XENO RENAL TRANSPLANTATION

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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 immunosuppressants and anti- inflammatory therapy, pig's tissues are shielded from the immunological reactions of the primates. 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 oof physiological aspects, genetical alterations and potential xenograft treatment alternatives.

KEYWORDS: Xenotransplantation, Non- Human Primates, Gene modified pigs, Immunosuppressants.

I. INTRODUCTION

Transplantation is a viable technique for treating the organ failure even if clinical transplantation is complicated by the imbalance between the supply and shortage of the organs of human. Xenotransplantation may therefore be a feasible different strategy to fill the gap between the supply and demand of organs, tissues and cells; nonetheless, immunological barriers are immunological barriers are limiting parameters 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 no longer xenograft survival times. The development and current state of xenotransplantation research, the gene modified pigs are used in xenotransplantation and advancements in pig- to pig to- non- Human Primate models are the primary topic 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 xenotransplantation field over the last ten years. We list the genetically altered pigs that are currently accessible for xenotransplantation as a result.

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 approach, but it is a transplantation of organ from one species to another species. For example, transplantation of kidney from pig to human is known as xenorenal transplantation (Figure 1).

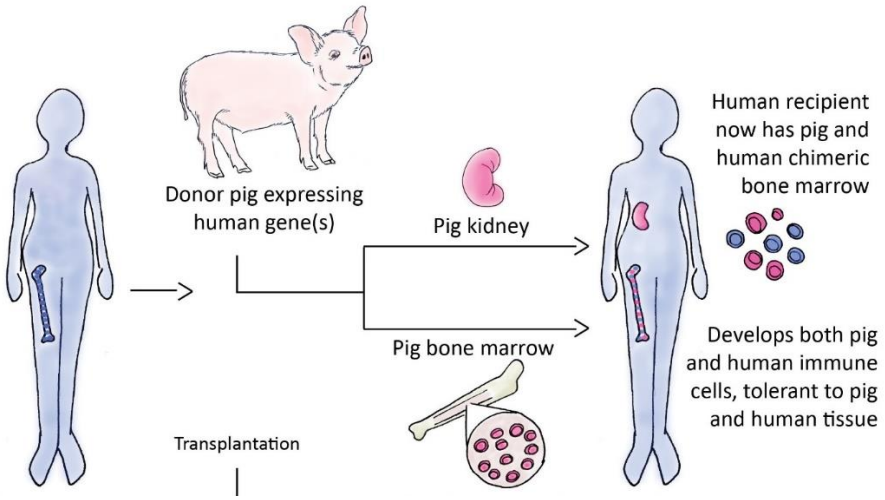

FIGURE 1. XENOTRANSPLANTATION

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 human living longer. End stage organ failure can be successfully treated by transplantation. Tragically, not everyone can get organs because of shortage of organs. 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 chance of rejection, the genes of the pigs has been modified by using recombinant DNA technology [1][2]. The modifications of genes are as follows (Figure 2).

1. Pig genes knockouts to avoid human antibodies hyperacute rejection of pig sugars.
    a) The enzyme 1-3 galactosyltransferase, which produce galactose 1-3 galactose (1-3GAL).
    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 avoid excessive kidney growth.
    a) Gene for the Growth Hormone receptor of Porcine.
3. Introduction of human genes into the pig genome
    a) Human compliment inhibitor genes
        i. Decay accelerating factor(hDAF), a membrane protein that prevents complement C3 activation
        ii. A membrane cofactor protein hCD46 that prevents complement activation of C3 component.
    b) Human anti-coagulant genes
        i. Prothrombinase is inhibited by human thrombomodulin (hTBM) and delays clotting in pig endothelial cells.
        ii. To reduce the thrombin generation and platelet aggregation hEPCR endothelial protein C receptor is modified.
    c) Immunomodulatory genes of human
        i. "Don't eat me" protein is served by hCD47, an integrin transmembrane protein.
        ii. hH01, an antioxidant enzyme that lowers inflammation and inhibits apoptosis.

