First pig-to-human heart transplantation

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The world's first porcine-to-human heart transplantation was performed at the University of Maryland School of Medicine (Baltimore, MD, USA), where a genetically modified pig heart was successfully transplanted into a 57-year-old man in the end stage of heart disease. After highly experimental surgery, the patient was able to move about freely in the absence of cardiopulmonary bypass assistance. The historic operation overcame the largest possible obstacle caused by hyperacute immune rejection and achieved a good short-term result.But the patient's condition began deteriorating, and died on March 9, 2022, two months after the transplant surgery.

Preclinical studies of xenotransplantation have been carried out for a long time. However, a poor understanding of xenotransplantation and a lack of effective immunosuppression strategies resulted in failure in the end. For example, an infant who was transplanted with a heart from a baboon in 1983 survived for only 20 days.[1] Due to novel genetic manipulation technologies, more appropriate donor organs, especially genetically engineered animal organs, can now be used for transplantation.The genetically modified pig heart was underwent 10 genetic modifications, knocked down 3 immune-rejection-related genes, and inserted 6 human genes and 1 growth gene for inactivation to control the size of the heart, which was provided by Revivicor, a regenerative medicine company based in Blacksburg, Virginia (USA).

Different from the previous primate-to-human xenotransplantation, strong immune response among different species is the biggest barrier to xenotransplantation. Genetic engineering seems to provide a pragmatic solution for confusing issues. The removal of xenoantigens by gene manipulation is an important approach to reducing human immune rejection response. For instance, the α-1,3-galactosidase encoded by α-1,3-galactosyltransferase (GGTA1) is an important cell surface xenoantigen. In addition, *N*-glycolylneuraminic acid encoded by cytidine monophosphate-*N*-acetylneuraminic acid hydroxylase (CMAH) and β-1,4-*N*-acetyl-galactosaminyltransferase 2 (B4GalNT2) is also related to cross-species immunity response. After these genes are knocked out, pigs remain healthy and large proportions of cells are less likely to evoke immune responses from human immune cells.[2] In another group of genetic-modified pig cells that remain immunoreactive to human cells, the immune responses may be attributed to swine leukocyte antigen (SLA) class I, which is equivalent to human leukocyte antigen (HLA) class I. Deletion of these SLA genes may help to improve the host tolerance to pig organs.[3] Another approach to minimize host rejection is the genetic engineering of complement components and pathways called immune cloaking, which regulates the expression of cell-surface molecules from host species in donor cells. The expression of several human proteins can downregulate the activity of human complement and help the transplants escape from human immune system recognition. These proteins include CD55 (a complement decay-accelerating factor), CD59 (a membrane attack complex-inhibitory protein), CD46 (a complement regulatory protein), and the CD47 signal protein.[4,5] With the development of genetic engineering technologies, the elimination of host rejections will be prospective.

The event would be a cornerstone in the development of organ transplantation, which provides an encouraging solution for the shortage of donor organs. However, animal organs bring great challenges to the present immunosuppression regimen, and it is still unknown whether the existing immunosuppressants can effectively control the response of the host rejections to xenografts. In the first attempt at pig heart-to-human transplantation, conventional antirejection drugs and a new immunosuppressing drug made by Kiniksa Pharmaceuticals (Lexington, MA, USA) were used. However, its long-term effects remain to be observed. Due to the different lifespans between humans and other animals, it will be interesting to know the longevity of transplanted organs. In addition, animal-derived diseases are another important issue in the setting of xenotransplantation. One reason for scientists to choose pigs as donor animals is that they are less likely than nonhuman primates to transmit pathogens because they are more distantly related to humans.

In addition to transplantation techniques, immune rejection, and transmission of heterogeneous pathogens, medical ethics is a problem that needs to be solved in the pig-to-human heart transplant operation (Figure 1). The genetically modified heart , which emergency authorized by the US Food and Drug Administration (FDA) , was transplanted into the end-stage heart disease patient who was ineligible for a conventional heart transplantation. The xenotransplantation would be the last chance for life. The type of animal species used is very important. Based on the transmission of pathogens and the objections raised by most societies and animal rights organizations, the transplantation of organs from primates will not be allowed. However, pigs are generally considered to be an ideal potential source of organs for human xenotransplantation. Pig organs are similar to human organs in size and shape. They are easy to obtain, and both inbred lines and outbred lines are used in preclinical research. In addition, pigs can be cloned by somatic cell nuclear transfer, and their genomes can be edited by engineered nucleases such as zinc finger nuclease, transcription activator-like effector nuclease (TALEN), and CRISPR-Cas9 systems. Based on the above reasons, scientists generally believe that pig organs are the best source for human xenotransplantation to eliminate the organ shortage crisis, which will be a great advance. After all, the long-term outcome is still unknown and whether these attempt can achieve great success in xenotransplantation remains to be seen.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

