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Swine as an animal model in interventional radiology in the post-genomic era

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Introduction

Swine (*Sus scrofa*) have been used as a model for the human disease and medical advancement dating back to the 2nd century C.E. Given the anatomic and physiologic similarities to humans, research in pigs has contributed to the development of interventional devices and therapies. With the recent decoding of the swine genome and improving tools of genetic manipulation, we are entering an era where customized porcine models of disease can be efficiently produced. Utilization of transgenic swine may provide an ideal preclinical platform to drive the next generation of image-guided interventions.

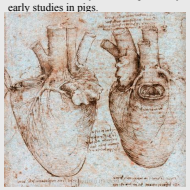
Pigs in Classical Medicine

Medical research in swine dates back to the works of Galen, whose studies defined medical knowledge for a millennium and a half. Through vivisection of pigs, Galen determined that the brain, spinal cord, and nerves controlled sensation, and movement (Figure 1). In the 15th century, Leonardo da Vinci visited slaughterhouses where he observed that a knife driven into the heart of the pig moved in synchronicity with pulsating blood. Da Vinci surmised that the heart was a muscle, a theory he later demonstrated with detailed anatomic drawing and functional studies using a glass model of the heart and aorta (Figure 2).

After the discovery of insulin, purification of the hormone from swine and bovine pancreas in industrial quantities became the primary source of medicinal insulin for much of the 20th century. Dr. Frederick Sanger would later demonstrate that porcine and human insulin differed by only one amino acid, foreshadowing the high degree of genetic similarity between the two species. Dr. Alain Carpentier utilized the homology of cardiac anatomy for the treatment of intractable valvular disease. In 1968, Carpentier's work culminated in the production of the glutaraldehyde treated porcine bioprosthetic valve, a model that remains the basis for many modern valve replacement operations.

Figure 1: Depiction of the "squealing pig" experiment in the Junta edition of *Galen's Works* (1541). Galen proved the existence of the nervous system by severing the recurrent laryngeal nerve of a squealing pig and thereby ceasing phonation.

Figure 2: Leonardo da Vinci's anatomical studies of the cardiovascular system inspired by early studies in pigs.



Swine and the Growth of Interventional Radiology

Swine as a large animal model of interventional therapies came to prominence in the 1990s as other preclinical models failed to predict deleterious side effects of stent therapy. Subsequent investigations demonstrated that pigs had human analogous vascular anatomy, genetic and dietary-induced atherosclerotic changes, and similar pathophysiological changes to stent thrombosis and stenosis. Swine have now become the accepted standard preclinical model for the evaluation of novel stent technologies.

In vivo studies in the porcine model were critical to the development of modern ablative therapies. Preclinical studies utilizing radiofrequency ablation (RFA) in pigs defined the three histological zones of ablative cellular death, time-dependent sonographic and radiographic findings post-therapy, and the relative limitations including the "heat-sink effect" near vasculature. Similar feasibility studies with respect to cryoablation therapy for renal pathology was first performed in the porcine model. In both cases, the technical, anatomic, histologic, and radiographic correlates to medical practice permitted early translation of ablative therapies into the clinic.

Acknowledgements

We would like to thank Dr. Lawrence Schook and Dr. Laurie Rund for their generosity of time and guidance in the field of swine genomics. Additionally, we would like to thank Dr. Ohran Oz and Dr. Xiankai Sun for providing the porcine cross-sectional and fluoroscopic images.

Porcine Comparative Anatomy and Physiology

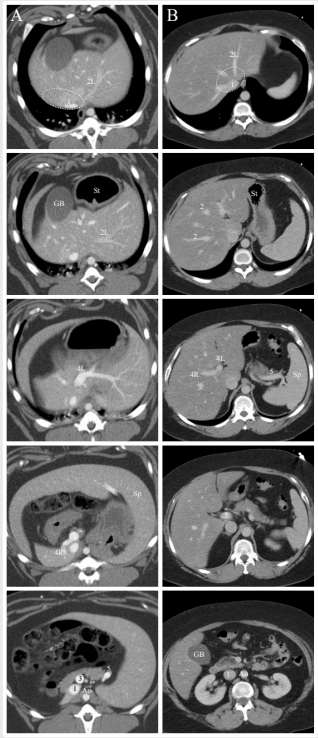


Figure 3: Pig versus human hepatic anatomy. CT of the abdomen in axial sections of the A) Swine and B) Human.
(1) Inferior Vena Cava
(2) Hepatic Veins, (2L) Left Hepatic Vein
(3) Hepatic Portal Vein
(4) Branches of the Portal Vein, (4L) Left, (4R) Right
(5) Splenic Vein
(Ao) Aorta, (Sp) Spleen, (St) Stomach, (GB) Gallbladder
* circled Couinaud equivalent Segment I

