Recent Advances in Pathology: the 2021 Annual Review Issue of The Journal of Path

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INTRODUCTORY ARTICLE

Recent Advances in Pathology: the 2021 Annual Review Issue of The Journal of Pathology

C Simon Herrington[1], Richard Poulsom[2], Hartmut Koeppen[3] and Philip J Coates[4]*

[1] *Edinburgh Cancer Research Centre, Institute of Genetics and Cancer, University of Edinburgh, Edinburgh, UK*
[2] *The Pathological Society of Great Britain and Ireland, London, UK*
[3] *Genentech, South San Francisco, CA, USA*
[4] *RECAMO, Masaryk Memorial Cancer Institute, Brno, Czech Republic*

**Correspondence to: PJ Coates, RECAMO, Masaryk Memorial Cancer Institute, zluty kopec 7, 656 53 Brno, Czech Republic.*
E-mail: coates_se@jpathol.org

Abstract

The 2021 Annual Review Issue of *The Journal of Pathology* contains 14 invited reviews on current research areas of particular importance in pathology. The subjects included here reflect the broad range of interests covered by the journal, including both basic and applied research fields but always with the aim of improving our understanding of human disease. This year, our reviews encompass the huge impact of the COVID-19 pandemic, the development and application of biomarkers for immune checkpoint inhibitors, recent advances in multiplexing antigen/nucleic acid detection *in situ*, the use of genomics to aid drug discovery, organoid methodologies in research, the microbiome in cancer, the role of macrophage–stroma interactions in fibrosis, and TGF-β as a driver of fibrosis in multiple pathologies. Other reviews revisit the p53 field and its lack of clinical impact to date, dissect the genetics of mitochondrial diseases, summarise the cells of origin and genetics of sarcomagenesis, provide new data on the role of TRIM28 in tumour predisposition, review our current understanding of cancer stem cell niches, and the function and regulation of p63. The reviews are authored by experts in their field from academia and industry, and provide comprehensive updates of the chosen areas, in which there has been considerable recent progress.

Keywords: 3D culture; acute respiratory distress syndrome (ARDS); angiotensin-converting enzyme 2 (ACE2); antifibrotic; atezolizumab; autoimmunity; bone; cancer; cancer predisposition; cancer progression; cancer stem cells (CSCs); cell of origin; cellular crosstalk; chromatin modification; coronavirus disease 2019 (COVID-19); CSC niche; dysbiosis; damage-associated molecular patterns; diffuse alveolar damage (DAD); direct-to-consumer; DNA damage; drug development; drug resistance; embryonic kidney development; epithelial to mesenchymal transition (EMT); endothelial to mesenchymal transition (endMT); epigenetics; extracellular matrix; gene enhancers; genetic diagnosis; genetics; genomics; GWAS; HDAC inhibitors; human genetics; idiopathic pulmonary fibrosis; IL-33; immuno-oncology; immunopathology; immunotherapy; inflammation; intratumoral microbiota; ipilimumab; KAP1; local microbiota; macrophages; MAPK; MDM2; metabolomics; microbial metabolites; microbial toxins; microbiome; mitochondrial disease; mitochondrial pathology; mTOR; microstructure; migration; mouse model; multiplex immunohistochemistry; multiplex in situ hybridization; oncogene; nephroblastoma; nivolumab; organoids; p53; p63; pathology; pathophysiology; PD-1; PD-L1; pembrolizumab; phagocytosis; polarization; polygenic risk score; precision medicine; profibrotic; proteomics; sarcoma; severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); shear stress; single cell transcriptomes; Smad; soft tissue; spatial transcriptomics; squamous cell cancer; stem cells; stiffness; stretch; TGF-β; therapeutic discovery; therapy; TIF1beta; treatment; TRIM28; tumorigenesis; tumour-infiltrating lymphocytes; tumour microenvironment; tumour suppressor; Wilms' tumour

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Conflict of interest statement: CSH is Editor-in-Chief of The Journal of Pathology, *RP is Scientific Editor of* The Journal of Pathology *and an employee of The Pathological Society of Great Britain and Ireland. PJC is Senior Editor of* The Journal of Pathology *and a co-author of one of the reviews in this issue. HK is a co-author of one of the reviews in this issue.*

Introduction

In this Introductory Article, we announce publication of the 23rd consecutive Annual Review Issue (ARI) in *The Journal of Pathology*. As always, the manuscripts contained herein are freely available online (https://onlinelibrary.wiley.com/journal/10969896). This year's ARI encompasses a wide range of areas in which there has been considerable recent progress and the articles were selected and edited by the four authors. Given the aims of the Journal to act as a translational bridge between basic biomedical science and clinical medicine, the subjects relate to advances that aid scientific understanding of fundamental disease processes, as well as reviews of more immediate clinical importance. We hope that these reviews will be useful for pathologists

and scientists alike, indeed for anyone with an interest in understanding human disease and applying this new information for diagnosis and therapy.

