ISSN 2091-2889 (Online)
ISSN 2091-2412 (Print)

Journal of Chitwan Medical College 2013; 3(5): 1-3
Available online at: www.jcmc.cmc.edu.np

REVIEW ARTICLE

REVIEW ON XENOTRANSPLANTATION

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ABSTRACT

There is an increasing interest in the potential clinical application of xenotransplantation. This interest derives in part from the need to identify a more abundant source of organs for transplantation and in part from rapid progress in understanding the cellular and molecular changes that contribute to hyperacute and acute vascular xenograft rejection. Recent areas of progress in understanding the immunological hurdles to xenotransplantation include the characterization of xenoreactive antibodies and the antigens they recognize, the role of complement regulatory proteins in immune recognition, the mechanism of complement activation in a xenograft, and the pathophysiologic changes in endothelial cells caused by the activation of complement. Several approaches have been proposed or used to prevent or reduce the xenogeneic immunologic rejection response, including immunosuppression, genetic engineering, complement inhibitors, and physical barriers.

Key Words: *Xenoreactive antibodies, Antigens and xenotransplantation.*

INTRODUCTION

Although the use of xenogeneic tissues in humans is becoming technically more feasible, many formidable biological obstacles still exist. Perhaps one of the most significant barriers is the human immune system that is capable of rejecting the xenotransplantation product. Overcoming the immune response to xenotransplantation products presents challenges not frequently encountered in all transplantation, in part because there are many more antigenic disparities in cross-species transplantation. [1,2]

Solid organ xenotransplantation performed to date in humans has resulted in extremely brief graft survival. The immunologic barriers to solid organ xenotransplantation appear to be greater than the barriers to xenotransplantation products composed of isolated cells or tissues. The reason for this is probably largely the fact that the vascular endothelial cells present in vascularized grafts (ie, whole organs), if damaged by human natural antibodies, severely compromise graft survival. [3] Endothelial cells also appear to have an important role in the activation of thrombosis, [4] which further compromises survival of vascularized grafts.

Without intervention, a vascularized xenogeneic organ will be destroyed within minutes to hours of transplantation by a process known as hyperacute rejection (HAR). HAR is mediated by natural antibodies present in human serum that react with a variety of antigens, including xenoantigens expressed by tissues of an unrelated species, and has been observed in all transplantation where ABO blood group incompatibilities exist.[5] Complement, a family of serum proteins that can lyses or destroy cells, plays a major role in this reaction. The binding of xenoreactive natural antibodies of the recipient to endothelial cells in the xenograft activates the vascular endothelium and complement. In addition, complement may be activated by the alternative pathway; incompatibility of complement regulatory proteins in the xenotransplantation product with the complement system of the recipient permits unchecked activation of the complement cascade. [6,7,8] These processes produce pathology characterized by interstitial hemorrhage and diffuse clotting or thrombosis of the graft. The strength of xenogeneic HAR is, in part, a function of the phylogenetic distance between the source donor animal and the recipient. It appears more vigorous between distantly related or discordant species such as humans and pigs than between phylogenetically close or concordant species such as humans and nonhuman primates. [9,10] As HAR has become better understood, various therapeutic interventions to avoid it have been proposed and are described below.

The next major cause of xenograft loss after HAR is delayed xenograft rejection. The pathogenesis of delayed xenograft rejection, though poorly understood, is characterized by a distinct and often intractable inflammatory process, which can occur within 36-48 hours but typically occurs days to months after transplantation. Delayed rejection may involve the recurrence of xenoreactive natural antibodies and also has endothelial cell activation as a central feature. [11,12] In a concordant animal model, it has been reported that certain cytokines (interleukin [IL]-12 and interferon-gamma) may ameliorate acute vascular rejection

caused by a B cell-dependent mechanism.[13]

In certain instances, depletion of recipient xenoreactive antibodies and manipulation of complement may permit longer survival of vascularized xenografts, even after antibodies return to the circulation and the complement system is restored. This development, which has been termed "accommodation," appears to be an acquired resistance of the vascularized xenograft to these types of rejection. Although the underlying mechanism(s) of accommodation have not been identified, [10] it has been suggested that it may involve expression of genes that protect against apoptosis or prevent increased production of proinflammatory cytokines by the host immune system. [8]

Finally, vascularized or other xenotransplantation products that survive long enough in the host may elicit a cell-mediated transplant rejection response that can occur within several days to many weeks after transplantation. [11,12] This response may be mediated by a variety of immune cells, including T cells and NK cells; monocytes or macrophages and polymorphonuclear leukocytes have also been demonstrated to infiltrate xenogeneic tissue undergoing rejection. [13,14]

If a xenotransplantation product survives the host immune response, it may still be uncertain as to whether the animal cells, tissues, and organs can perform all the functions of the human counterpart. For example, porcine thrombomodulin has not yet been shown to function with human coagulation proteins in vivo, and it functions poorly with human coagulation proteins in vitro. [14] This and similar observations raise questions about whether a pig liver would be able to replace all necessary human liver functions.

