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EDITORIAL

EBV and human cancer

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Epstein–Barr virus (EBV) was the first virus shown to cause cancer in humans and is associated with a wide range of human cancers originating from epithelial cells, lymphocytes and mesenchymal cells. EBV-associated neoplasms affect both immune-competent hosts and immune-compromized patients who have received an organ transplant or who exhibit iatrogenic immune suppression. The development of an EBV-associated neoplasm is largely dependent on environmental factors and genetic susceptibility to viral infection that is associated with genetically prone immune deregulation.[1]

EBV leads to the extensive methylation of both the host and viral genome, and these changes facilitate cellular functions that promote viral persistence and propagation.[2] EBV-positive neoplasms exhibit genetic alterations that are distinct from those exhibited by EBV-negative neoplasms. For example, EBV-positive gastric adenocarcinoma displays recurrent PIK3CA mutations, extreme DNA hypermethylation, and amplification of JAK2, CD274 and PDCD1LG2.[3] Meanwhile, endemic Burkitt lymphoma is associated with lower frequencies of ID3 and TCF3 mutations compared with sporadic Burkitt lymphoma and shows strong evidence of chronic antigenic stimulation.[4,5]

Last year was the 50th anniversary of the discovery by Michael Anthony Epstein and Yvonne Barr of EBV particles in cell lines cultured from tumor tissue from a Burkitt lymphoma.[6] As the initial discovery of the virus, $>20\,000$ scientific papers on the characteristics, functions and oncogenic mechanisms of viral genes, the spectrum of EBV-associated diseases and the treatment of patients have been published. To provide an overview of our current understanding of Epstein–Barr virology and oncogenesis and of EBV-associated neoplasm, for this special feature on EBV and Human Cancer, authors were invited to submit six review articles, entitled 'Epstein–Barr virus latent genes,' 'EBV-driven B-cell lymphoproliferative disorders,' 'Epstein–Barr virus-positive T/NK cell lymphoproliferative disorders,' 'Genomic assays for Epstein–Barr virus-positive gastric adenocarcinoma,' 'Modeling EBV infection and pathogenesis in new-generation humanized mice' and 'Epstein Barr virus-associated lymphoproliferative diseases: the virus as a therapeutic target.'

Understanding the role of EBV latent genes is essential for identifying the mechanism underlying EBV-induced cell transformation and immune evasion, although lytic EBV reactivation also contributes to the development of EBV-associated neoplasm.[7] Myong-Soo Kang is a molecular biologist and virologist at Sungkyunkwan University School of Medicine, Seoul, Korea, whose previous work on EBV latent genes identified the mechanism of EBV LMP1-induced NF-κB activation.[8] This review discusses the roles of latent EBV genes and the miRNAs whose functions are known.

EBV is associated with a subset of Hodgkin's lymphoma, a subset of diffuse large B-cell lymphoma (DLBCL), and endemic Burkitt lymphoma. In addition to EBV-associated malignant B-cell lymphoma, age-related EBV-positive B-lymphoproliferative diseases (LPDs), which pathologically span from reactive hyperplasia to monomorphous lymphoma, have been recently recognized.[9,10] Ken H Young is a hematopathologist at The University of Texas MD Anderson Cancer Center, Houston, TX, USA. His studies showed that EBV-positive DLBCL exhibited rare genetic alterations. However, similar to other EBV-positive LPDs, EBV-positive DLBCL more frequently expressed NF-κB p50, phosphorylated STAT-3 and CD30 compared with EBV-negative DLBCL.[11–13] Here, Ken H Young and his colleague review the current understanding of EBV-induced lymphomagenesis, with a focus on the biology, diagnosis and management of EBV-associated B-cell LPD.

