International Journal of Research in Engineering, Science and Management
Volume-3, Issue-2, February-2020
www.ijresm.com | ISSN (Online): 2581-5792

A Review of Xenotransplantation

N. Greeshma[1], A. Avinash[2], P. Venkatesh[3], D. Hepcy Kalarini[4], R. Prema[5]
[1,2]*Student, Department of Pharmacology, Jagan's Institutions of Pharmaceutical sciences, Nellore, India*
[3,4,5]*Professor, Department of Chemistry, Jagan's Institutions of Pharmaceutical sciences, Nellore, India*

***Abstract*: Xenotransplantation involves the transplantation of cells, tissues, and whole organs from one species to another. Interest in animal-to-human xenotransplants has been spurred by the continuing shortage of donated human organs and by advances in knowledge concerning the biology of organ and tissue rejection. The domestic pig is the optimum donor for xenotransplantation. In addition, the development of novel strategies to protect animal cells and tissues from rejection has resulted in experimental application of xenotransplantation to treat a wide range of diseases, including diabetes and Parkinson's disease. Xenotransplantation using the pig as a donor species may provide a potential solution to the lack of human organs available for transplantation. However, two major immunological obstacles have impeded the survival of porcine organs transplanted into primates. The first is hyperacute rejection (HR), Acute vascular rejection (AVR) is the second major immunological obstacle to successful xenotransplantation, and other minor rejections are Cellular rejection and Cronic rejection.**

***Keywords*: Non-human primate, Genetically modified pig, Immunological barriers, Antibody, Antigens.**

1. Introduction

Xenotransplantation (xenos- from the Greek meaning "foreign" or strange), [1][2] or heterologous transplant is the transplantation of living cells, tissues or organs from one species to another. [3] Such cells, tissues or organs are called xenografts or xenotransplants. It is contrasted with allotransplantation (from other individual of same species), syngeneic transplantation or isotransplantation (grafts transplanted between two genetically identical individuals of the same species) and auto transplantation (from one part of the body to another in the same person).

Xenotransplantation of human tumor cells into immune compromised mice is a research technique frequently used in pre-clinical oncology research. Human xenotransplantation offers a potential treatment for end-stage organ failure, a significant health problem in parts of the industrialized world. It also raises many novel medical, legal and ethical issues. [4] A continuing concern is that many animals, such as pigs, have a shorter lifespan than humans, meaning that their tissues age at a quicker rate. Disease transmission (xenozoonosis) and permanent alteration to the genetic code of animals are also causes for concern. Similarly to objections to animal testing, animal rights activists have also objected to xenotransplantation on ethical grounds.[5] A few temporarily successful cases of xenotransplantation are published.[6]

It is common for patients and physicians to use the term "allograft" imprecisely to refer to either allograft (human-to-human) or xenograft (animal-to-human), but it is helpful scientifically (for those searching or reading the scientific literature) to maintain the more precise distinction in usage.

2. History

Cross species transplantation (xenotransplantation) offers the prospect of an unlimited supply of organs and cells for clinical transplantation, thus resolving the critical shortage of human tissues that currently prohibits a majority of patients on the waiting list from receiving transplants. Between the 17th and 20th centuries, blood was transfused from various animal species into patients with a variety of pathological conditions. Skin grafts were carried out in the 19th century from a variety of animals, with frogs being the most popular. In the 1920s, voronoff advocated the transplantation of slices of chimpanzee testis into aged men whose "Zest for life" was deteriorating, believing that the hormones produced by the testis would rejuvenate his patients. Following the pioneering surgical work of carrel, who developed the technique of blood vessel anastomosis, numerous attempts at non-human primate organ transplantation in patient were carried out in the 20th century. In 1963-1964, when human organs were not available and chronic dialysis was not yet in use, Reemtsma transplanted chimpanzee kidneys into 13 patients, one whom return to work for almost 9 months before suddenly dying from what was believed to be an electrolyte disturbance. The first heart transplant in human ever performed was by hardly in 1964, using a chimpanzee heart, but the patient died within 2 hours. Starzl carried out the first chimpanzee to human live transplantation in 1966; in 1992 he obtained patient survival for 70 days following a baboon liver transplant. With the advent of genetic engineering and cloning technologies, pigs are currently available with a number of different manipulations that protect their tissues from the human immune response, resulting it increasing pig graft survival in non-human primate models. Genetically modified pigs offer hope of a limitless supply of organs and cells for those in need of a transplant. [7] An early blood transfusion from lamb to man (1705). L0000096, Welcome Library, London. Picture retrieved from https://museumofhealthcare.wordpress.com

