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Animal and cellular models of human disease

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Abstract

In this eighteenth (2016) Annual Review Issue of *The Journal of Pathology*, we present a collection of 19 invited review articles that cover different aspects of cellular and animal models of disease. These include genetically-engineered models, chemically-induced models, naturally-occurring models, and combinations thereof, with the focus on recent methodological and conceptual developments across a wide range of human diseases.

Key Words: tumourigenesis; invasion; Wnt signalling; organoid culture; tumour microenvironment; immunotherapy; melanoma; HPV; viral oncogenesis; ovarian serous carcinoma; endometriosis; endometrioid carcinoma; clear cell carcinoma; pancreatic ductal adenocarcinoma; 3D xenografts; patient-derived tumour xenografts; inflammatory bowel disease; fibrosis; idiopathic pulmonary fibrosis; regeneration; CRISPR/Cas9; atherosclerosis; neurodegenerative disease; non-invasive bio-imaging; behavioural testing; xenotransplantation; macular degeneration; cone dystrophy; cystic fibrosis; obesity; diabetes; incretin; hydrogen sulphide; gasotransmitter; epigenetic mutation; animal pathology reporting guidelines; MINPEPA

Introduction

Animal and cellular models provide opportunities for experimental testing of disease mechanisms. This central tenet of biological investigation provides the route to increase our understanding of the biological basis of human and animal diseases as well as developing and testing new therapies [1-3]. In many fields, such models comprise the 'standard' *in vivo* approach to biomedical investigation. However, with advances in our understanding of human diseases comes the necessity to revisit whether 'standard' models really tell us what we want to know. Modelling studies have been increasing in number, variety and sophistication, with some showing similarities and others divergent results compared with human disease [4, 5].

Models of Neoplasia

Both animal and cellular models of cancer have provided powerful tools to understand the biology of some human cancers and to experimentally investigate the roles and functions of genetic and epigenetic changes identified in human tumours. One of the best examples is the large number of murine models of intestinal tumour formation, which have been pivotal in confirming *in vivo* the activities and effects of selected genetic mutations in intestinal carcinogenesis, thus improving the understanding of tumour biology and also allowing the testing of therapies. Recent developments identifying the importance of the tumour microenvironment and the potential for immunotherapy have included the use of preclinical studies of genetically engineered mouse models. Jackstadt and Sansom explore these developments in their review [6], a tour de force tracing mouse models of intestinal cancer from the initial models of genetically-engineered mice to the state-of-the-art cellular organoid models.

Van der Weyden and colleagues have similarly produced an authoritative and comparative overview of models of human melanoma [7] that examines melanocyte biology across a range of animal species. Such comparisons inform the study of both comparative genomics and comparative pathology to identify key molecular and pathological events in melanomagenesis. Importantly, these types of comparisons also allow investigators to select the appropriate model to address specific hypotheses and should serve as a 'roadmap' for the melanoma investigator.

Three articles in the series cover models of gynaecological cancers, including papillomavirus-associated cancers [8], ovarian cancer [9], and endometriosis and ovarian clear-cell carcinoma [10]. The papillomavirus review by Doorbar [8] highlights important similarities and differences among viral tropisms and immune regulation, and casts light on the effects of persistent viral oncogene

expression, including E6 and E7 genes of high risk human papillomaviruses (types 16 and 18), together with the interaction with cofactors such as hormones and UV radiation, in the development of premalignant neoplasia and invasive cancers. Morin and Weeraratna, in their review [9], discuss several genetically-defined mouse models and the implications of these models for newer concepts of ovarian serous carcinoma pathogenesis. In the third review, King and colleagues describe models of endometriosis [10], as well as the molecular and epidemiological evidence that endometriosis is the most plausible precursor of clear cell carcinoma and endometrioid carcinoma of the ovary.

Finally, Hwang et al explore the world of preclinical modelling of pancreatic ductal adenocarcinoma [11]. One of the most difficult cancers to detect and treat successfully, pancreatic ductal adenocarcinoma models have evolved over the recent past. This review discusses classic models of human cancer cell lines, cell line based xenografts and patient-derived tumour xenografts, as well as the recently developed models of pancreatic ductal organoids in three-dimensional culture systems and organoid-based xenografts.

Models of Immune, Inflammatory and Fibrotic Disorders

As cancer modelling remains an important aspect of tumour biology, so does modelling of inflammatory, immune-mediated, and fibrotic disorders. To better appreciate the nuanced differences in modelling of such disorders, this issue includes a series of reviews focused on inflammatory bowel disease [12], respiratory diseases [13], and regenerative biology [14]. The first article, by Mizoguchi and colleagues [12] reviews the complex mechanisms that mediate chronic intestinal inflammatory conditions, and discusses the interplay between genetic, immune and environmental factors that contribute to disease pathogenesis. Similarly, Williams and Roman [13] have authored a comprehensive review of both induced and naturally-occurring models of respiratory diseases that the pulmonary investigator will find of immense value when planning their next series of experiments. Finally, Jaźwińska and Sallin [14] discuss studies on naturally-occurring limb and organ regeneration in lower vertebrate species and the intrinsic plasticity of involved mature tissues. Harnessing such properties of cells and tissues may well pave the way for advances in human tissue regeneration.

