

Viruses and disease: emerging concepts for prevention, diagnosis and treatment

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Abstract

Viruses cause a wide range of human diseases, ranging from acute self-resolving conditions to acute fatal diseases. Effects that arise long after the primary infection can also increase the propensity for chronic conditions or lead to the development of cancer. Recent advances in the fields of virology and pathology have been fundamental in improving our understanding of viral pathogenesis, in providing improved vaccination strategies and in developing newer, more effective treatments for patients worldwide. The reviews assembled here focus on the interface between virology and pathology and encompass aspects of both the clinical pathology of viral disease and the underlying disease mechanisms. Articles on emerging diseases caused by Ebola virus, Marburg virus, coronaviruses such as SARS and MERS, Nipah virus and noroviruses are followed by reviews of enteroviruses, HIV infection, measles, mumps, human respiratory syncytial virus (RSV), influenza, cytomegalovirus (CMV) and varicella zoster virus (VZV). The issue concludes with a series of articles reviewing the relationship between viruses and cancer, including the role played by Epstein–Barr virus (EBV) in the pathogenesis of lymphoma and carcinoma; how human papillomaviruses (HPVs) are involved in the development of skin cancer; the involvement of hepatitis B virus infection in hepatocellular carcinoma; and the mechanisms by which Kaposi's sarcoma-associated herpesvirus (KSHV) leads to Kaposi's sarcoma. We hope that this collection of articles will be of interest to a wide range of scientists and clinicians at a time when there is a renaissance in the appreciation of the power of pathology as virologists dissect the processes of disease.

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In this, the seventeenth Annual Review Issue of the *Journal of Pathology*, we have collected together a series of 19 review articles that each deal with an aspect of 'Viruses and disease'. Study of the relationships between a viral infection and the host are critical, not only for enhancing our knowledge of known viral diseases but also for understanding how viruses may be involved in diseases of unknown aetiology [1], and for attempting to predict how viruses emerge from animals to infect humans [2]. As in many other arenas, pathology plays a vital part in improving our understanding of the mechanisms by which viruses cause disease. Pathological assessment sheds light on the ways viruses interact with cells and tissues, spread within and transmit between hosts. The eventual pathological outcomes are a complex interplay between the host response to, and the direct effects of, the virus infection. In keeping with these considerations, this issue contains articles that address the roles that cell and tissue biology and pathology are playing in the

elucidation of the mechanisms of virus-associated diseases.

Emerging viral diseases

In 2015, the subject area of viruses and disease is particularly pertinent, since we live at a time when viruses are regularly in the news. This is exemplified by the ongoing outbreak of Ebola virus in West Africa and, at the time of writing, the importation of infections into Europe and the USA. Such events act as timely reminders of the potential for viruses to cause global disease and it is fitting that our first article deals with filoviruses. Zaki and colleagues have produced a *tour de force*, describing what Ebola and Marburg viruses are and how and why they are so highly pathogenic in humans. As two of the most virulent human pathogens yet discovered, this review presents what is currently known about filovirus epidemiology, modes of transmission, entry and spread,

and the complex way in which these viruses induce disease through multiple effects on the immune system and endothelium [3]. In the first of two reviews on coronaviruses, Grolinski and Baric discuss the importance of the innate immune response in the development of lung pathology following human coronavirus infection, whilst van den Brand, Smits and Haagmans review the available clinical and pathological data on Middle East respiratory syndrome (MERS) in comparison to severe acute respiratory syndrome (SARS), and how these inform our understanding of both the different pathological effects of these viruses and their responses to interferon-based therapies [4,5]. Staying with the theme of emerging infectious diseases and viral zoonoses, de Wit and Munster review the pathogenesis of encephalitis and vasculitis caused by the outbreaks of Nipah virus. They focus on dissemination of the virus through its host, current knowledge of the determinants of pathogenicity and the routes of zoonotic and human-to-human transmission, emphasizing the key role played by animal models in advancing our understanding of this virus and the diseases it causes [6]. Karst *et al* review the molecular pathology of norovirus (the cause of 'winter vomiting disease'), one of the main causes of acute gastroenteritis, but also now appreciated as causing chronic effects and extra-intestinal spread [7].

Advances in the viral pathology of well-known infectious diseases

Muehlenbachs *et al* provide a comprehensive review of the enteroviruses, including their diverse pathological effects and how histopathology, immunohistochemistry and molecular studies have provided insight into tissue tropism and viral pathogenesis [8]. Similarly, Lucas and Nelson combine to provide an equally comprehensive review of the diversity of diseases associated with human immunodeficiency virus (HIV)-1 infection, including discussing the additional problems that are likely to be encountered as successfully treated HIV-infected individuals age [9].

