Chinese Journal of Cancer

Editorial

Epstein-Barr virus at 50—future perspectives

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Abstract

The special November and December issues of the *Chinese Journal of Cancer* celebrate the 50th anniversary of the discovery of Epstein-Barr virus (EBV) with a series of reviews covering the association of the virus with various cancers, with special emphasis on the role of EBV in the pathogenesis of nasopharyngeal cancer (NPC). The restricted geographic prevalence of NPC along with the tumor's consistent association with EBV infection has fascinated scientists and clinicians ever since it was first suggested in 1966. As in all cancers, NPC development reflects the complex interplay between host genes and environmental factors, but the essential role of EBV infection provides important insight into the etiology of this tumor. Indeed, it is this understanding that is now translating into exciting diagnostic and therapeutic opportunities.

Key words Epstein-Barr virus, carcinoma, virus, cancer

This year marks the 50th anniversary of the discovery of Epstein-Barr virus (EBV), the first human tumor virus to be identified. EBV was first visualized on electron micrographs of cells cultured from Burkitt's lymphoma, a tumor common in sub-Saharan Africa where its unusual geographic distribution had suggested a novel environmental etiology, such as a viral infection. Far from being an infection with a restricted distribution, EBV—a gamma herpesvirus—was found to be widespread in all human populations, in which it exploits normal physiologic processes to colonize the B-lymphocyte pool, persisting as a lifelong, asymptomatic infection. EBV has subsequently been found to be associated with a diverse wide range of tumors of both lymphoid and epithelial origins. Progress in the molecular analysis of EBV has revealed fundamental mechanisms of more general relevance to the oncogenic process.

The special November and December issues of the *Chinese Journal of Cancer* celebrate EBV's 50th anniversary with an array of reviews from eminent researchers. While not ignoring the importance of EBV's role in the development of B-cell-derived tumors (see reviews by Rowe *et al*.[1] and Vockerodt *et al*.[2]), the November and December issues unashamedly focus on the virus's most consistent cancer association—that with nasopharyngeal carcinoma (NPC) (see review by Young *et al*.[3]). This is not only because of the obvious importance of this tumor in China but also reflects the progress that has been made in our understanding of the role of EBV infection in the pathogenesis of NPC and how this is now translating into exciting approaches to tumor diagnosis and treatment.

So, what about the next 50 years? Where should our research efforts be focused, and what are the major challenges?

We still know little about the replicative life cycle of EBV *in vivo*, particularly with regard to the relative role played by B cells versus epithelial cells in this process. The impact of EBV infection on the development of NPC and EBV-associated gastric cancer (EBVaGC) may be a consequence of the aberrant establishment of virus latency in epithelial cells that have already undergone pre-malignant genetic changes (see the review by Tsang *et al*.[4]). Understanding the genetic and epigenetic landscape of NPC has already been providing important insight into the pathogenesis of NPC and the role that EBV infection plays in influencing the host cell environment (see reviews by Lung *et al*.[5] and Li *et al*.[6]). The development of more efficient *in vitro* systems for studying EBV infection and replication in different cell types is helping to unravel the complex interplay between the virus and the host cell. Furthermore, the use of EBV recombinants continues to shed light on the role of latent genes in the transformation process, on the requirements for the efficient production of progeny virus, and on the role of membrane glycoproteins in the infection process (see the review by Chesnokova *et al*.[7]). These approaches will also facilitate our understanding of the role of microRNAs in the development and progression of NPC and how these might be exploited in the clinical context (see the review by Bruce *et al*.[8]). In addition, new high-throughput sequencing technologies are beginning to shed light on the contribution of EBV strain variation to the development of virus-associated

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doi: 10.5732/cjc.014.10208

cancers. Although this has been a long-standing question, these new approaches allow for appropriate comparisons and will drive exciting *in vitro* studies that are likely to have a significant impact on our understanding of the natural history of EBV infection and its association with various diseases. Nonetheless, an understanding of the host cell-virus interaction is imperative and will be dependent on the generation of appropriate *in vitro* and *in vivo* models, particularly systems that allow a more detailed understanding of the contribution of the tumor microenvironment and of cancer stem-like cells (see the review by Lun *et al*.[9]).

Regardless of the precise role of EBV in the carcinogenic process, there is clearly the opportunity to exploit this association for the clinical benefit of patients. EBV is the ultimate biomarker, and the routine application of serum testing for virus DNA will not only provide invaluable prognostic information for NPC patients but also facilitate the implementation of mass screening programs to identify patients in the early stages of NPC (see the review by Chan[10]). This approach will be further enhanced by the development of additional adjunctive tests (e.g., EBV microRNAs). Novel therapeutic approaches using targeted drugs, gene therapy, or therapeutic vaccination are currently being evaluated and well predict our ability to effectively target the clinically challenging aspects of locally recurrent and metastatic disease. Alongside these therapies, the advent of personalized medicine raises the possibility of using molecular classification to subdivide NPC and EBVaGC and thereby improve patient management and outcomes. Our growing understanding of EBV-associated oncogenesis provides paradigms for the development of targeted cancer therapies and diagnostics and further confirms the far-reaching value of tumor virology to the entire cancer field.

I hope that you enjoy the special November and December issues of the *Chinese Journal of Cancer* and that it gives you a sense of how far we have come over the last 50 years since EBV was discovered. While I am sure that the next 50 years will be just as exciting, the translation of our knowledge into tangible benefits for patients is the most challenging yet offers the greatest reward.

Received: 2014-10-08; accepted: 2014-10-11.

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