- Swine are considered the preferred xenographic model for liver transplantation given the metabolic, anatomic, and physiologic similarities to humans.
- Pigs produce a comparable amount of Cytochrome P450 enzyme capable of performing all major metabolic functions of the human analog.[7, 8]
- Damage to porcine hepatocytes is predictive of toxicity in humans. [7]
- Histologically, pigs and humans both have portal triad structures.
- Classically, the pig liver has six anatomic segments. By Couinaud functional definition of hepatic segments, the the porcine liver can be broken down into eight functional segments with individual biliary drainage, venous outflow, and arterial supply.
- Similar to the human physiological response, perfusion of the porcine liver by the dominant hepatic portal venous blood flow is inversely proportional to hepatic arterial flow. [12]

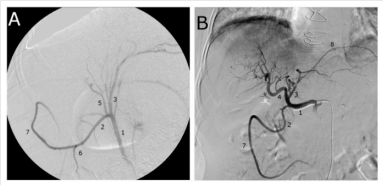


Figure 4: Pig versus human hepatic arterial anatomy. Digitally subtracted angiography of the hepatic artery in the anteroposterior projection A) Swine and B) Human.
(1) hepatic artery,
(2) gastroduodenal artery,
(3) left hepatic artery,
(4) right hepatic artery,
(5) right medial hepatic artery,
(6) cranial duodenopancreatic artery
(7) right gastroepiploic artery,
(8) inferior phrenic artery.

Transgenic Swine as a Model of Human Disease

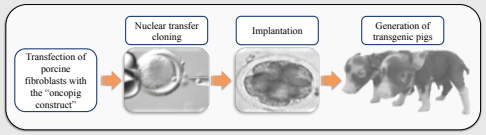


Figure 5: Schematic of modern Somatic Cell Nuclear Transfer (SCNT) in the creation of of transgenic pigs.

Transgenic animal models have been critical to advancing our understanding of human disease. Recent advances in techniques of genetic manipulation with Somatic Cell Nuclear Transfer (SCNT) have been vital in the genesis of transgenic large animal models of human disease. SCNT is performed by transferring genetically altered somatic cell nucleus to an embryonic cell to create transgenic offspring (depicted in Figure 5). Propagation of cloning techniques has lead to the development of many transgenic pigs model (Figure 6). Decoding of the swine genome in 2012 now allows for identification and manipulation of disease homologous sequences between species. Recent development of *APC*, *TP53*, and *p53/K-ras* "oncopigs" represent exciting and unique animal models for the study and treatment of cancer.

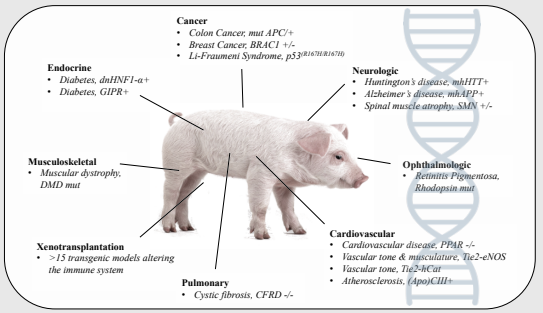


Figure 6: Selected transgenic porcine models of human disease.

Conclusion

Pigs have played an important role in the history of medicine and more recently to many innovations in the growth of Interventional Radiology. In the post-genomic era of swine, we now have the opportunity to efficiently produce customized swine genetic models that more faithfully recapitulate human disease anatomically, physiologically and genetically. It is important for Interventional Radiology to recognize the importance and utility of porcine genetic models and become involved in the tailoring of genetic models to our clinical interests. Genetic porcine models of human cancer ("Oncopigs") are currently under development and may provide a crucial preclinical platform to the development of the next generation of interventional therapies in oncology. Additional potential genetic models of interest to Interventional Radiology include liver fibrosis, hereditary hemorrhagic telangiectasia and vascular disease.

Literature Cited

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