Xenotransplantation — A special case of One Health

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A R T I C L E   I N F O

A B S T R A C T

The chronic shortage of human transplants to treat tissue and organ failure has led to the development of xenotransplantation, the transplantation of cells, tissues and organs from another species to human recipients. For a number of reasons, pigs are best suited as donor animals. Successful, routine xenotransplantation would have an enormous impact on the health of the human population, including the young, who sometimes require a replacement organ or islet cells, but especially the elderly, who more often suffer the consequences of organ failure. The first form of xenotransplantation applied to humans is the use of pig islet cells to treat insulin-dependent diabetes, a procedure that will have a significant economic impact. However, although xenotransplantation using pig cells, tissues and organs may save and prolong the lives of patients, it may also be associated with the transmission of porcine microorganisms to the recipient, eventually resulting in emerging infectious diseases. For this reason, the health of both the donor animals and the human recipients represents a special and sensitive case of the One Health concept. Basic research leading to strategies how to prevent transmission of porcine microorganisms by selection of virus-free animals, treatment of donor pigs by antiviral drugs, vaccines, colostrum deprivation, early weaning, Caesarean delivery, embryo transfer and/or gene editing should be undertaken to supply an increasing number of potential recipients with urgently required transplants. The methods developed for the detection and elimination of porcine microorganisms in the context of xenotransplantation will also contribute to an improvement in the health of pig populations in general and an increase in the quality of meat products. At present, there is evidence for transmission of porcine viruses to humans eating pork and having contact with pigs, however the impact of these viruses on public health is still unknown.

Contents

1. The need for xenotransplantation

Due to the increase in life expectancy of the human population, increasing numbers of people suffer from tissue and organ failure that can, in most cases, only be treated by transplantation of cells, tissues or organs. However, the number of human transplants available is insufficient to treat all patients in need. For example, in the USA there are more than 122,000 people waiting for much-needed organs [1] and an average of 22 people in the USA die each day while waiting for a transplant. Xenotransplanation using pig cells, tissues or organs may help overcome this shortage of human materials.

Furthermore, the number of patients with diabetes mellitus type 1 (insulin-dependent diabetes) is increasing world-wide [2]. Despite the

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ability to treat the disease with insulin (derived for decades from pigs) the highest economic burden results from serious and potentially life-threatening complications [3]. Xenotransplantation using porcine islet cells would allow physiological regulation of the insulin production and is considered to be a promising approach to treat type 1 diabetes. An alternative therapy using pluripotent stem cells or committed cells and cellular reprogramming is at present only at the beginning of development [4].

2. Safety aspects of allotransplantation and xenotransplantation

Despite the potential to save and prolong lives, xenotransplantation using pig cells, tissues and organs can be associated with the transmission of potentially zoonotic porcine microorganisms. In this context, it is well known that allotransplantation has been associated with the transmission of viruses and other microorganisms to the recipient, including viruses such as the human immunodeficiency virus 1 (HIV-1), human hepatitis B and hepatitis C viruses, rabies virus, West Nile virus, hepatitis E virus (HEV), human cytomegalovirus, bacteria such as *Trepanoma pallidum*, fungi such as Aspergillus and many others as well as parasites [4–17]. The future development of pigs free of potentially zoonotic porcine microorganisms would render xenotransplantation a considerably safer technology compared with allotransplantation. Evaluating the benefit/risk ratio of xenotransplantation means to estimate the benefit coming from the survival with a well-functioning organ on one hand, and the risk of transmission of porcine microorganisms including bacteria, fungi, and viruses to the recipient on one hand. Therefore and independent from the fact, that the national and regional regulations covering the microbiological screening of donors for allotransplantation, as well as the microbiological assays available, varies considerably, the rules governing xenotransplantation need to be developed [18,19].

