

Preface

A relationship between viruses and neoplasia has been suspected ever since the turn of the 20th century, when Ellerman and Bang, followed by Rous, showed that cell-free extracts of a chicken leukemia and sarcoma, respectively, induced the same disease upon inoculation into healthy chickens (Chapter 1). These observations eventually led to the unequivocal demonstration that several viruses of different families can cause malignancies in animals. The hunt was thus on, to search for similar viruses that may cause human cancers. Initially, the biomedical community was disappointed by the lack of positive results, until Epstein, Achong, and Barr demonstrated that Burkitt's lymphoma cells cultured *in vitro* contained a herpesvirus, subsequently named the Epstein-Barr virus. However, the ubiquity of this virus meant that the possibility of its merely being a "passenger" in the lymphoma cells could not be ruled out. The situation changed dramatically with the seminal epidemiological work of Beasley and colleagues, showing that hepatitis B virus infection in men was associated with a dramatic increase in risk of primary liver cancer in Taiwan; this association has since been proven to be causal (Chapter 2). More recently, hepatitis C virus, an entirely unrelated virus, has also been shown to cause liver cancer (Chapter 3). Similarly, the Nobel Prize-winning work of zur Hausen and colleagues revealed that certain types of human papillomaviruses cause cancers of the uterine cervix and other epithelial tissues, such as the oropharynx (Chapter 4). Indeed, the National Institute of Environmental Health and Safety (<http://ntp.niehs.nih.gov/ntp/roc/toc11.html>) lists these viruses as known human carcinogens. Human oncogenic viruses

are not limited to these three, however. Two γ -herpesviruses, the above-mentioned Epstein-Barr virus and the Kaposi's sarcoma herpes virus (also known as human herpesviruses 4 and 8, respectively), cause lymphoid as well as non-lymphoid neoplasms (epithelial cancers for the former, endothelial tumors for the latter) (Chapters 5 and 6, respectively). Finally, the human retrovirus human T-cell leukemia virus I, a distant relative of the Rous sarcoma virus, gives rise to leukemia (Chapter 7). Undoubtedly, additional viruses that cause human malignancies will be discovered or confirmed in the future, with members of the polyomaviruses being the most likely candidates (Chapter 1).

It has been estimated that each year approximately 1.3 million people develop malignancies caused by these viruses (D. M. Parkin, 2006. *Int J Cancer* **118**: 3030–3044). The majority of them (up to 1 million people) will die from their cancers. This number does not include death from other diseases caused by these viruses (e.g. cirrhosis in chronic hepatitis B or C), nor does it account for the lost productivity from chronic illness and the cost of medical treatment. These viruses clearly represent an extraordinary burden on global human health as well as an enormous drag on economic resources. This book aims to give a concise yet comprehensive and up-to-date view of these viruses. The reader will see that in addition to the expected differences among these disparate viruses, there are commonalities as well. One is that, unlike the case for Rous sarcoma virus and similar oncoretroviruses, a long latency period of chronic infection prior to neoplastic transformation is the rule. Thus, secondary genetic and/or epigenetic changes in the host genome, in addition to mutations in the viral genome, are likely critical for oncogenesis. Another similarity is that only a minority of people infected by each of the viruses develop neoplasia, implying the importance of co-factors, both environmental and genetic. Perhaps the most striking similarity is that each virus appears to have multiple independent mechanisms that can contribute to oncogenesis, ranging from dysregulation of cell growth and loss of genomic integrity to induction of inflammation, cell injury, and regeneration. Thus, it is unlikely that a single “magic bullet” can block malignant transformation of an infected cell, and

the best “therapy” for virus-associated cancers is to prevent infection in the first place. This goal has been achieved for hepatitis B virus and the most common oncogenic human papillomaviruses, with the development of effective vaccines. Unfortunately, many of the populations most at risk of being infected by these viruses cannot obtain the vaccines, mostly for economic reasons. In any case, large numbers of people in the world are already infected. Therefore, the neoplasms caused by these viruses, as well as the other viruses presented in this book, will unfortunately afflict humankind for many more decades to come. Thus, the importance of understanding these viruses and their pathogenesis cannot be overstated. It is hoped that readers of this book will be inspired to continue the ground-breaking research described herein and develop new, more effective treatments for these viruses and the cancers that they cause.

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