# Preface: virus-associated lymphomas

Seven human viruses are associated with approximately 12–20% of all human cancers, comprising a diverse range of epithelial, endothelial, Merkel cell, smooth muscle and hepatocellular carcinomas. Notably, four of these viruses (Epstein Barr virus, Kaposi sarcoma-associated herpesvirus, Human T-lymphotropic virus-1 and Hepatitis C virus) have well documented causal associations with a heterogeneous array of lymphomas arising from multiple lymphocyte subsets. The first human cancer to be documented with a viral aetiology was endemic Burkitt lymphoma (eBL). Discovered in eBL tumour tissue in 1964, Epstein Barr virus was shown to have a near 100% association with eBL. This transpired to be the first of an unexpectedly wide range of associations discovered between this virus and tumours, including a spectrum of B cell, T cell and NK cell lymphomas. Since this seminal discovery it has become apparent that, although these oncogenic viruses each have distinct lymphotropism, lymphomas only develop in a small minority of infected individuals. Thus, it is clear that other co-factors, particularly disruption of antiviral immunity, are likely to be implicated in the initial stages of lymphomagenesis.

Increasingly sophisticated research techniques have afforded an enhanced understanding of how each of these oncogenic viruses contribute to lymphoma pathophysiology. Next generation sequencing has enabled us to identify common somatic mutations and changes in gene transcriptional regulation. Indeed, for many lymphomas, such analyses have characterised an inverse correlation between virus-driven cellular epigenetic changes and somatic mutation, whereby the viruses provide a distinct function that substitute for the cellular genetic changes. Although many somatic mutations observed are common to different lymphomas, it appears that virus-associated lymphomagenesis may be predominantly mediated through epigenetic changes rather than virus-induced mutation.

Whilst this new wealth of information has not yet translated into the development of new and effective targeted therapies, our understanding of the genetic and epigenetic landscapes of lymphomas has led to the realisation that virus-associated lymphomas should be considered as distinct clinical entities to their virus-negative counterparts with potentially different therapeutic vulnerabilities. Furthermore, as focus has shifted from treating the virus infection to treating the lymphoma, a deeper understanding how the virus contributes to these therapeutic vulnerabilities is of paramount importance.

Arguably, the most important therapeutic advances for lymphomas in recent years have involved approaches that harness the patient's own immune system to augment tumour control or cure. Such approaches include: targeting lineage-specific surface molecules (for example CD20, CD79b and CD19) with monoclonal antibodies to augment both complement-mediated and cellular cytotoxicity; bi-specific antibodies, to directly engage autologous T cells with the malignant B cells; and genetically modified autologous chimeric antigen receptor (CAR) T cell therapies to target CD19. A further immunotherapeutic paradigm, with more limited success in lymphoma therapy to-date, are the so-called 'checkpoint inhibitors' aimed at disrupting specific immune-evasion mechanisms such as PD-1 and PD-L1.

Whilst these immunotherapeutic approaches have proven beneficial for many B cell lymphomas, adoptive T cell therapies have been particularly successful when targeting the EBV-associated lymphomas arising in immunosuppressed patients post-transplant (PTLD). The success of this approach is largely due to the expression of the highly immunogenic viral latency proteins in PTLD and has led to numerous studies to evaluate the adoptive transfer of EBV-specific T cells to other, less immunogenic, EBV-associated lymphomas. Importantly, the lessons learnt from this research highlights the need to precisely map the targets to ensure the target-specific CTLs are present in sufficient numbers. Together with the advent of T cell receptor cloning, this approach should enable the production of sufficient numbers of CTLs with the desired sensitivity and specificity in order to target the less immunogenic virus-associated lymphomas. There is a clear clinical need and developmental path towards delivery of virus-specific arm within the burgeoning immunotherapy repertoire.

This unique review series has been assimilated to summarise discoveries and developments in what constitutes a large and complex area of lymphoma biology and therapy. This series of scientific and clinical manuscripts, written by international experts in their respective fields, allow us to reflect upon how studies of virus-associated lymphomas have contributed substantially to our understanding of lymphoma pathogenesis and design of novel therapeutic strategies across the spectrum of lymphomas. The innate complexity and heterogeneity of virus-associated lymphomas has meant any successes have been hard won, yet many challenges remain particularly in the ultra-rare disease areas and for those patients with chemotherapy-resistant disease.

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