COVID-19

The last 12 months has been dominated worldwide by the COVID-19 pandemic, which is an ongoing problem that will last well beyond 2021. Thus, the first article in this year's collection deals with the immunopathology, pathophysiological mechanisms, and treatment options for SARS-Cov-2 infections [1]. Experts from centres in the Netherlands led by Jan Luuk Hillebrands and Harry van Goor provide an in-depth analysis of the current knowledge, revealing a complex interplay between multiple pathophysiological mechanisms. Special attention is paid to immune-mediated pathways during SARS-CoV-2 infection, which relate to innate immunity, adaptive immunity, and autoimmunity. They also review the pathological findings in tissue specimens, which have provided valuable information for understanding pathophysiology and for the development of evidence-based novel and re-purposed treatment regimens. This review can be taken alongside another recent review in the journal relating specifically to the SARS viral receptor, ACE2 [2]. Together, these articles provide an extensive assessment of the basic mechanisms of viral entry and spread, the pathogenesis of viral disease, and potential avenues for treating and/or preventing disease.

Cell communication and tissue microenvironments

The second review in this issue comes from González-Sánchez and DeNicola, who take on the increasingly recognised area of the influence of the microbiome in cancer [3]. They examine how different tissue microbiomes influence cancer initiation, progression and response to therapy through the generation of toxins, creation of pro- or anti-inflammatory environments and by modulating nutrient levels. Microbiome effects can be either systemic, mainly from gut microbiota, or locally-derived from the tumour microbiota. Thus, the microbiome has multiple types and multiple roles in cancer and represents a major under-developed area of research. The third review, from Barbro Melgert, Janette Burgess *et al*, investigates the roles of macrophages in fibrosis, underlining their influences during this process. The authors provide a thorough review of the biochemical, biophysical and cellular processes involved in stromal-macrophage interactions and how these influence fibrosis and fibrotic disease. They also discuss the potential for this knowledge to be applied for selective targeting of these interactions in therapy [4]. Another area important in fibrosis in health and disease is the role of TGF-β, the major profibrotic cytokine. The article by Rik Derynck *et al* [5] focuses on the roles of increased TGF-β activities and the underlying signalling mechanisms in activated fibroblasts and other cell types during fibrosis. As a universal driver of fibrosis, therapeutics that interfere with TGF-β signalling are showing promise in pre-clinical and clinical trials. The next article in this section deals with the ongoing issue of tumour immune blockade, an area full of controversies. Mark Kockx *et al* from CellCarta and Genentech provide their perspective of the microenvironment in cancer and how this influences adaptive anti-tumour immunity, the response to immune checkpoint inhibitor therapy and the ability to predict clinical outcome. While our understanding of this highly complex environment remains incomplete, it is an area of very active investigation; progress will facilitate design of novel clinical modalities and rational approaches for companion diagnostic development [6]. We also include a timely review on the cancer stem cell concept, focussing on the role of cellular interactions that define the cancer stem cell niche [7]. This niche is composed of a specialised tumour microenvironment that maintains tumour growth and may play roles in the therapeutic resistance of cancer stem cell populations. Oshimori, Guo and Taniguchi review the broad aspects of tumour microenvironments and focus on a novel niche signalling pathway involving IL-33 and TGF-β in squamous carcinoma, with the attendant implications for therapeutic interventions [7].