Human pathogens that can be transmitted by allotransplantation are in most cases well characterised, for example HIV-1, HEV, rabies virus, and sensitive detection methods are generally available. However, in the case of xenotransplantation, the potentially zoonotic microorganisms remain partially unknown and sensitive detection methods are under development. There are indeed a lot of veterinary diagnostic laboratories with assays for infectious disease monitoring in pig herds, however their assays are usually monitoring pig diseases with high impact on meat production. Based on early findings showing that some detection methods are not sensitive enough [20], new and improved methods for potentially zoonotic microorganisms are under development. There is evidence that some porcine viruses are able to infect human cells *in vitro* or humans *in vivo, e.g.,* HEV. Whereas the microorganisms transmitted after allotransplantation are adapted to humans, many porcine microorganisms fail to infect humans due to the innate and adaptive immune response, due to the absence of suitable receptors on human cells or due to human intracellular restriction factors. Restriction factors are cellular proteins that inhibit viral replication and represent a first line of defense against viral pathogens [21]. They show an enormous structural and functional diversity and target nearly every step if the viral replication cycle. Examples of such restriction factors are APOBEC3 (apolipoprotein B mRNA editing enzyme catalytic polypeptide 3), which induces hypermutation by deamination, or tetherin, which prevents virus release by tethering budding progeny virions to the plasma membrane of the infected cell [21]. Bacteria, fungi, parasites and viruses are potentially zoonotic porcine microorganisms. Whereas bacteria and fungi can be treated and eliminated by antibiotics and antifungals, treating viral infections with antivirals is more complicated and it seems that therefore viruses represent a greater risk. Among the potentially zoonotic viruses, porcine endogenous retroviruses (PERVs), porcine cytomegalovirus (PCMV), HEV genotype 3, porcine lymphotropic herpesviruses (PLHV), and porcine circoviruses (PCV) are the best characterised (Table 1). Whereas PCMV, HEV, PLHV, PCV as well as bacteria and fungi may be eliminated from pigs using different methods, this is impossible with PERVs, since these viruses are integrated into the genome of all pigs (for review see [22]).

It is important to note that processing, transport and manufacture processes of the potential transplant should be performed so that no additional microorganisms will be introduced.

3. Detection methods and elimination programs

Sensitive detection methods and refined detection strategies are required to detect potentially zoonotic porcine microorganisms and exclude infected pigs from the herds. Recently, detection of PCMV in Göttingen Minipigs was reported when using sensitive, but not when using less sensitive methods [20]. Since it is unclear whether PCMV can infect humans in general or whether a minimal amount of virus (threshold) is required, it remains unclear how sensitive the detection methods should be. On the other hand, despite using sensitive methods, PCMV was not detected in the blood of two donor pigs, but later in the blood of two non-human primate recipients ([23], Denner et al., unpublished). Therefore, in addition to sensitive methods also new testing strategies should be developed, *e.g.*, testing other samples such as oral and anal swabs, ear biopsies or organs. Screening 10 days old piglets for PCMV, virus was more effectively detected using oral and anal swabs in comparison to blood samples [24]. The sensitive assays may also be used to screen the human recipients of xenotransplants but only in the case the donor pigs were positive. There is no need to screen the recipient when the donor pigs were negative. Most importantly, the improved and sensitive detection methods developed for xenotransplantation can be used to screen pig herds bred for meat production in order to increase the quality and safety of pork products. For some porcine microorganisms, methods that directly detect their DNA or RNA genomes by PCR, that measure proteins or virus particles using specific antibodies or that measure infectious viruses using infection assays have recently been developed. The readout of such infection assays may involve detection of virus by PCR or detection of genome expression at the mRNA or protein level. Indirect detection methods are based on measuring humoral immune responses induced by infection using common methods such as ELISA or Western blot analysis. These methods require virus-specific antigens, either purified virus particles or recombinant viral proteins, and, if possible, positive control sera produced in goats, rats or other animals against purified virus antigens. Immunological detection methods (Western blot assays, ELISAs) have the advantage that they can determine virus infection even when the virus is undetectable by PCR methods. Prerequisite of successful immunological assays are well characterised antigens such as purified recombinant viral proteins or purified viruses, not lysates of infected cells. Unless it is impossible to discriminate between viral latency and elimination of the virus by the immune response, antibody-positive animals should not be used as donors for xenotransplantation. Highly sensitive PCR-based and immunological methods have already been developed for PERVs ([for review see [22]), PCMV [25–29], HEV genotype 3 [30–35], PCV2 [36–38] and PLHV1, 2, 3 [39,40] in some specialised laboratories and there is hope that they will be used and improved in future in many test laboratories. As mentioned above, sensitive methods are the prerequisite for an effective detection of PCMV whereas detection methods of low sensitivity failed [20]. Since the virus load is often extremely low and the viruses may be latent and/or hidden in specific organs making them difficult to detect, new screening strategies should be developed. Important in this context is also the time of testing. In the case the virus is going latent, detection may be easy immediately after infection. In contrast, in the case the virus is replicating, the highest probability to detect it, is immediately before transplantation. Possible approaches to eliminate specific porcine microorganisms, apart from selection of negative animals, include treatment of infected animals with antiviral drugs and prevention of infection by vaccination. Unfortunately, for many potential pathogens, neither antiviral drugs nor vaccines are currently available [14,41–43]. In addition, Caesarean section, colostrum