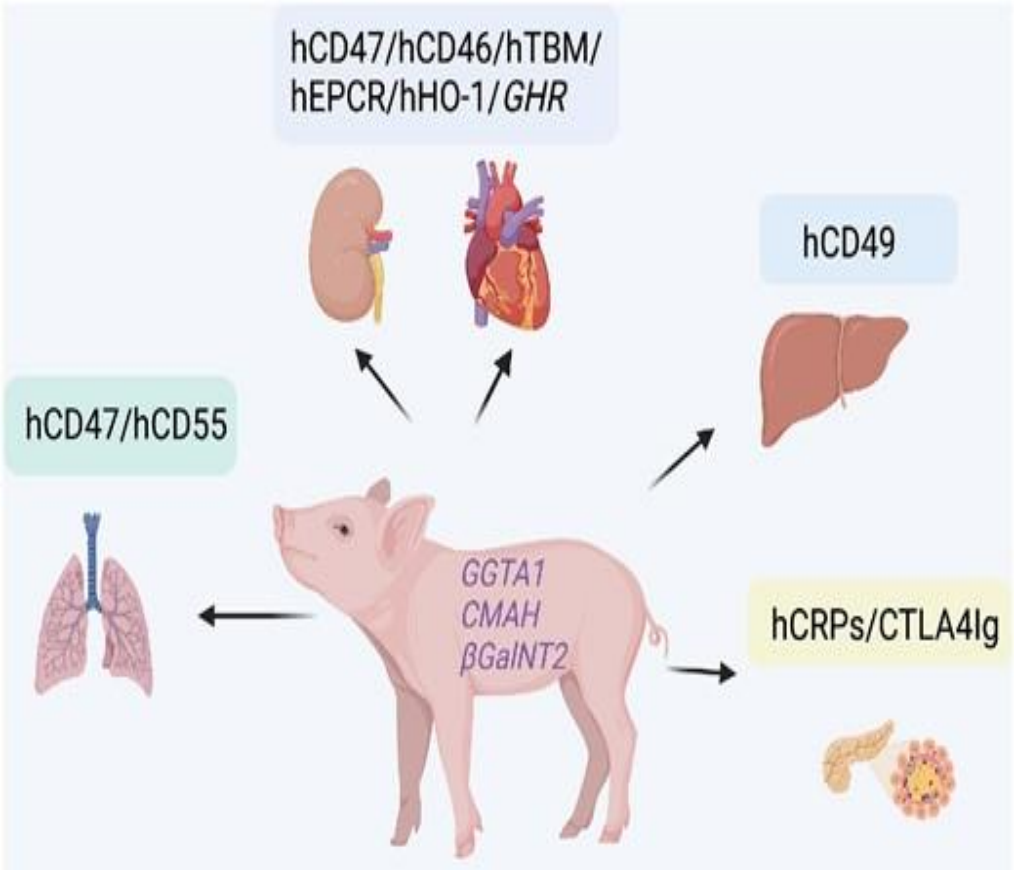

FIGURE 2. CUSTOMISED GENE MODIFIED PIG

V. Similarities of pig kidneys to human

In terms of anatomy, physiology (such as Glomerular Filtration Rate and Blood flow of the total kidney), and relative size, pig's 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 Blood Urea Nitrogen, serum Creatinine, salt and chloride concentration are similar and pigs have higher level of Potassium, calcium and Phosphorus values than baboons and humans. But physiologic incompatibilities may arise.

VI. 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 physiological incompatibilities may arise. Some of physiological incompatibilities has been discussed below.

A. Serum creatinine:

The blood creatinine level essentially remained steady and mostly fell within the normal range in reports of life sustaining pig kidney xenotransplantation in NHP dating back more than ten years. 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 a result of immune- related graft failure rather than incompatibilities of physiologic, which is no longer observed.

B. Proteinuria

Even in low amounts, proteinuria is considered harmful (for example, in Glomerulopathies and in 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 caused other than graft rejection. In the early tests of pig-to-Non- Human Primate kidney xenotransplantation, moderate to severe proteinuria and hypoalbuminemia were seen. To maintain the normal range of serum albumin concentration, repeated IV infusion of human albumin were required.

C. Serum electrolytes

According to studies of Pig-to-NHP kidney transplantation, most serum electrolytes including Sodium, Potassium, Chloride and Calcium remains within normal levels in recipients those who are with healthy pig kidney grafts. Although blood calcium can increase. After transplantation, serum phosphate levels may briefly increase, but they soon return to normal levels and remain 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:

Human body produces uric acid as a byproduct of purine metabolism; however, in lower mammals such as pig's uric acid is further oxidized by urate oxidase [7] and exerted 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 maintenance and bodily fluid volume maintenance. Human angiotensinogen cannot be broken down by pig renin. An alternative regulatory mechanism ma 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 humans [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 of human erythropoietin receptors.

G. Kidney size and growth

Early research suggested that kidney graft size has been 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 the stricture is 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 aft4er the partial stricture was relived.

VII. 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, when 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 might have leads to outgrowth of kidney in the human body.

VIII. The pre- clinical trial of human study

Although the alterations made to the pig's kidneys 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 xenorenal transplantation inn a person who had been declared brain dead and it 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.

IX. Conclusion

Even though this was important step in the correct direction, it may be sometimes before the humans receives 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's approval before going to a living human clinical trial. The clinically study proposal must then be approved by the Institutional Review Board for Human UAE at UAB. As initial trials are initiated, carried out and reported in a scientific format, recent mdi attention surrounding the first clinical trials has drawn attention to the field and hopefully this will continue to spark discussion about the moral and public issues surrounding the use of porcine xenografts

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