3. Types of xenotransplantation

- Solid organ xenotransplantation is a procedure in which a source animal organ such as kidney or liver is transplanted into a human;
- Cell and tissue xenotransplantation is the transplantation of tissues and cells from a source animal without surgical connection of any animal blood vessels to the recipient's vessels;
- Extracorporeal perfusion occurs when human blood is circulated outside of the human body through an animal organ, such as a liver or a kidney, or through a bioartificial organ produced by culturing animal cells on an artificial matrix;
- Exposure to living animal-derived material is a procedure in which human body fluids, cells, tissues or organs are removed from the body, come into contact with animal cells, tissues or organs and are then placed back into a human patient.

A. Donors used in xenotransplantation

Genetically modified pigs as organ donors for xenotransplantation.

B. Types of immunological barriers

Immunologic rejection remains the major barrier to xenotransplantation. The stages of rejection, in order of temporal occurrence, are

- Hyperacute rejection (HAR),
- Acute vascular rejection (also known as delayed xenograft rejection),
- Acute cellular rejection, and
- Chronic rejection.

C. Hyper acute rejection

This rapid and violent type of rejection occurs within minutes to hours from the time of the transplant. It is mediated by the binding of XNAs (xeno reactive natural antibodies) to the donor endothelium, causing activation of the human complement system, which results in endothelial damage, inflammation, thrombosis and necrosis of the transplant. XNAs are first produced and begin circulating in the blood in neonates, after colonization of the bowel by bacteria with galactose moieties on their cell walls. Most of these antibodies are the IgM class, but also include IgG, and IgA. [8]

The epitope XNAs target is an α-linked galactose moiety, Gal-α-1,3Gal (also called the α-Gal epitope), produced by the enzyme α-galactosyl transferase. [9] Most non-primates contain this enzyme thus, this epitope is present on the organ epithelium and is perceived as a foreign antigen by primates, which lack the galactosyl transferase enzyme. In pig to primate xenotransplantation, XNAs recognize porcine glycoproteins of the integrin family. [8]

The binding of XNAs initiate complement activation through the classical complement pathway. Complement activation causes a cascade of events leading to: destruction of endothelial cells, platelet degranulation, inflammation, coagulation, fibrin deposition, and hemorrhage. The end result is thrombosis and necrosis of the xenograft. [8]

D. Preventing of hyperacute rejection

- The recipient's complement cascade can be inhibited through the use of cobra venom factor (which depletes C3), soluble complement receptor type 1, anti-C5 antibodies, or C1 inhibitor (C1-INH). Disadvantages of this approach include the toxicity of cobra venom factor, and most importantly these treatments would deprive the individual of a functional complement system. [1]

Transgenic organs (Genetically engineered pigs)

- 1, 3 galactosyl transferase gene knockouts – These pigs don't contain the gene that codes for the enzyme responsible for expression of the immunogeneic gal-α-1,3Gal moiety (the α-Gal epitope). [10]
- Increased expression of H-transferase (α 1, 2 fucosyltransferase), an enzyme that competes with galactosyl transferase. Experiments have shown this reduces α-Gal expression by 70%. [11]
- Expression of human complement regulators (CD55, CD46, and CD59) to inhibit the complement cascade. [12]
- Plasmaphoresis, on humans to remove 1, 3 galactosyltransferases, reduces the risk of activation of effector cells such as CTL (CD8 T cells), complement pathway activation and delayed type hypersensitivity (DTH).

