XENO RENAL TRANSPLANTATION

PREETHI. G, DEPARTMENT OF RENAL DIALYSIS TECHNOLOGY
SCHOOL OF ALLIED HEALTH SCIENCES
VINAYAKA MISSION'S RESEARCH FOUNDATION-DU
AVMC CAMPUS, PUDUCHERRY, INDIA
preethiammu6898@gmail.com

ABSTRACT

Now a days kidney transplantation is a common treatment for chronic renal failure. Not all patients are receiving kidneys because of shortage of donors. Transplantation of xenogeneic kidneys might be a solution. Because of the increasing accessibility of genetically modified pigs, effective immunosuppressive drugs, and anti-inflammatory therapy, pig tissues are shielded from the primate immune response. These techniques can also be used to address molecular incompatibilities. In NHP, xenografts of pig kidneys that are capable of supporting life have persisted for more than six months without showing signs of consumptive coagulopathy. Although the production of amount of urine and creatinine clearance. In this article, we have discussed the current situation, need for xenotransplantation, issues, physiological aspects, genetical alterations and potential xenograft treatment alternatives.

Keywords: Xenotransplantation, Non-human Primates, Gene modified pigs, Immunosuppresants.

I. INTRODUCTION

Transplantation is a viable technique for treating end stage organ failure even if clinical transplantation is complicated by the imbalance between the supply and demand of human organs. Xenotransplantation may therefore be a feasible alternative approach to bridge the gap between the supply and demand of organs, tissues, and cells; nonetheless, immunological barriers are limiting factors in clinical xenotransplantation. Clinical xenotransplantation is now more feasible because of improvements in immunosuppressive medication, gene editing techniques, and pig-to-non-human primate models that have longer xenograft survival times. The development and current state of xenotransplantation research, genetically modified pigs used in xenotransplantation, and advancements in pig-to-pig-to-non-human primate models are the main topics of this review. Understanding of immunological mechanisms underlying graft rejection is also discussed. The creation of genetically modified pigs has contributed most to advancements in the field of xenotransplantation over the last ten years. Accordingly, we list the genetically modified pigs that are currently available for xenotransplantation.

II. XENOTRANSPLANTATION

In general, transplantation refers to transplanting an organ from one person to another. This is known as transplantation or allotransplantation (within the same species).

Xenotransplantation is also the same concept, but it is a transplantation of organ from one species to another. For example, transplantation of kidney from pig to human is known as xenorenal transplantation.

