International Journal of Surgery 23 (2015) 306–311

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.journal-surgery.net

Review

Preventing transfer of infectious agents

Joachim Denner [a, *], Nicolas J. Mueller [b]

[a] Robert Koch Institute, Berlin, Germany
[b] Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Switzerland

HIGHLIGHTS

- PCMV, PLHV, HEV and PERV were identified as main risk factors in xenotransplantation.
- Detection methods and elimination programs for PCMV, PLHV, and HEV were developed.
- PERVs are integrated in the genome of all pigs and infect human cells in vitro.
- Strategies how to prevent PERV transmission are also under development.

ARTICLE INFO

Article history:
Received 3 June 2015
Received in revised form
27 July 2015
Accepted 4 August 2015
Available online 24 August 2015

Keywords:
Xenotransplantation
Virus safety
Porcine endogenous retroviruses
Porcine cytomegalovirus
Porcine lymphotropic herpesviruses
Porcine circoviruses
Hepatitis E virus
Elimination programs

ABSTRACT

Xenotransplantation using pig cells, tissues and organs may be associated with the transfer of porcine infectious agents, which may infect the human recipient and in the worst case induce a disease (zoonosis). To prevent this, a broad screening program of the donor animals for putative zoonotic microorganisms, including bacteria, viruses, fungi and others, using sensitive and specific detection methods has to be performed. As long as it is still unknown, which microorganism represents a real risk for the recipient, experience from allotransplantation should be brought in. Due to the fact that pigs can be screened long before the date of transplantation, xenotransplantation will become eventually safer compared with allotransplantation.

Screening and selection of animals free of potential zoonotic microorganisms, Caesarean section, vaccination and/or treatment with chemotherapeutics are the strategies of choice to obtain donor animals not transmitting microorganisms. In the case of porcine endogenous retroviruses (PERVs) which are integrated in the genome of all pigs and which cannot be eliminated this way, selection of animals with low virus expression and generation of genetically modified pigs suppressing PERV expressions may be performed.

Contents

* Corresponding author.
E-mail address: DennerJ@rki.de (J. Denner).

http://dx.doi.org/10.1016/j.ijsu.2015.08.032
1743-9191/

1. Introduction

Xenotransplantation using pig cells, tissues and organs has to overcome three hurdles before being applied in the clinic for the treatment of organ failure: immunological rejection, physiological incompatibility and transfer of infectious agents. The microbiological safety of xenotransplantation is an important issue, however it can be managed easily. The risk of infection is also known in allotransplantation. Numerous infectious agents have been transmitted together with human donor transplants, including human cytomegalovirus (HCMV), human immunodeficiency virus-1 (HIV-1) and rabies virus [1]. Since xenotransplantation allows screening the donor animals beforehand, most risks can be excluded by careful testing and xenotransplantation finally will be a microbiologically safer technology compared with allotransplantation.

Like all animals, pigs carry numerous microorganisms in their digestive tract and on their skin, and therefore cells, tissues and organs to be used for transplantation should be removed under aseptic conditions. The number of microorganisms present in the tissues and organs of interest should be zero [2]. In some reviews concerning the microbiological safety of xenotransplantation numerous microorganisms are listed which were thought to induce zoonoses when transmitted to the human recipient [2]. Zoonosis means that the microorganisms not only infect the new host, but cause a disease. In general, bacteria, fungi, parasites and viruses may be transmitted. However, at present it is rather difficult to classify most of the porcine microorganisms into pathogenic and non-pathogenic for human recipients. In addition, when a microorganism is pathogenic in the pig it does not mean that it is also pathogenic in humans and vice versa. The risk of transmission is certainly higher when pharmaceutical immunosuppression to prevent immunological rejection of the transplant will be applied. Therefore it is still unclear which microorganisms should be monitored. The Auckland island pigs which had been used in the first clinical trials performed by the New Zealand company LCT were screened regularly for 10 bacteria, 15 viruses and toxoplasma (Table 1) [3]. The Göttingen Minipigs which are used for numerous biomedical investigations are screened regularly for 27 bacteria, 16 viruses, three fungi and four parasites (http//www.minipigs.dk/). An additional screening of the Göttingen Minipigs involved PERV [4], hepatitis E and 89 other microorganisms [5,6].

