

Preface: Epstein–Barr Virus and Oncogenesis

On the golden jubilee of the discovery of the virus of Sir Michael Anthony Epstein, Bert Geoffrey Achong, and Yvonne Barr, a PubMed search retrieved almost 31,000 peer-reviewed publications.^{1,2} In December 2019, the year of the 55th anniversary, more than 38,000 publications had been published, an impressive increase of about 22.5% in only 5 years, highlighting the importance and relevance of the field. The Epstein–Barr virus (EBV) was the first human oncovirus discovered. This event sparked remarkable progress in the knowledge of human tumor etiology and the existence of tumor-inducing viruses, as well as paved the way for additional breakthroughs in basic and clinical virology.

In the early 1960s, Dr. Epstein, while working at Middlesex Hospital Medical School in London, attended a lecture by Dr. Denis Parsons Burkitt, a British surgeon who worked in Uganda. In his lecture, Burkitt described an unusual type of malignant tumor affecting children and highlighted the bizarre anatomical location and its fatal progression within a few months. This disease was called Burkitt's lymphoma. Some epidemiological aspects of the malignancy caught Dr. Epstein's attention. He soon hypothesized that the disease was associated with a microbiological agent and tried to grow the virus from biopsy samples sent from Kampala (Uganda's capital) to his laboratory in London.²

After nearly 2 years of research, the team had not recovered any viruses in the specimens analyzed. At the end of 1963, upon receiving the specimen tube, they noted an abnormally cloudy fluid in the biopsy tube. Under optical microscopy, they saw numerous viable free-floating malignant cells, probably released from the tissue during the flight. From this episode, they grew a lymphoma-derived cell line, which was provisionally called the EB (Epstein & Barr) line. Indeed, this was the first time that human lymphocytic cells had been cultured for a long time *in vitro*.³ However, it was on February 24, 1964, that Epstein successfully observed viral particles in the EB lineage by electron microscopy. His experience led to the conclusion that the morphology was that of a member of the Herpesvirus family. Epstein

classified the new particles as a “virus, like herpes.” Their results were published on March 28, 1964, in *The Lancet*, making it a classic citation in the area.¹

In the following years, EBV was associated with infectious mononucleosis,⁴ nasopharyngeal carcinoma,⁵ and Hodgkin disease.⁶ Subsequently, EBV was found in hairy leukoplakia, posttransplant lymphoproliferative disorder (PTLD), NK/T-cell lymphoma, and gastric carcinoma. EBV has also been observed in some other solid tumors such as hepatocarcinoma, breast, and head and neck carcinomas.⁷ This special edition addresses the association of EBV with cancers in which the role of EBV is not fully elucidated or the literature on the subject is still limited. Thus, it intends to present a compilation of the latest evidence prepared by renowned researchers in the field. This issue contains seven chapters focused on up-to-date findings in brain and thyroid EBV-associated tumors as well as in oral and anogenital carcinomas.

In the first chapter, a notable researcher from the Hospital Infantil de México Federico Gómez, Dr. J. Arellano-Galindo and his colleagues deal with the relationship between the Epstein-Barr virus and glioblastomas, performing a detailed review on the features of these cancers, as well as a thorough description of the virology aspects of EBV and known molecular pathways. In the second chapter, still in the context of brain tumors, an honorable researcher from the Faculty of Medicine, Lisbon University, and Vice-President of European Academy of Paediatrics/Paediatric Section of the Union of European Medical Specialties, Dr. A. Neves, along with her colleagues Dr. C. Freixo and Dr. S. Hermouet, conducted an accurate systematic review on EBV and astrocytoma. In the third chapter, Dr. M. de Lima and colleagues, affiliated with the Federal University of Cariri (UFCA) and Ceará Cancer Institute (ICC), Brazil, carried out a systematic review with meta-analysis concerning the involvement of EBV in oral carcinomas. In the fourth chapter, another eminent contributor, Dr. L. Ward and her team at the Laboratory of Cancer Molecular Genetics (Gemoca), State University of Campinas (FCM-Unicamp),