E. Acute vascular rejection

Also known as delayed xeno active rejection, this type of rejection occurs in discordant xenografts within 2 to 3 days, if hyperacute rejection is prevented. The process is much more complex than hyperacute rejection and is currently not completely understood. Acute vascular rejection requires de novo protein synthesis and is driven by interactions between the graft endothelial cells and host antibodies, macrophages, and platelets. The response is characterized by an inflammatory infiltrate of mostly macrophages and natural killer cells (with small numbers of T cells), intravascular thrombosis, and fibrinoid necrosis of vessel walls. [9]

Binding of the previously mentioned XNAs to the donor endothelium leads to the activation of host macrophages as well as the endothelium itself. The endothelium activation is considered type II since gene induction and protein synthesis are involved. The binding of XNAs ultimately leads to the development of a procoagulant state, the secretion of inflammatory cytokines and chemokines, as well as expression of leukocyte adhesion molecules such as E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1). [8]

This response is further perpetuated as normally binding

between regulatory proteins and their ligands aid in the control of coagulation and inflammatory responses. However, due to molecular incompatibilities between the molecules of the donor species and recipient (such as porcine major histocompatibility complex molecules and human natural killer cells), this may not occur. [9]

F. Prevention of acute vascular rejection

Due to its complexity, the use of immunosuppressive drugs along with a wide array of approaches are necessary to prevent acute vascular rejection, and include administering a synthetic thrombin inhibitor to modulate thrombogenesis, depletion of anti-galactose antibodies (XNAs) by techniques such as immunoadsorption, to prevent endothelial cell activation, and inhibiting activation of macrophages (stimulated by CD4+ T cells) and NK cells (stimulated by the release of Il-2). Thus, the role of MHC molecules and T cell responses in activation would have to be reassessed for each species combo. [9]

G. Cellular rejection

Rejection of the xenograft in hyperacute and acute vascular rejection is due to the response of the humoral immune system, since the response is elicited by the XNAs. Cellular rejection is based on cellular immunity, and is mediated by natural killer cells which accumulate in and damage the xenograft and T-lymphocytes which are activated by MHC molecules through both direct and indirect xenorecognition.

In direct xenorecognition, antigen presenting cells from the xenograft present peptides to recipient CD4+ T cells via xenogeneic MHC class II molecules, resulting in the production of interleukin 2 (IL-2). Indirect xenorecognition involves the presentation of antigens from the xenograft by recipient antigen presenting cells to CD4+ T cells. Antigens of phagocytosed graft cells can also be presented by the host's class I MHC molecules to CD8+ T cells. [1] [13]

The strength of cellular rejection in xenografts remains uncertain, however it is expected to be stronger than in allografts due to differences in peptides among different animals. This leads to more antigens potentially recognized as foreign, thus eliciting a greater indirect xenogenic response. [1]

H. Prevention of cellular rejection

A proposed strategy to avoid cellular rejection is to induce donor non-responsiveness using hematopoietic chimerism. Donor stem cells are introduced into the bone marrow of the recipient, where they coexist with the recipient's stem cells. The bone marrow stem cells give rise to cells of all hematopoietic lineages, through the process of hematopoiesis. Lymphoid progenitor cells are created by this process and move to the thymus where negative selection eliminates T cells found to be reactive to self. The existence of donor stem cells in the recipient's bone marrow causes donor reactive T cells to be considered self and undergo apoptosis. [1]

I. Chronic rejection

Chronic rejection is slow and progressive, and usually occurs in transplants that survive the initial rejection phases. Scientists are still unclear how chronic rejection exactly works, research in this area is difficult since xenografts rarely survive past the initial acute rejection phases. Nonetheless, it is known that XNAs and the complement system are not primarily involved. [9] Fibrosis in the xenograft occurs as a result of immune reactions, cytokines (which stimulate fibroblasts), or healing (following cellular necrosis in acute rejection). Perhaps the major cause of chronic rejection is arteriosclerosis. Lymphocytes, which were previously activated by antigens in the vessel wall of the graft, activate macrophages to secrete smooth muscle growth factors. This results in a buildup of smooth muscle cells on the vessel walls, causing the hardening and narrowing of vessels within the graft. Chronic rejection leads to pathologic changes of the organ, and is why transplants must be replaced after so many years [13]. It is also anticipated that chronic rejection will be more aggressive in xenotransplants as opposed to allotransplants. [14]

J. Drugs used in prevention of xenotransplantation rejection

The most common immunosuppressive agents used in xenotransplantation are:

- Anti-CD154 antibody,
- Mycophenolate mofetil,
- Anti-thymocyte globulin,
- Tacrolimus,
- Rapamycin cyclosporine,
- Belatacept,
- Abatacept,
- Sirolimus,
- Fingolimod and everolimus.