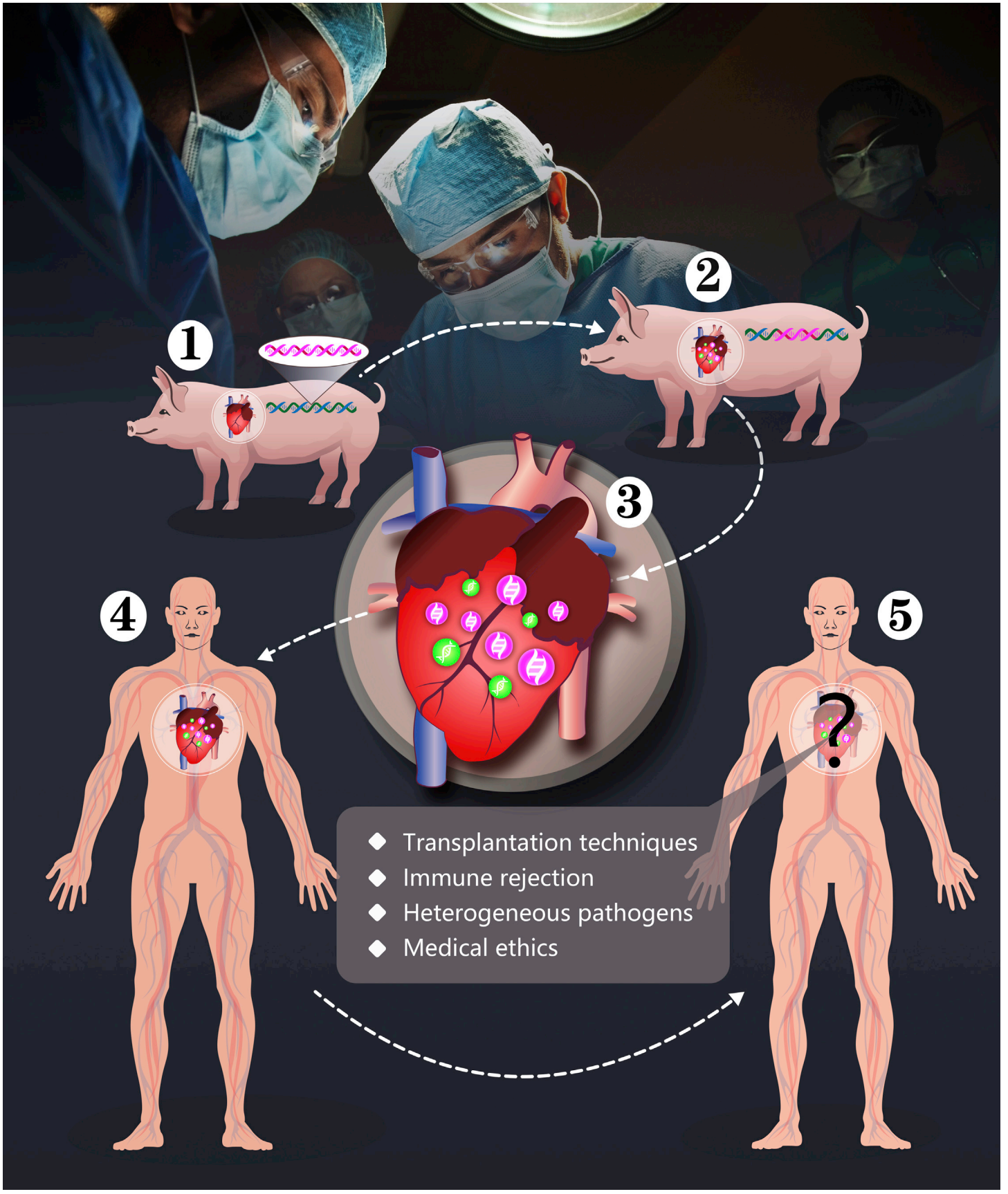

Figure 1. The world first porcine-to-human heart transplantation