EBV-positive T-cell and natural killer (NK)-cell LPDs comprize several disease entities with a broad clinicopathological spectrum. Aggressive NK-cell leukemia and extranodal NK-/T-cell lymphoma are recognized as the prototypes of EBV-positive T- or NK-cell leukemia/lymphoma, respectively. Chronic active EBV infection (CAEBV), hydroa-like T-/NK-cell LPD, and severe mosquito bite allergy are peculiar forms of EBV-associated systemic or cutaneous T-/NK-cell LPDs. These diseases have various clinical findings that range from indolent to aggressive and varying degrees of cellular transformation, which depend on the host's immunity, as well as viral factors.[14,15] The development of EBV-positive T- and NK-cell LPDs is closely associated with ethnicity and occurs more frequently in Asia and Latin America than in North America and Europe.[16,17] Qingqing Cai is a medical oncologist at Sun

Yat-sen University Cancer Center, Guangzhou, China. Here, he and his colleagues review the current knowledge about the genetics, oncogenesis, biology, diagnosis and treatment of EBV-associated T-/NK-cell LPDs.

Nasopharyngeal carcinoma and gastric adenocarcinoma are representative epithelial malignancies associated with EBV. Approximately 9% of gastric carcinomas have EBV in the tumor cells.[18] A unique feature of EBV-positive gastric carcinoma is extreme CpG island hypermethylation, including both promoter and nonpromoter CpG islands of the human genome.[19,20] Margaret L Gulley is a pathologist at the University of North Carolina whose work includes molecular assays of EBV in human samples, EBV carcinogenesis and EBV-positive gastric carcinoma.[21–24] Her article describes the characteristics of EBV-positive gastric carcinoma, the current state of the development of genomic assays to detect gastric cancer, and the opportunities to capitalize on EBV and its effectors as targets for therapy.

EBV infects only humans in nature and a limited number of animal species under experimental conditions. Humanized mice can serve as infection models for human-specific viruses that target cells of the immune system, such as EBV. NOD/Shi-scid/IL-2Rγ^{null} (NOG) is a highly immunodeficient mouse strain that, after transplantation with cord blood hematopoietic stem cells (HSCs), is able to reconstitute most major components of the hematolymphoid system, including T cells, B cells, NK cells, macrophages and dendritic cells.[25] These properties make the NOG mouse an excellent model of human virus infections that target the immune system. Shigeyoshi Fujiwara, a pediatrician and virologist at the National Research Institute for Child Health and Development, Japan, has used the NOG mouse to develop models of asymptomatic persistent EBV infection, EBV-positive B-cell LPD and erosive arthritis resembling rheumatoid arthritis and has investigated the EBV-specific immune response.[26–28] Mouse xenografts using the NOG mouse develop CAEBV and hemophagocytic syndrome,[29] which occur more frequently in children in Asia and Latin America than in other regions. Fujiwara's review discusses recent findings on the recapitulation of human EBV infection and pathogenesis in these mouse models, as well as the application of this knowledge to preclinical studies of experimental anti-EBV therapies.

The final article discusses the therapeutic approach to EBV-associated LPDs. The clinical impact of EBV infection in cancer cells differs according to the tumor type. In Hodgkin's lymphoma and EBV-positive DLBCL, the prognosis is poor in elderly patients but not in younger patients.[30,31] EBV-positive T- and NK-cell leukemia is an aggressive disease that is resistant to the usual chemotherapy,[32] but the development of L-asparaginase-containing regimens, together with allogeneic HSC transplantation, has led to reasonable improvements in survival.[33] Yok-Lam Kwong, a hematologist and medical oncologist at Queen Mary Hospital, Hong Kong, reviews the conventional approach to EBV-positive LPDs and the treatment strategies to target EBV.

Accumulating scientific data have led to substantial improvement in our understanding of the oncogenic mechanisms responsible for EBV-associated cancer. Future directions for EBV research include identifying the mechanisms responsible for the cellular immune control of EBV infection, the genetic and epigenetic control of the cell pathways involved in viral persistence and cellular transformation, and the discovery of new therapeutic targets. New technologies, such as deep sequencing with systems biological analysis, are expected to hasten EBV research and biomarker detection.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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