Phylogenetic differences exist between cytokines from humans and nonhuman primates and even greater differences exist between those from humans and pigs. [15] Therefore, the majority of cytokines may exhibit species-specific activities. The impact of such differences is largely unknown, because each clinical application of xenotransplantation may require that a different subset of cytokines is functional. Other anatomic and physiologic disparities among species that may influence the appropriate function of xenotransplantation products have also been identified. Although experiments in vitro may provide important information regarding such issues, clinical studies will ultimately be needed to demonstrate whether known anatomic and physiologic similarities are sufficient to determine the adequacy or necessity of specific functional compatibilities for therapeutic xenotransplantation in humans.

Several approaches have been proposed or used to prevent or reduce the xenogeneic immunologic rejection response, including immunosuppression, genetic-engineering, complement inhibitors and physical barriers.

Immunosuppressive chemotherapy: Immunosuppressive chemotherapy, such as that used in all transplantation, provides some protection from cell-mediated rejection, and combinations of drugs have shown activity in nonhuman models of xenotransplantation. [8] These therapies, however, do not affect preexisting antibodies or complement. Immunosuppression also increases the risk in the host to opportunistic infections, which may be particularly problematic in patients undergoing xenotransplantation procedures.

Genetic engineering: Genetic engineering of source animals (transgenesis to add genes or replace an endogenous gene with another) has been suggested as a means to provide better immunologic compatibility between the xenotransplantation product and the human recipient, especially for reducing the strength of complement-mediated rejection. [9] One approach for decreasing HAR in the xenograft is the use of transgenically engineered pigs that express human complement regulatory proteins on their cellular surfaces, which potentially inhibit the activity of human complement to impede activation of a complement-mediated response. [15,16] Another approach is to reduce the expression of the alpha-Gal epitope [Gal-alpha-(1,3) Gal-beta-(1,4)GlcNAc-R, frequently abbreviated Gal-alpha-(1-3)Gal], one of the main antigens on porcine tissues recognized by the human immune system. [17,18]

For example, transgenic pigs have been developed that express an enzyme, alpha-1,2-fucosyltransferase, which is capable of competing for substrate with the enzyme that synthesizes Gal-alpha-(1-3)-Gal. [18] Production of animals lacking the enzyme that synthesizes the Gal-alpha-(1-3)-Gal antigen has also been reported.17 Engineering of xenogeneic cells expressing other protective genes, such as apoptosis-protective molecules, has also been suggested to achieve accommodation and better survival of the xenograft. [16,19,20]

Complement inhibitors: Another approach to decreasing the immediate HAR response is to administer complement inhibitor molecules. For example, soluble complement receptors [14] or cobra venom factor, [12] both known to inhibit complement activity, have been used to obtain prolonged survival of the xenotransplantation product in animal-to-animal model systems. Administration of apyrase, a family of enzymes with thromboregulatory activity, has been shown to decrease platelet thrombi formation and thus increase survival of a transplanted xenogeneic heart in an animal model. [13]

Depletion of preexisting antibodies: Preclinical studies have been performed in animal models in which preexisting natural antibodies have been depleted, usually by adsorption or by perfusion of recipient blood through antigen-containing columns. Results have been reported suggesting that this approach may ameliorate hyperacute rejection. [13] However, acute vascular rejection is still problematic after removal of natural antibodies. [14]

Physical barriers: Physical barriers, such as encapsulation in semipermeable membranes, capsules, or other devices, are thought to protect transplanted cells (eg, pancreatic islets) from immune attack. [14] These types of barriers have been studied extensively in preclinical models. In addition, certain types of xenotransplantation involve the perfusion of patients' blood through filter-containing devices that contain viable nonhuman animal cells, such as porcine liver cells or whole porcine livers [15] to assist failing human organ function. Such xenotransplantation products would be expected to be somewhat protected from the

host immune response.

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