Mumps and measles are two of the oldest-recognized infectious diseases and have been the subjects of intensive worldwide vaccination programmes. It has been suggested that it may be possible to eradicate measles virus (MV), and even though this is probably not feasible for mumps virus (MuV), huge advances in reducing the disease burden have been achieved for both. Despite these successes, these viruses continue to cause human disease in both the developing and the developed world. Rubin *et al* have combined their expertise to review the renewed interest in mumps pathogenesis arising from the resurgence of this disease in the highly vaccinated populations in Europe and the USA. They emphasize the need to develop clinically-relevant animal models of disease, which are necessary to ensure that

unsafe vaccines are not licensed [10]. In addition, Ludlow *et al* provide an up-to-date review of measles pathogenesis. They highlight how recent advances in understanding virus-receptor usage explains why the virus infects both epithelial and immune cells and how the inter-related, and opposing, effects of these two distinct tissue tropisms modulate disease [11]. These reviews are followed by articles that provide an in-depth analysis of human respiratory syncytial virus (RSV) and influenza. In the first of these, Pickles and DeVincenzo review the pathogenesis of bronchiolitis caused by RSV, with a particular emphasis on the cytopathological effects of viral infection on columnar cells, leading to the pathological sequelae of bronchiolar obstruction and inflammation [12]. The review on influenza by Kuiken *et al* discusses how the olfactory system acts as an important conduit for virus spread to the central nervous system. Using data from human and animal infections, they provide compelling evidence that many viruses use this route and discuss current understanding of the molecular mechanisms involved [13].

The next two articles are dedicated to the diseases associated with the human herpes viruses cytomegalovirus (CMV) and varicella zoster virus (VZV), each of which infects the majority of humans in the world and establish lifelong, latent infections. In their review of CMV, Griffiths *et al* discuss how epidemiology, and molecular and cellular pathology, account for the variable clinical aspects of CMV-associated disease and how the host immune responses designed to control the virus contribute to immune impairment [14]. In their review of varicelloviruses, Ouwendijk and Verjans include an up-to-date analysis of both human and animal infections. These studies, using an excellent animal model of disease and targeted pathology approaches driven by macroscopic imaging, have been highly informative in progressing our understanding of the pathogenesis of varicella and herpes zoster in terms of primary infection, latency and reactivation [15].

Viruses associated with cancer

The idea that viruses can cause cancer is more than a century old [16] and it is now well recognized that a number are responsible for human cancer [17]. In this Annual Review Issue, we have six articles that provide updates on the mechanisms involved in virus-induced cancers and the potential for targeting these viruses therapeutically. There are three reviews on Epstein-Barr virus (EBV). The first article, from Vockerodt *et al*, reviews recent insights into the mechanisms of EBV-associated lymphoma development [18], whilst Lo and colleagues re-evaluate the mechanisms by which EBV causes epithelial malignancies [19]. Fåhraeus *et al* provide an update on the mechanisms through which EBV establishes latency without evoking immune responses, and how these processes might be

exploited as targeted therapy for EBV-associated malignancies [20]. Feltkamp *et al* provide a comprehensive review of the role played by β -human papillomaviruses (HPVs) in human basal and squamous carcinomas of the skin, and their synergy with immunosuppression and exposure to UV radiation [20], contrasting with the more well-defined relationship between α -HPV types and cervical and other squamous cancers. Ringelhan *et al* provide a timely update on the role of chronic hepatitis B virus infection in the pathogenesis of hepatocellular carcinoma (HCC), which involves both direct effects of viral gene expression and indirect effects of infection [22]. Finally, but by no means least, Gramolelli and Schultz discuss recent advances in identifying and understanding the mechanisms by which Kaposi's sarcoma-associated virus causes the unusual vascular tumour after which it is named, with an in-depth discussion of the viral proteins that are responsible [23].

Perspective

These articles not only provide a comprehensive view of how viruses cause disease but also demonstrate the critical role that pathology plays in this field [24]. Recently there has been a true renaissance in appreciating the power of sound observations, where pathology is not 'just descriptive' but rather is the bedrock for meaningful hypothesis-driven research. This illustrates the unique opportunities for virologists and pathologists interested in dissecting the molecular mechanisms of viral disease to work together, develop partnerships and drive the field forward. Such studies will help extend our understanding of virus transmission from animals to humans and from humans to humans. The need to understand transmission fully is exemplified by the current Ebola virus outbreak in West Africa. Moreover, the development of animal models that can be used to test novel vaccines and antivirals is vital. Only by understanding how these interventions modulate the resulting disease, through the involvement of pathologists, can basic scientists know their translational goals are closer. We hope that these contributions demonstrate that this is the case not only for the cancer-associated viruses, where the interface with pathology is more widely appreciated, but also for the more classical infectious diseases, for which tissue-based studies can also provide essential information in the context of 'real' disease. Going forward, the increasing availability and use of 'omics' technologies in virology [25–27] has tremendous potential for rapidly identifying new viruses and their host interactions, including immune responses. Nevertheless, in this new era, pathology will continue to be a vital component of identifying the true relationships between viruses and human disease, and we hope that this Annual Review Issue will serve as a blueprint for future studies in the diagnosis, treatment and prevention of virus-related conditions through an improved understanding of the processes involved.

Author contributions

All authors contributed to writing the manuscript.

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