REVIEW ARTICLES

Porcine models of digestive disease: the future of large animal translational research

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There is increasing interest in nonrodent translational models for the study of human disease. The pig, in particular, serves as a useful animal model for the study of pathophysiological conditions relevant to the human intestine. This review assesses currently used porcine models of gastrointestinal physiology and disease and provides a rationale for the use of these models for future translational studies. The pig has proven its utility for the study of fundamental disease conditions such as ischemia-reperfuion injury, stress-induced intestinal dysfunction, and short bowel syndrome. Pigs have also shown great promise for the study of intestinal barrier function, surgical tissue manipulation and intervention, as well as biomaterial implantation and tissue transplantation. Advantages of pig models highlighted by these studies include the physiological similarity to human intestine and mechanisms of human disease. Emerging future directions for porcine models of human disease include the fields of transgenics and stem cell biology, with exciting implications for regenerative medicine. (Translational Research 2015;166:12–27)

Abbreviations: AMI = acute mesenteric ischemia; CF = cystic fibrosis; CRF = corticotropin-releasing factor; ENS = enteric nervous system; FAP = familial adenomatous polyposis; GLP-2 = glucagon-like peptide 2; IESCs = intestinal epithelial stem cell; NEC = neonatal necrotizing enterocolitis; ROM = reactive oxygen metabolites; SBS = short bowel syndrome; TPN = total parenteral nutrition

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INTRODUCTION

Digestive disease results in more than 230,000 deaths annually in the United States, with colorectal cancer as the leading cause of mortality in adults from digestive disease.[1] Animal models are imperative for translational research targeted at improving human health. Because of the limitations of directly studying human disease in a clinical setting, animal models have been used extensively to expand basic science knowledge. Rodents, particularly mice, have been commonly used animal models of disease because of their relatively low cost, ease of maintenance, and rapid reproduction rate.[2,3] This has been facilitated by the creation of inbred strains that represent spontaneous models of disease. Examples include TNFΔARE and SAMP1/YitFc mice strains that

exhibit Crohn's disease–like ileitis as is seen in human patients.[4,5] They also make for effective models of cancer because of their high susceptibility to developing chemically induced malignancies.[6] Furthermore, they are highly amenable to genetic manipulation.[2,7] The use of transgenic and knockout mice has provided invaluable insight into the impact of genetic mutations and specific genes on disease etiology and progression.[8-10] However, murine models often lack key clinical signs or pathologic changes representative of human gastrointestinal disease, which are essential to improve translational studies and drug discovery (Table I).[7,11-19] Therefore, there is renewed interest in large animal models that more closely resemble human disease processes[20,21] and provide a nonrodent model for drug discovery. Aside from physiological considerations, the larger size of pigs is advantageous for models requiring surgical manipulation, such as Thiry-Vella loops in which an isolated cannulated segment of intestine is studied in vivo,[22] or where research involves tissue transplantation.[23] Of other large animals used in biomedical research, dogs have been used extensively, particularly for the study of ischemia-reperfusion injury. However, with increasing social pressures to limit use of dogs as experimental animals and the high mortality rate associated with some disease models, the use of dogs is declining.[18,23] However, dogs are particularly well suited and are increasingly used for the study of spontaneous naturally occurring diseases that also affect humans, such as cancer. In fact, clinical trials in veterinary oncology have been used to inform drug efficacy and safety in humans.[24]

The pig has a number of distinct advantages that has made this species a useful translational research animal model (Table I). In particular, there are important anatomic and physiological similarities to human beings.[19,25] The pig has a comparably sized genome with extensive homology to humans. The pig genome has a 60% sequence homology to humans compared with rodents with only 40% homology.[26,27] Additionally, compared with mouse, rat, dog, cat, or horse, the pig chromosomal structure is more like humans.[28,29] Pigs, like humans, are omnivores and share similar metabolic and intestinal physiological processes.[19,30,31] For example, a comparison of the recommended daily allowances of vitamins and minerals in the human diet and the daily nutrient requirement of pigs reveal striking similarities between the 2 species in infancy, growth, reproduction, and lactation.[19,32] This likely contributes to their comparable mucosal barrier physiology and enteric microbiota, as well as susceptibility to select enteric pathogens.[19,33] The role of the intestinal microbiota in maintaining intestinal health has been highlighted in recent years, and disturbances in microbial composition have been associated with important human diseases such as diarrhea, neonatal necrotizing enterocolitis (NEC), and obesity. Conversely, studies focusing on the relationship between the composition of the gut microbiota and disease have shown widely diverging results when comparing mice with humans.[33-35] This has been addressed most recently by using humanized germ-free mice transplanted with human microbiota.[36-39] However, similarities in the intestinal microbial ecology between pigs and humans have made the pig a useful nonprimate animal model for studies of dietary modulation of microbiota.[40] Furthermore, a humanized germ-free pig model has also been established.[33,39] Under natural conditions, both human and porcine gut microbiota consist mainly of Firmicutes and Bacteroidetes phyla in spite of the fact that their overall gastrointestinal microbial diversity is affected by diet, age, and environmental conditions.[40-42] Additionally, pharmaceutical bioavailability and nutrient digestibility in pigs closely resemble that of humans.[19,25,43] These characteristics have led to the use of pigs for the development of pig models of a number of gastrointestinal diseases including NEC,[16,44-48] acute mesenteric ischemia (AMI),[18,49-52] short bowel syndrome (SBS),[43,53-57] Acquired Immune Deficiency Syndrome-associated cryptosporidium infection,[17,58,59] stress-induced intestinal dysfunction,[60-63] cystic fibrosis (CF),[64,65] and familial adenomatous polyposis (FAP).[14] This review will highlight strengths and limitations of pig models of intestinal ischemia-reperfusion injury, stress-induced intestinal dysfunction, and SBS. In addition, we have reviewed information that will extend the discussion on animal models in the fields of transplantation, bioengineering, and transgenics.

COMPARATIVE GASTROINTESTINAL ANATOMY: SIMILARITIES AND DIFFERENCES BETWEEN HUMANS AND PIGS

Pigs have significant anatomic and physiological similarity with human beings, with some key comparisons noted in Table II and Fig 1. The structure of the small intestine is very similar in humans and pigs, including macroscopic features such as the ratio of intestinal length per kilogram bodyweight (Table II).[19] Other gross similarities include the presence of sacculations and tenia (bands of longitudinal muscle) extending along most of the colonic length in both human and porcine colons.[30,66] These anatomic similarities contribute to the comparable transit time and analogous digestive and absorptive processes reported for these species.[67] Shared microscopic features also