Large animal models of human diseases

Despite the overwhelming use of rodents in biomedical research, there has recently been a surge in the use of large animals to model human diseases, driven largely by major leaps in technological advance. To address this, Whitelaw and colleagues [15] discuss the recent use of genome editing tools

such as CRISPR/Cas9 and similar methodologies in large animal livestock to produce newer models that may replicate the human condition with more fidelity. Indeed, domestic pigs and mini-pigs bear remarkable similarity to humans; thus, Shim and colleagues [16] review the field of atherosclerosis research by examining small animal models of coronary heart disease and ischaemic stroke as well as large animal models that take advantage of the new genome editing tools in mini-pigs. Additionally, Holm and colleagues [17] comprehensively examine the use of porcine models of many neurodegenerative diseases, such as Alzheimer's disease, in modified pig models, and highlight advantages such as use of non-invasive bio-imaging and behavioural testing. Taking advantage of the knowledge that porcine and human immune systems bear striking similarities, Cooper and coworkers [18] explore the up-to-date xenotransplantation research suggesting that genetically-engineered pigs could one day serve as a source of organs for human transplantation. The potential for future clinical trials of pig kidney, heart and islet transplantation is discussed. Finally, Kostic and Arsenijevic [19] elegantly present recent advances in our understanding of inherited retinal cone degeneration. Using animal models (including newer large animal models) with the appropriate genetically engineered changes allows correlation of phenotype with genotype and evaluation of new therapeutic strategies.

Models of genetic and epigenetic diseases

One of the many advantages of animal modelling is the ability to gain insights into genetic and epigenetic disease mechanisms. However, not all animals are appropriate models. In the case of human cystic fibrosis, murine models have not faithfully recapitulated either pulmonary or pancreatic disease. Thus, Gibson-Corley and colleagues [20] discuss alternative models of cystic fibrosis which have advanced our understanding of effects on both exocrine and endocrine pancreatic functions. Research into obesity and diabetes, two common health problems in the developed world, has also been hampered by the reliance on animal models that may not closely resemble the human disease. Carter and Morton [21] highlight this fact, and review evidence from transgenic animal models and pharmacological investigations to suggest that both cysteine and hydrogen sulfide play important roles in the pathogenesis of these disorders.

Human diseases that have an etiologic basis in epigenetic modifications have more recently been recognized. Brazel and Vernimmen [22] elaborate on studies that have identified pathogenic mutations in enhancer regions and epigenetic regulators over the last 30 years, from both genome wide association studies (GWAS) and epigenome wide association studies (EWAS). Further, Renner and colleagues [23] describe how animal models have informed us of the actions and

consequences of incretin hormones on pancreatic beta-cells by focusing on genetically-engineered rodent and non-rodent models, such as pigs and non-human primates.

Animal model pathology reporting guidelines

Despite all these advances, it remains clear that in order for science to move research fields forward, it must be both valid and reliable. Confirmatory studies can only be performed when the initial study provides enough information for other investigators to replicate the work. To address this critical criterion, Scudamore and colleagues [24] propose recommendations for the minimum data for publication of experimental pathology experiments. Following on from the previously published ARRIVE guidelines [25] that set out the basic information to be provided when reporting animal studies, these authors now provide complementary recommendations on the minimum information needed when reporting pathology data gathered from such studies to maximize reproducibility.

Summary

In sum, this Annual Review Issue presents a collection of articles providing in-depth, up-to-date reviews of disease modelling that will assist investigators in planning future experiments, understanding the advantages and limitations of the various models, and reporting their data. A common theme being the need to identify appropriate models, recognising both the advantages and limitations of each model system. The approaches described herein should have widespread applicability not only in basic scientific research, but also in the more applied medical and pathological research of particular diseases and tissues, including the pharmacological study of drug mechanisms and testing of new therapeutic strategies. Looking to the future, the increasing use of 'omics' technologies (e.g. genomics, transcriptomics, proteomics, and metabolomics, to name a few) and non-invasive methods offer tremendous potential for more-detailed analysis of early and late disease mechanisms in models that are the most appropriate for study of the relevant stages of the disease of interest, and help researchers follow the principles of the 3Rs (Replacement, Reduction and Refinement) [26].

We sincerely hope that this Annual Review Issue will provide new ideas for future studies in many different areas of detection, diagnosis, treatment and prevention of human disease through the use of improved models for understanding human disease.

Author contributions:

All authors contributed to the writing and editing of this introductory article.

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