Advances in methodologies and technologies

Advances in medical research are underpinned by the development of new and improved approaches to answer questions and this year we have three reviews on very different aspects of emerging and improving technologies. First is a consideration of organoids and their use for both basic research and their potential use for therapy testing for personalised, tumour specific, medicine [8]. Laura Wood and Andrew Ewald include a definition of organoids distinct from other 3-D culture approaches, a summary of the advances made so far, and their perspective on the future of these methodologies. They also include a valuable section on how to introduce organoid cultures into the workplace for newcomers to this specific field. The second review in this section deals with multiplexing of immunohistochemistry and *in situ* hybridization. This is another area that is rapidly evolving with the introduction of improved methods and detection equipment and can allow in-depth proteomic and transcriptomic analyses at single cell resolution whilst maintaining spatial information. James Ziai *et al* provide an update on the state-of-the-art technical features, discussing the advantages and limitations of the platforms currently available for multiplexed immunohistochemistry and spatial transcriptomics [9]. The use of genomics to aid therapeutics is the final area considered in this section, where Xin Wang *et al* consider the use of genomics to advance drug discovery [10]. They review the history and principles behind using human genetics to accelerate drug discovery, using specific examples as illustration. They also discuss how polygenic risk scores may improve drug efficacy in personalised medicine

and highlight the added value of direct-to-consumer platforms. The review leaves no doubt that the current era of big data biotechnology with large-scale genetic and health data will lead to significant societal benefits.

Advances in mitochondrial diseases

Mitochondria are well-known for their roles in metabolism, particularly oxidative respiration and the production of ATP, although they are also involved in other metabolic pathways. Mitochondrial diseases can occur through mutations in either mitochondrial-encoded genes or in nuclear-encoded genes (about 10% of the nuclear genome codes for mitochondrial proteins). Charlotte Alston *et al* review the spectrum of human mitochondrial diseases and their genetic causes. They discuss how next generation sequencing of minimally-invasive blood samples has revolutionised diagnosis, but situations exist where there is insufficient evidence for pathogenicity, requiring a multi-omics approach to assess genomic, transcriptomic, proteomic and metabolomic profiles of affected tissues [11]. These studies of patient tissue samples will be vital to understand the molecular mechanisms underlying mitochondrial pathologies.

Advances in cancer research

The tumour suppressor protein, p53, has a long history of intensive research and *TP53* is the most commonly mutated gene in human malignancies. Despite this, analysis of p53 has not provided significant clinical benefit for diagnosis, prognosis, or treatment. Robin Fahraeus *et al* review the current state of knowledge, highlighting examples of previous studies that have driven people's thinking on p53 and its regulation by MDM2, with attendant implications for therapy. By re-considering the interpretation of such data, they discuss how the resulting dogmas may have hindered the clinical application of this major cancer pathway. Thus, the p53 field and science in general must beware entrenched views – to paraphrase them, we need to see if 'an old dogma can be taught a new trick' – and critical re-evaluation must be the cornerstone of scientific endeavour if we are to achieve clinical success [12]. Our next review covers the p53-family member, p63, that exists as TAp63 and ΔNp63 variants. Discovering the functions of ΔNp63 in epithelial cell development, stem cell maintenance and squamous differentiation led to the clinical application of p63 and ΔNp63 (also called p40 in pathology) in cancer diagnosis. Pokorná *et al* [13] discuss how p63 variants are themselves regulated, which has been relatively neglected. The review highlights numerous inconsistencies in the literature, suggesting complex cell-specific regulatory pathways including epigenetics, multiple gene enhancers and post-translational modifications. Consideration of these provides potential therapeutic approaches for carcinomas that overexpress ΔNp63 and haemopoietic malignancies that overexpress TAp63, a poorly understood and under-researched area. The 13th review in this issue is concerned with current knowledge of the cells of origin and the genetics of sarcomas. Kevin Jones *et al* provide a *tour de force* of this area, highlighting the steady development of knowledge of these disparate tumour types, with an insightful consideration of how these discoveries were dictated to some extent by the changing technologies that became available over time. Thus, the review serves not only as a detailed source of contemporary knowledge of sarcomagenesis, diagnoses and treatments, but also a broader consideration of the ever evolving approaches to cancer research and medical sciences [14]. Last, but by no means least in this years' ARI is a summary of recent advances on *TRIM28*, a predisposition gene for Wilms' tumour. Roland Kuiper *et al* review the roles of *TRIM28* as a tumour suppressor gene. TRIM28 is a ubiquitously expressed protein that cooperates with tissues-specific factors to act as a transcriptional co-repressor and influences transposable elements. Research in this area allows both the targeted analysis of individual patients/families and provides additional information into the underlying pathway disruptions that lead to Wilms' tumour development [15].

Author contributions statement

All authors were involved in writing and editing the manuscript. All authors approved the final manuscript for publication.

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