, Sablinski T (1995) Tolerance across discordant xenogeneic barriers. Xenotransplantation 2: 234–239
22. Sandrin MS, Fodor WL, Mouhtouris E, Osman N, Cohney S, Rollins SA, Guilmette ER, Setter E, Squinto SP, McKenzie I (1995) Enzymatic remodelling of the carbohydrate surface of a xenogeneic cell substantially reduces human antibody binding and complement-mediated cytolysis. Nat Med 1: 1261–1267
23. Ullman E (1914) Tissue and organ transplantation. Ann Surg 60: 195–219