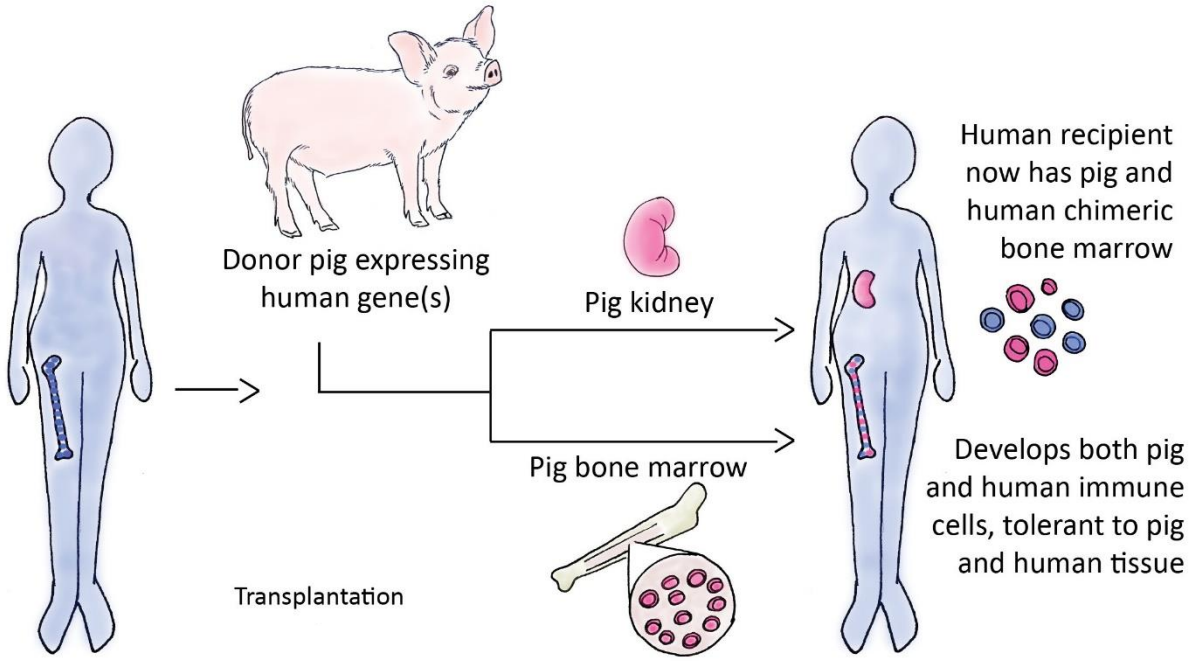

FIGURE 1. XENOTRANSPLANTATION

III. Why do we need xenotransplantation

A growing number of individuals are suffering from end-stage organ failure and chronic diseases as a result of humans living longer. End-stage organ failure can be successfully treated by transplantation. Unfortunately, there are not enough organs available for everyone. As of now we have a critical shortage of organs all around the world. This xenorenal transplantation will be a better option for patients who are having chronic renal failure.

IV. Genetical alterations

To reduce the chances of rejection, the genes of the pigs has been modified by recombinant DNA technology.[1][2]

1. Pig gene knockouts to prevent hyperacute rejection from human antibodies to pig sugars
    a) The enzyme -1-3 galactosyltransferase, which produces galactose--1-3-galactose (-1-3GAL),
    b) b) 1,4-N-acetylgalactosyltransferase, also referred to as Sda antigen, is an enzyme that produces non-GAL polysaccharide DBA-reactive glycan. [1]
    c) The enzyme CMP-N-acetylneuraminic acid hydroxylase, which is in charge of producing Neu5Sc.
2. Pig gene knockout to prevent excessive growth of pig kidney
    a) Gene for the porcine growth hormone receptor
3. Insertions of human genes into pig genome
    a) Human compliment inhibitor genes
        i. Decay-accelerating factor (hDAF), a membrane protein that prevents complement C3 component activation
        ii. hCD46 is a membrane cofactor protein that controls the human complement cascade.
    b) Human anti-coagulant genes
        i. Human thrombomodulin (hTBM) inhibits prothrombinase and delays clotting in pig endothelial cells
        ii. hEPCR—endothelial protein C receptor to reduce thrombin generation and platelet aggregation
    c) Human immunomodulatory genes
        i. hCD47, an integrin transmembrane protein that serves as a "don't eat me" protein,
        ii. hHO1, an antioxidant enzyme that lowers inflammation and inhibits apoptosis,

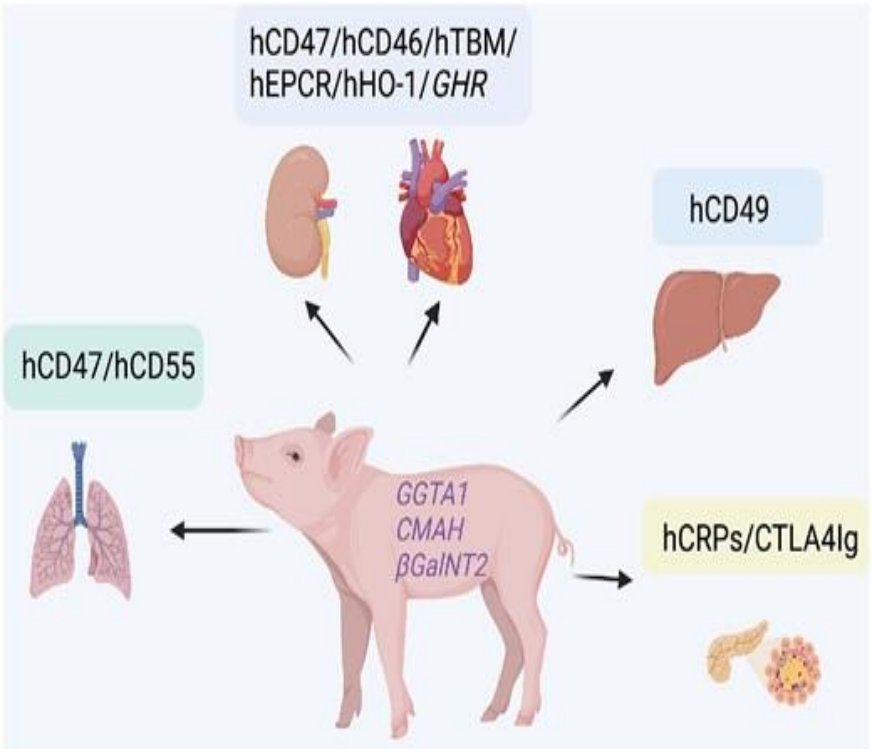

FIGURE 2. CUSTOMISED GENE MODIFIED PIG

I. Similarities of pig kidneys to human

In terms of anatomy, physiology (such as glomerular filtration rate and total kidney blood flow), and relative size, pig kidneys are equivalent to human kidneys; nonetheless, there may be physiologic incompatibilities. The location of the pig's kidneys on its body may affect renal blood flow, however pigs are also claimed to have renal blood flow that is similar to that of humans. Healthy pigs had mean WBC and RBC levels that were substantially higher than those of healthy baboons and humans. Although BUN, serum creatinine, salt, and chloride concentrations are similar, pigs have higher potassium, calcium, and phosphorus values than baboons and humans. But physiologic incompatibilities may arise.