K. Uses of xenotransplantation

Xenotransplantation could benefit thousands of people by providing an unlimited supply of cells, tissues and organs with many uses:

Organ transplants-replacing diseased organs, such as hearts, lungs, livers, pancreases and kidneys.

Cell transplants-replacing damaged or destroyed cells in diseases such as diabetes, alzheimer's and parkinson's disease

Bridging transplants-providing organ function externally to patients with organ failure.

L. Disadvantages of xenotransplation

1. It has very high rejection rate.
2. It risks shorter life spans of animal organs.

Animals have much shorter life spans than humans, which means that if the success rate improves for transplanting animal organs to humans, there would still be a risk of the organ wearing out or dying prematurely. This would also mean that a person would need to undergo multiple transplants over his life time, as the organs would be wearing out.

1. It poses the risk of disease transmission.

There are diseases that animal, like pigs, contact and humans do not, sparking some concerns that xenotransplantation would introduce new diseases to people.

2. It brings about moral issues.

4. Conclusion

Xenotransplantation may also be valuable for the treatment of human diseases. However, it is well recognized that infectious agents can be transmitted from animals to humans and that organisms benign in one species can be fatal when introduced into other species. Further, it is known that the pathogenicity of infectious organisms can change under a variety of conditions and that the effects of infection by some organisms, such as the human immunodeficiency virus, are delayed for years or even decades. Because xenotransplants involve the direct insertion of potentially infected cells, tissues, or organs into humans, there is every reason to believe that the potential for transmission of infectious agents (some of which may not even now be recognized) from animals to human transplant recipients is real. If established in the recipient, the potential for transmission to caregivers, family, and the population at large must be considered a real threat. The committee concludes that, although the degree of risk cannot be quantified, it is unequivocally greater than zero.

References

[1] Dooldeniya, Warrens, (2003). "Xenotransplantation: where are we today?". Journal of the Royal Society of Medicine. 96 (3): 111–117.
[2] Mitchell, C Ben, "Xenotransplanation and Transgenics: The Need to Discuss Limits". Cbhd. CBHD. November 2018.
[3] Xenotransplantation. Definition by the World Health Organization
[4] Kress, J. M. (1998). "Xenotransplantation: Ethics and economics". Food and Drug Law Journal. 53 (2): 353–384.
[5] "Interviews - Dan Lyons". PBS. 2018.
[6] "Organ Transplants from Animals: Examining the Possibilities". Fda.gov. Internet Archive.
[7] Jack-Yves Deschamps, Francoise A, Roux, Pierre Sai, Edouard Gouin Xenotransplantation 2005.
[8] Taylor, L. (2007) Xenotransplantation. Emedicine.com
[9] Candinas, D.; Adams, D. H. (2000). "Xenotransplantation: Postponed by a millennium?". QJM. 93 (2): 63–66.
[10] Latemple, D. C.; Galili, U. (1998). "Adult and neonatal anti-Gal response in knock-out mice for alpha1, 3 galactosyltransferase". Xenotransplantation. 5 (3): 191–196.
[11] Sharma, A.; Okabe, J.; Birch, P.; McClellan, S. B.; Martin, M. J.; Platt, J. L.; Logan, J. S. (1996). "Reduction in the level of Gal(alpha1,3) Gal in transgenic mice and pigs by the expression of an alpha (1,2) fucosyltransferase". Proceedings of the National Academy of Sciences of the United States of America. 93 (14): 7190–7195.
[12] Huang, J.; Gou, D.; Zhen, C.; Jiang, D.; Mao, X.; Li, W.; Chen, S.; Cai, C. (2001). "Protection of xenogeneic cells from human complement-mediated lysis by the expression of human DAF, CD59 and MCP". FEMS Immunology and Medical Microbiology. 31 (3): 203–209.
[13] Takahashi, T.; Saadi, S.; Platt, J. L. (1997). "Recent advances in the immunology of xenotransplantation". Immunologic Research. 16 (3): 273-297.
[14] Abbas A, and Lichtman A. (2005) Cellular and Molecular Immunology, 5th ed., pp. 81, 330–333, 381, 386. Elsevier Saunders, Pennsylvania, ISBN 0-7216-0008-5.