In general, most microorganisms found in pigs to be used for xenotransplantation may be eliminated by specified pathogen free (spf) or designated pathogen-free (dpf) breeding of the animals. In the case there is a bacterial or fungal infection in the donor pig, treatment with antibiotics or chemotherapeutics may be successful. At the moment hepatitis E virus (HEV), porcine cytomegalovirus (PCMV), porcine circoviruses (PCV), porcine lymphotropic herpes viruses (PLHV), and porcine endogenous retroviruses (PERVs) are thought to pose the main risk for reasons to be discussed below and therefore these microorganisms will be analysed in the next chapters in more details.

2. HEV as risk factor

In most cases HEV causes self-limiting hepatitis in humans. Whereas HEV of the genotype (gt) 1 and gt2 are found in people, are transmitted mainly by contaminated water and are causing a high mortality during pregnancy, HEV gt3 and gt4 are swine viruses and do not cause a disease in pigs, however, when they infect humans they may cause in rare cases a zoonotic disease (for review see [5,7]). A severe hepatitis after infection with HEV gt3 and gt4 was observed only in the case of other underlying liver diseases. Importantly, neurological disorders have also been described for HEV gt3 and gt1. Note, that only HEV gt3/4 may pose a risk when xenotransplantation using pig cells, tissues and organs is performed, not gt1 or gt2.

Usually HEV gt3/4 are transmitted by contaminated meat or direct contact with infected pigs. HEV gt3 RNA was detected in pig liver at grocery stores and infectious virus could be isolated [5,7]. HEV transmission by shellfish and vegetables possibly contaminated by pig manure as well as by blood transfusion and allotransplantion was also reported. A chronic infection was more likely to develop in immunosuppressed patients, including HIV-1 infected individuals [5,7]. Sensitive PCR-based methods have been developed to determine a HEV infection and to genotype the virus. Detection of HEV and its elimination from pigs seems not to be easy. First, the virus is heterogeneous, e.g., 10 subtypes of genotype 3 exist, what makes it difficult to design efficient PCR or real-time PCR. Second, the virus load seems to be very low so that even highly sensitive PCRs may be unable to detect the virus. Although HEV gt3/4 are widely distributed, the prevalence in pigs, especially in multitransgenic pigs generated for usage in xenotransplantation, is not well studied.

In contrast, the non-transgenic Auckland island pigs, generated by Living Cell Technologies (LCT) in New Zealand are better

Table 1
Microorganisms tested in Auckland island pigs used for islet cell transplantation [3].

Bacteria	
Leptospira tarrasovi	
Leptospira hardjo	
Leptospira pomona	
Mycoplasma hyopneumoniae	
Campylobacter	
Isospora	
Cryptosporidium	
E. coli K88	
Yersinia	
Viruses	
PCMV	Porcine cytomegalovirus
PCV1	PCV1, porcine circovirus type 1
PCV2	PCV2, porcine circovirus type 2
PLHV2	Porcine lymphotrophic herpesvirus type 2
HEV	Hepatitis E virus
ReoV	Reovirus (all types)
RotaV A-C	Rotavirus A, rotavirus B and rotavirus C
PEVB	Porcine enterovirus B
PHEV	Porcine hemagglutinating encephalomyelitis virus
PTV	Porcine teschovirus
BVD	Bovine virus diarrhea
AujD	Aujesky's disease
PPV	Porcine parvovirus
PRRSV	Porcine reproductive and respiratory syndrome virus
EMCV	Encephalomyocarditis virus
Protozoa	
Toxoplasma	