II. Physiological aspects of pig kidney transplantation in Non-Human Primates (NHP)

Although the functions of pig's kidney and human kidney have some similarities, some physiologic incompatibilities may arise. Some of physiological incompatibilities has been discussed below.

A. Serum creatinine:

In reports of life-sustaining pig kidney xenotransplantation in NHP dating back more than ten years, the blood creatinine level essentially remained constant and mainly within the normal human range. However, the creatinine level was greater than normal throughout the initial trials. Given the enhanced defence against immune-mediated harm provided by contemporary genetically modified pig kidneys, it is more likely that it was the result of immune-related graft failure rather than physiologic incompatibility, which is no longer observed.

B. Proteinuria

Even in low amounts, proteinuria is considered harmful (for example, in glomerulopathies and allograft rejection). Because proteins are often not permeable across the human glomerular membrane [3]. On the other hand, mature pigs can easily develop increased proteinuria in response to physical and environmental stress. Furthermore, healthy neonatal pigs can develop proteinuria, which is linked to undeveloped proximal renal tubules. Therefore, proteinuria is a sign of renal failure, however it may have causes other than graft rejection. In the early tests of pig-to-NHP kidney xenotransplantation, moderate to severe proteinuria and hypoalbuminemia were seen. To maintain the serum albumin concentration within the normal range, repeated IV infusions of human albumin were required.

C. Serum electrolytes

Most serum electrolytes, including sodium, chloride, potassium, and calcium, remain within normal levels in recipients with healthy pig kidney grafts, according to studies on pig-to-NHP kidney xenotransplantation. Although blood calcium can increase. After transplantation, serum phosphate levels may briefly increase, but they soon return to normal levels and remains in normal range or less than normal. This impact is due to the higher glomerular Filtration Rate in pigs [4][5][6].

D. Serum uric acid

Humans produce uric acid as a byproduct of purine metabolism; however, in lower mammals, such as pigs, uric acid is further oxidized by urate oxidase [7] and excreted through both filtration and secretion [8], hyperuricemia is not likely to be an issue in xenotransplantation of pig kidneys. Pig kidneys have an additional function that should make them superior to human kidneys, which are unable to oxidize uric acid.

E. Plasma renin

Renin cleaves the liver-secreted angiotensinogen, converting it to angiotensin I and then angiotensin II [9]. It supports potassium maintenance and bodily fluid volume maintenance. Human angiotensinogen cannot be broken down by pig renin. An alternative regulatory mechanism may be required in NHP with fully functional pig kidney grafts to maintain fluid balance and body weight despite Renin's diminished activity [10]. Abnormalities of Renin function has been associated with increased serum creatinine and urea in the state of intermittent hypovolemia or dehydration. Baboons with transplanted pig kidneys don't seem to be aware that they are losing water. since, while having normal urinary output, their fluid consumption does not correspond to their clinical needs. Therefore, patients receiving pig kidney transplants might need to consume a lot of fluids even when they don't feel thirsty.

F. Erythropoietin

About 82% of the amino acids in erythropoietin, which is produced in the kidney, are same in pigs and human [11]. Life-sustaining pig-to-NHP renal xenotransplantation was connected with the gradual emergence of normocytic, normochromic anemia in the absence of recombinant human erythropoietin therapy. This impact may have been caused by a molecular mismatch between the primate erythropoietin receptor and pig erythropoietin. Alternatively, frequent blood draws for lab testing along with drug-associated myelosuppression may cause the anemia. It is unknown whether or not pig erythropoietin serves an adequate function in NHP. Recombinant human erythropoietin therapy, as it is in NHP, should correct any erythropoietin deficiencies even if pig erythropoietin does not perform as well in humans. Another option is for genetically modified pigs to produce human erythropoietin, which would then interact with recipients' human erythropoietin receptors.

G. Kidney size and growth

Early research suggested that kidney graft size has increased [12]. But in recent studies, development of partial stricture of ureter has been observed. It may be more challenging to assess the graft's growth because this stricture was not always produced on by the ureterovesical anastomosis and was occasionally caused by an immunological reaction. Additionally, just a slight drop in pig kidney weight was achieved after the partial stricture was relieved.