Table 1
Selected porcine microorganisms with zoonotic potential.

Virus	Diseases in pigs	Infects human cells *in vitro*?	Infects humans *in vivo*?	Possible consequences in the recipient	References
PCMV	Immunosuppression, fatal disease in newborn pigs	Unknown[a]	Unknown	Transplant rejection	For review see Denner [41]; Yamada et al. [55]; Sekijima et al. [56]
PCV2	Yes[b]	Yes	No	Unlikely[c]	For review see Segales et al. [103]
HEV	Transient febrile illness	Yes	Yes	Liver disease or asymptomatic	For review see Denner, [14]; Meng et al. [64]; Schlosser et al. [104]
PERV	Unknown	Yes[d]	Unknown	Unknown, theoretically retroviruses may induce tumours, immunodeficiencies or may be apathogenic	For review see Denner and Toenjes [22]

[a] Infection of human fibroblasts was reported (Whitteker et al. [105]), but also lack of infection of different human cells (Tucker et al. [106]).

[b] Postweaning multisystemic wasting syndrome (PMWS), PCV2 disease (PCVD), PCV2-systemic disease (PCV2-SD, directly replacing PMWS), PCV2-subclinical infection (PCV2-SI), PCV2-reproductive disease (PCV2-RD), porcine dermatitis and nephropathy syndrome (PDNS).

[c] Contamination of vaccines against rotaviral gastroenteritis from two different manufacturers with PCV1 and PCV2 did not result in PCV-infection of the vaccinees (Gilliland et al. [107]; McClenahan et al. [108]; Baylis et al. [109]; Dubin et al. [110]).

[d] Infection was observed mainly with tumor cells lacking APOBEC (for review see Denner and Tönjes [22]), but infection of primary cells with human-adapted PERV was also observed (Denner [111]).

deprivation, early weaning and clean embryo transfer are effective approaches in eliminating infectious pathogens from the herd [29,44–46]. The most important part of all elimination programs is isolation of the clean animals to avoid *de novo* infection.

The situation with PERVs is more complicated, as these are integrated as DNA copy into the pig genome and are able to infect human cells (for review see [22]). Since each pig genome carries multiple copies of PERV proviruses, gene editing may be the best approach to inactivate them. Attempts at gene editing using the zinc finger nuclease (ZFN) resulted in very high expression of the ZFN to toxic levels, presumably a result of cutting the genome at multiple sites and destabilising it [47]. However, when the recently developed CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats/CRISPR-associated) technology was applied, 62 PERV proviruses were successfully knocked-out in immortalised PK-15 pig cells [48]. It remains to be seen whether it will be possible to knock-out all PERV proviruses in primary cells and to use these to obtain healthy PERV-free piglets [49].