Brazil, bring an excellent review chapter on the possible link between EBV and thyroid cancers. In the fifth chapter, Dr. M. Carvalho and Dr. Y. Furtado, both outstanding researchers at the Federal University of Rio de Janeiro (UFRJ), Brazil, elaborated a manuscript on the role of EBV and HPV in cervical cancers. In the sixth chapter, Dr. S. Cavalcanti, another prominent researcher from the Virological Diagnostic Laboratory at Universidade Federal Fluminense, Rio de Janeiro, Brazil, and her colleagues wrote about not only the role of EBV but also HPV and Merkel cell polyomavirus (MCPyV) in penile cancers. Finally, in the seventh chapter, Dr. M. de Lima and coauthors describe the potential cooperation mechanisms between EBV and HPV in oral and anogenital carcinomas and explore possible tumorigenic signaling pathways involved.

We are immensely thankful to all the authors for their efforts, commitments, and contributions, and for their willingness to share their precious knowledge and expertise, preparing valuable manuscripts that enriched the current issue, and undoubtedly contribute to the scientific literature. On behalf of the guest editors, we are grateful to Editor-in-Chief, Dr. Benjamin Bonavida, for the opportunity, guidance,

comprehension, and support provided during this process. We hope the readers enjoy this special edition.

REFERENCES

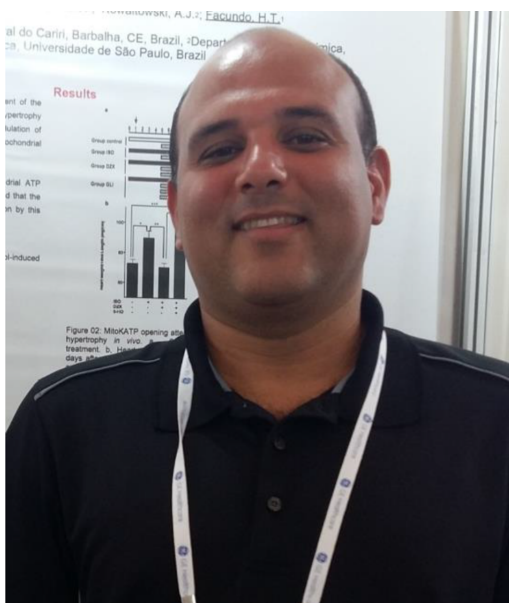
1. Epstein MA, Achong BG, Barr YM. Virus particles in cultured lymphoblasts from Burkitt's lymphoma. *Lancet*. 1964 Mar 28;1(7335):702-3.
2. Epstein A. Why and how Epstein-Barr virus was discovered 50 years ago. *Curr Top Microbiol Immunol*. 2015; 390(Pt 1):3-15.
3. Epstein MA, Barr YM. Cultivation in vitro of human lymphoblasts from Burkitt's malignant lymphoma. *Lancet*. 1964 Feb 1;1(7327):252-3.
4. Henle G, Henle W, Diehl V. Relation of Burkitt's tumor-associated herpes-type virus to infectious mononucleosis. *Proc Natl Acad Sci U S A*. 1968 Jan;59(1):94-101.
5. Henle W, Henle G. Evidence for a relation of Epstein-Barr virus to Burkitt's lymphoma and nasopharyngeal carcinoma. *Bibl Haematol*. 1970;(36):706-13.
6. Levine PH, Ablashi DV, Berard CW, Carbone PP, Waggoner DE, Malan L. Elevated antibody titers to Epstein-Barr virus in Hodgkin's disease. *Cancer*. 1971 Feb; 27(2):416-21.
7. de Lima MAP, Rabenhorst SHB. Association of Epstein-Barr virus (EBV) with solid tumors. *Revista Brasileira Cancerologia*. 2006;52(1):87-96.



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Dr. de Lima received a Master's Degree in Medical Microbiology at the Federal University of Ceará - UFC (2006) and a PhD in Biotechnology in Health, by the Northeast Network of Biotechnology - UFC/RENORBIO-UFC (2013). Has experience in the area of oncogenic microorganisms, with emphasis on the Epstein-Barr virus (EBV), human papillomavirus (HPV), and *Helicobacter pylori*, investigating their roles in malignancies such as gastric, oral, and anogenital carcinomas; he has also been working in the field of Tropical Diseases, focusing on leishmaniasis.



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