III. Immune system and transplantation

To reduce the chances of rejection, surgeons even do compatibility checks for human-to-human transplants. Immunosuppressants are used by patients after surgery to prevent their immune systems from attacking the new kidney. Therefore, if the body attacks another person's kidney, it will reject it right away. To reduce the rejection, genetically modified pig's kidney has been used. Six human genes were introduced to the pig's DNA to assist control the immunological and blood coagulation systems, while three pig genes were removed, including one growth hormone receptor that would have caused the kidney to outgrow the human body.

IV. The pre- clinical trial human study

Although the alterations made to the pig kidney appeared to be sound in theory, a transplant is the only method to determine whether they would work in a human body. Researchers sought to perform the xenotransplant on a person who had been declared brain dead and was unable to offer their organs for transplantation in order to reduce the inherent risk of a novel technique. After 77 hours, the experiment was successful because the kidney continued to function despite the effects of brain death, such as varying blood pressure.

V. Conclusion

Even though this was an important step in the right direction, it may be some time before humans receive kidney transplants from pigs. Although the team's preclinical trial model was successful, using genetically altered pig kidneys in humans requires U.S. Food and Drug Administration approval before going to a living human clinical trial. The clinical study proposal must then be approved by the Institutional Review Board for Human Use at UAB. As initial trials are developed, carried out, and reported in a scientific format, recent media attention surrounding the first clinical trials has drawn attention to the field, and this will hopefully continue to stimulate a conversation about the ethical and social concerns regarding the use of porcine xenografts.

References

[1] Porrett PM, Orandi BJ, Kumar V, Houp J, Anderson D, Cozette Killian A, Hauptfeld-Dolejsek V, Martin DE, Macedon S, Budd N, Stegner KL. First clinical-grade porcine kidney xenotransplant using a human decedent model. American Journal of Transplantation. 2022 Apr;22(4):1037-53.

[2] Cooper DK, Ekser B, Ramsoondar J, Phelps C, Ayares D. The role of genetically engineered pigs in xenotransplantation research. The Journal of pathology. 2016 Jan;238(2):288-99.

[3] Miltenyi M. Urinary protein excretion in healthy children. Clinical Nephrology. 1979 Nov 1;12(5):216-21..

[4] Higginbotham L, Mathews D, Breeden CA, Song M, Farris III AB, Larsen CP, Ford ML, Lutz AJ, Tector M, Newell KA, Tector AJ. Pre-transplant antibody screening and anti-CD154 costimulation blockade promote long-term xenograft survival in a pig-to-primate kidney transplant model. Xenotransplantation. 2015 May;22(3):221-30.

[5] Higginbotham L, Mathews D, Breeden CA, Song M, Farris III AB, Larsen CP, Ford ML, Lutz AJ, Tector M, Newell KA, Tector AJ. Pre-transplant antibody screening and anti-CD154 costimulation blockade promote long-term xenograft survival in a pig-to-primate kidney transplant model. Xenotransplantation. 2015 May;22(3):221-30.

[6] Iwase H, Klein EC, Cooper DK. Physiologic aspects of pig kidney transplantation in nonhuman primates. Comparative medicine. 2018 Oct 1;68(5):332-40.

[7] Coulter A, McPherson K. Waiting times and duration of hospital stay for common surgical operations: trends over time. Journal of Public Health. 1987 Aug 1;9(3):247-53.

[8] Simmonds HA, Hatfield PJ, Cameron JS, Cadenhead A. Uric acid excretion by the pig kidney. American Journal of Physiology-Legacy Content. 1976 Jun 1;230(6):1654-61.

[9] Hackenthal EM, Paul M, Ganten D, Taugner R. Morphology, physiology, and molecular biology of renin secretion. Physiological reviews. 1990 Oct 1;70(4):1067-116.

[10] Sen SU, Hirawawa K, Smeby RR, Bumpus FM. Measurement of plasma renin substrate using homologous and heterologous renin. American Journal of Physiology-Legacy Content. 1971 Nov 1;221(5):1476-80..

[11] David RB, Blom AK, Sjaastad ØV, Harbitz I. The porcine erythropoietin gene: cDNA sequence, genomic sequence and expression analyses in piglets. Domestic Animal Endocrinology. 2001 Feb 1;20(2):137-47.

[12] Iwase H, Hara H, Ezzelarab M, Li T, Zhang Z, Gao B, Liu H, Long C, Wang Y, Cassano A, Klein E. Immunological and physiological observations in baboons with life-supporting genetically engineered pig kidney grafts. Xenotransplantation. 2017 Mar;24(2):e12293.