4. Recent achievements in xenotransplantation

In recent years remarkable achievements have been reported in the various different fields of xenotransplantation. First, genetically modified pigs expressing multiple human genes and with knock-outs of pig genes responsible for hyperacute rejection have been generated [50,51]. Second, these genetic modifications in combination with new immunosuppressive regimens resulted in longer survival times in preclinical pig-to-nonhuman primate xenotransplantions compared to earlier attempts (Table 2) [52–54]. In these trials neither PERVs nor other porcine microorganisms were transmitted (for review see [22,54]). In contrast, transplantations of pig PCMV-infected kidneys to baboons [55] or cynomolgus monkeys [56] were associated with a dramatically reduced survival time of the transplants compared with transplantations of uninfected kidneys. In the transplant a high titer of PCMV was found. High virus titers were also observed in the blood of two baboons after orthotopic pig heart transplantation ([23], Denner et al., unpublished data). There is clear evidence that PCMV was transmitted by the transplanted heart to the recipient. However, it is still unclear whether the virus established infection in cells of the primate host or whether it remained restricted to the cells of the transplant. Based on these results and the experience with human CMV in human transplant recipients [57], it may be suggested that PCMV may be similarly harmful for human recipients. At present it is unclear whether PCMV can infect human cells or cells from non-human primates or whether the pathogenic effect observed in non-human primates is due to indirect effects. Third, with regard to microbiological safety, pigs are being analysed in more detail and programs to eliminate potentially zoonotic microorganisms have been proposed (see above). Fourth, clinical xenotransplantations have now been performed in New Zealand and in Argentina that resulted in a low medical benefit, but transmission of porcine microorganism was not observed [58–61]. Although reduction in HbA1c (glycated hemoglobin which is a form of hemoglobin that is measured primarily to identify the three-month average plasma glucose concentration) and insulin doses were marginal, the efficacy in the first trial was assessed by calculating the transplant estimated factor (TEF), which indicated in all cases a low transplant function and only in one case full graft function [58,60]. In the second clinical trial the HbA1c

Table 2
Recent achievements in preclinical xenotransplantation: Longest survival times, 2016.[a]

Transplant	Recipient	Longest survival time (days)	Remarks[b]	Immunosuppression[c]	References
Islet cells	Rhesus	|600	Non-transgenic pigs used	CVF, ATG, anti-CD154, sirolimus	Shin et al. [112]
Kidney	Baboon	136	Life-supporting GTKO:CD46:CD55:hTM:CD39:blood type 0 (non-A)[d]	ATG, anti-CD20mAb, CVF, anti-CD40mAb, rapamycin, MP[e]	Iwase et al. [113]
Heart	Baboon	945	Heterotopic GTKO:CD46:hTM	ATG, anti-CD20mAb, anti-CD40mAb, CVF, MMF, steroid	Mohiuddin et al. [114]
Liver	Baboon	25	GTKO PCMV-negative	Octaplex, thymoglobulin, CVF, belatacept, FK-506, methylprednisone	Shah et al. [115]

[a] For details and previous trials see Cooper et al. [54] and Denner et al. [55].

[b] GTKO, α-galactosyltransferase knockout;CD39, endothelial protein C receptor; CD46, membrane cofactor protein; CD55, complement decay-accelerating factor, DAF; hTM, human thrombomodulin.

[c] ATG, anti-thymocyte globulin; belatacept, fusion protein composed of the Fc fragment of a human IgG1 immunoglobulin linked to the extracellular domain of CTLA-4 CVF, cobra venom factor; FK-506, tacrolimus; MMF, mycophenolate mofetil; octaplex, human prothrombin complex.

[d] hTM and hCD39 were not expressed in the kidney.

[e] In addition anti-inflammatory (tocilizumab, IL-6 receptor blockade, etanervept, TFN-a antagonist) and adjunctive (aspirin, low molecular weight heparin) treatment.

was reduced to less than 7% and the average TEF indicated partial transplant function [60].

