Xenotransplantation and its Potentials in Medicine (Volume 4, Issue 3, July- September 2020)

Author: Prof Niranjan Bhattacharya

Xenotransplantation (*xenos* from the Greek word meaning "foreign") is the transplantation of living cells, tissues, or organs from one species to another, such as from chimpanzee to man. Such cells, tissues, or organs are called xenografts or xenotransplants. In contrast, the term allotransplantation refers to a same-species transplant. Human xenotransplantation offers a potential treatment for end-stage organ failure; however, it also raises many novel medical, legal, and ethical issues.

Problem of Disease Transmission in Xenotransplantation:

Zoonosis, also called zoonotic disease, refers to diseases that can be passed from animals, whether wild or domesticated, to humans. Evidence of the danger of zoonotic infections can be observed in the ebola (from monkeys) and nipah (from pigs) viruses, recent outbreaks of which have been observed in humans.

Researchers have postulated that retroviruses such as human immunodeficiency virus (HIV) entered the human population after cross-species infection. Xenotransplantation may increase the chance of disease transmission for three reasons: (a) Loss of physical barrier, (b) immunosuppression of the host, and (c) human complement regulators (CD46, CD55, and CD59) expressed in transgenic pigs have been shown to serve as virus receptors and may also help to protect viruses from attack by the compliment system.

Success of Xenotransplantation:

Xenotransplantation is not entirely novel, as pig heart valves have been used for many years without apparent ill effect, but they are essentially inert tissue and seldom elicit rejection. Transplantation of pig cells and tissues to treat diabetes and degenerative conditions such as Parkinson's disease and Huntington's chorea have also been done. Another example of xenotransplant is the attempted piscine-primate (fish to non-human primate) transplant of islet tissue. The latter research study was intended to pave the way for potential human use. The authors recommend an interesting review on cellular xenotransplantation which summarises the current knowledge on immunological and functional aspects of xeno(allo)-cellular transplantation for cardiomyopathy, diabetes, liver failure, neural diseases, and bone regeneration just to name a few[1] .

Xenotransplantation of ovarian tissue into immunodeficient nude mice has already been used in research to study the development of ovarian follicles. Mature follicles have developed, even after use of cryopreserved ovarian tissue. Both host and graft vessels contribute to the revascularisation of xenografted human ovarian tissue in mice[2]. Similarly, human foetal testis

tissue xenografts demonstrate normal structure, function, and development after xenografting, including normal germ cell differentiation. This provides an *in vivo* system to study normal human foetal testis development and its susceptibility to disruption by exogenous factors (eg, environmental chemicals). This should provide mechanistic insight into the foetal origins of disorders of sex development (DSDs) and testicular dysgenesis syndrome (TDS) disorders. Human foetal testis xenografts are a comparable *in vivo ex situ* model of normal seminiferous cord formation, germ cell development, and testosterone production[3] .

Potential Future Animal Organ Donors:

Non-human primates were first considered as a potential organ source for xenotransplantation to humans. Since they are the closest relatives to humans, chimpanzees were originally considered to be the best option since their organs are of similar size and they have good blood type compatibility with humans. However, since chimpanzees are listed as an endangered species, other potential donors were sought out. Baboons are more readily available; however, they are also not practical as potential donors. Problems include their smaller body size, the infrequency of blood group O (the universal donor), and their long gestation period; moreover, they typically produce few offspring. In addition, a major problem with the use of non-human primates is the increased risk of disease transmission. The biggest challenge in xenotransplantation is overcoming the aggressive response of the human body's immune system to the foreign tissue when antibodies attach to sugar molecules on the surface of the donor organ, for instance, from the pig. The gene that has been knocked out in cloned pigs, α-1, 3-galactosyltransferase, is responsible for making an enzyme that adds the sugar to the surface of the cells.

Immunological Problems:

To date, no xenotransplantation trials have been entirely successful due to the many obstacles arising from the response of the recipient's immune system. This response, which is generally more extreme than in allotransplantations, ultimately results in rejection of the xenograft and can in some cases result in the immediate death of the recipient. There are several types of rejection organ xenografts are faced with. These include:

***(a) Hyperacute 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 xenoreactive 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[4]. Since hyperacute rejection presents such a barrier to the success of xenografts, several strategies to overcome it are under investigation like the use of cobra venom to deplete C3, anti-C5 antibodies, or C1 inhibitor (C1-INH) with very limited success. Other attempts include the use of transgenic organs (genetically engineered pigs), 1,3-galactosyltransferase gene knockout pigs[5]. These pigs do not contain the gene which codes for the enzyme responsible for expression of the

immunogenic gala- 1,3Gal moiety (the a-Gal epitope). There has also been an attempt to use H-transferase (α-1,2-fucosyltransferase), an enzyme that competes with galactosyl transferase. This may even reduce a-Gal expression by 70 % [6], and further prevent the expression of human complement regulators (CD55, CD46, and CD59) to inhibit the complement cascade[7] .

(b) ***Acute vascular rejection*** **:** This is due to graft endothelial cells and host antibodies, macrophages, and platelets. The response is characterised by an inflammatory infiltrate of mostly macrophages and natural killer cells with small numbers of T cells.

(c) ***Cellular rejection*** **:** Cellular rejection is based on cellular immunity and is mediated by natural killer cells and T-lymphocytes. 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). Interesting strategy to avoid cellular recognition is creation of haematopoietic chimeras. These donor stem cells are introduced into the bone marrow of the recipient. 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[8].

(d) ***Chronic rejection*** **:** Scientists are still unclear how chronic rejection exactly works, Fibrosis in the xenograft occurs as a result of immune reactions, cytokines, or the healing process. 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.

Ethicality of Xenotransplant Procedures :

Xenografts have been a controversial procedure since they were first attempted. Many, including animal rights groups, strongly oppose killing animals in order to harvest their organs for human use[9]. Religious beliefs, such as the Jewish and Muslim prohibition against eating pork, have been sometimes thought to be a problem. Some ethical issues include informed consent complexities for research subjects as well as the selection of human subjects, rights of patients and medical staff, and public education (as many companies may go ahead with experiments without public awareness).

As medicine advances at what sometimes seems like lightening speed, it is important for society to make an ethical assessment of technology as it develops, instead of waiting for it to hit the marketplace. All said and done transgenic animal creation remains an answer to the problem of limited organ availability for transplantation purposes; however, the ethical concern will continue to focus on potential zoonosis and the probability of xenorejection.

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