5. Impact on animal and public health

The methods developed for xenotransplantation to screen pig donors and human recipients can also be used to screen pigs bred for meat production. The prevalence of some viruses is very high in most pig populations. For viruses causing economically important diseases in pigs, such as porcine reproductive and respiratory syndrome virus (PRRSV) and PCV2, sensitive detection methods and effective vaccines have been developed und successfully employed [62]. There may be viruses and other microorganisms present in the pigs which obviously do not harm the pig, but may be zoonotic for the human recipient, for example PCMV and HEV. 85% of pigs in a slaughterhouse in the Berlin area were found to be PCMV-positive [63]. HEV is a good example that pig viruses can be easily transmitted to humans and that they therefore pose a risk for xenotransplantation [14,64,65]. Pigs are infected with HEV genotype (gt) 3 and gt4 [14,64–66] (not to be confused with HEV gt1 and gt2, which are only found in humans and which can cause infections with fatalities approaching 25% in pregnant women). The main route of infection with HEV gt3 is food-borne transmission, e.g., contact with contaminated meat, or by direct contact with infected animals [67–72], by shellfish [73,74],but also by vegetables (probably contaminated with pig manure) [75], blood transfusion [76–78] and allotransplantation [79–82]. Most infections with HEV gt3 and gt4 are asymptomatic, whereas severe hepatitis occurs only in combination with other pre-existing chronic liver diseases. In addition, chronic infection with HEV is more likely to develop in profoundly immunosuppressed patients, for example during chemotherapy [83] and HIV infection [84,85]. Patients undergoing xenotransplantation will certainly require immunosuppression. In Germany, the HEV seroprevalence of domestic pigs varied between 42.7% and 64.8% [86,87], and genomic HEV RNA was found in 22% of pig liver sausages (although infectivity was not tested in this case) [88]. Antibodies specific for HEV were found in 67% of older hunters and in 17% of the general population [89,90]. Although the impact of HEV infections on the health of infected human individuals and on public health in general is unknown, it may be assumed that detection of HEV in domestic pigs using the sensitive methods developed for xenotransplantation and the selection of virus-free animals will prevent infection of humans. This raises the question of whether the expense of eliminating HEV from pig herds might be lower than the direct and indirect costs of medical treatments for infected individuals. In addition, as elimination of HEV from pigs prevents infection of humans, it would also prevent transmission by blood transfusion.

Evaluating the potential risk associated with xenotransplantation using pig cells, tissues and organs requires also an analysis of epidemiological data comparing diseases in individuals eating red meat (beef, pork, lamb, veal, mutton) and vegetarians. The International Agency for Research on Cancer classified consumption of red meat as "probably carcinogenic to humans" and of processed red meat as "carcinogenic to humans" based on the assessment of more than 800 epidemiological studies in many countries, different continents, with diverse ethnicities and diets [91]. Other studies came to the same or slightly different results [92–100]. At present it is impossible to determine whether pig meat transmits tumor-inducing viruses or other infectious agents to customers, whether these results are due to chemical carcinogens or both. It is also unknown which impact such infectious agents may have on xenotransplantation if they indeed exist. Interestingly, replication-competent circular DNA molecules were described in serum and milk from healthy cattles and an association of milk and beef with cancer and multiple sclerosis was suggested [101,102].

6. Conclusion

Naturally occurring emerging infectious diseases continue to impose an enormous burden on global health and economy. Therefore it is important to avoid producing new diseases when using pig cells, tissues or organs to treat human diseases. The development of sensitive methods to detect porcine microorganisms in donor pigs is a prerequisite in order to select negative animals and to prevent transmission to the transplant recipients. The same detection methods may also be used to monitor the recipient (although, obviously, if the microorganism in question has been eliminated from the donor pig, there would be no need to test the recipients). Finally, using these same detection methods developed for xenotransplantation to screen pigs bred for meat production will allow to select virus-free animals and to eliminate these microorganisms from the herd and to improve the health of the animals. This would prevent transmission by meat eating and contact and prevent the clinical and subclinical infections that may have an enormous impact on public health. Therefore, research on the microbiological safety of xenotransplantation may eventually improve animal health and public health and should be a task for all Public Health Institutes.

Conflict of interest statement

The author of this paper has no conflicts of interest.

Acknowledgments

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