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Review

Viral Carcinogenesis Beyond Malignant Transformation: EBV in the Progression of Human Cancers

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Cancer progression begins when malignant cells colonize adjacent sites, and it is characterized by increasing tumor heterogeneity, invasion and dissemination of cancer cells. Clinically, progression is the most relevant stage in the natural history of cancers. A given virus is usually regarded as oncogenic because of its ability to induce malignant transformation of cells. Nonetheless, oncogenic viruses may also be important for the progression of infection-associated cancers. Recently this hypothesis has been addressed because of studies on the contribution of the Epstein–Barr virus (EBV) to the aggressiveness of nasopharyngeal carcinoma (NPC). Several EBV products modulate cancer progression phenomena, such as the epithelial–mesenchymal transition, cell motility, invasiveness, angiogenesis, and metastasis. In this regard, there are compelling data about the effects of EBV latent membrane proteins (LMPs) and EBV nuclear antigens (EBNAs), as well as nontranslated viral RNAs, such as the EBV-encoded small nonpolyadenylated RNAs (EBERs) and viral microRNAs, notably EBV miR-BARTs. The available data on the mechanisms and players involved in the contribution of EBV infection to the aggressiveness of NPC are discussed in this review. Overall, this conceptual framework may be valuable for the understanding of the contribution of some infectious agents in the progression of cancers.

Trends

The Epstein–Barr virus (EBV) is implicated in many neoplastic diseases, notably lymphomas and epithelial cancers.

Nasopharyngeal carcinoma (NPC) is strongly associated with EBV infection, and EBV products partially contribute to the aggressiveness of this cancer.

Several EBV products enhance cell motility and invasiveness, and they can also modulate the epithelial–mesenchymal transition.

Challenges in the manipulation of EBV genomes hampered the assessment of the extent of cancer addiction to viral products. New genetic editing tools (e.g., CRISPR/Cas9) will be valuable to create new informative models to address this issue.

Accumulated data on the role of EBV in the biological features of NPC makes it conceivable that some oncoviruses contribute to malignant transformation and have a role in the aggressiveness of the associated cancers due to effects on tumor progression phenomena.

Oncogenic Viruses

Worldwide, more than 50% of cancer cases are associated with preventable causes, including infections [1]. The population-attributable fraction for malignant neoplasms associated with infectious agents globally in 2008 was 16.1%, ranging from 3.3% in New Zealand to 32.7% in sub-Saharan Africa. About 2 million of all new malignant neoplasms reported in humans were associated with infections, and 1.6 million occurred in less developed regions. More than two-thirds of cancer cases (1.37 million) in 2008 were linked to well-known oncogenic viruses, namely, human T lymphotropic virus type 1 (HTLV-1), human hepatitis B and C viruses (HBV and HBC, respectively), human papillomavirus (HPV), Kaposi sarcoma-associated herpesvirus (KSHV), and EBV [2].

The oncogenic properties of a given virus are usually defined based on its ability to induce malignant cell transformation, and carcinogenic viruses typically interfere with multiple homeostatic cellular processes. For instance, viruses associated with malignant tumors hijack

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intracellular and extracellular signaling, induce genomic instability, increase the life span of the infected cell (by inhibiting apoptosis), and subvert cell senescence, resulting in unrestricted cell proliferation. These are some of the biological phenomena previously categorized as cancer hallmarks [3], and they can be actively induced during the infection by known human DNA oncoviruses [4,5].

The knowledge generated under this classical approach to viral carcinogenesis was pivotal to defining the etiopathogenesis of several neoplasms, as well as clarifying cancer biology itself. Nonetheless, an intriguing question has emerged in the past two decades: do cancers caused by oncogenic viruses evolve during progression like cancers that originate from other carcinogenic insults? Accumulating data indicate that viruses may be instrumental in phenomena related to cancer progression, and these findings provides new insights on the impact of infection on the natural history of cancers. This review consolidates the available information on putative effects of EBV on the aggressive behavior of nasopharyngeal carcinoma, aiming to delineate a conceptual framework for the impact of viral infection in cancer progression.

General Properties of EBV

Formerly designated human herpesvirus type 4 (HHV-4), EBV is a γ-herpesvirus associated with human proliferative diseases involving mostly lymphoid or epithelial cells. The former group of diseases predominantly encompasses Burkitt lymphoma (BL) and classical Hodgkin lymphoma (HL). EBV is also causative in immunodeficiency-associated lymphoproliferative disorders, such as post-transplant lymphoproliferative disease (PTLD), and non-Hodgkin lymphomas (NHL) in HIV-infected patients, such as primary central nervous system lymphoma (PCNSL), primary effusion lymphoma (PEL), and the plasmablastic lymphoma of the oral cavity [6]. Conversely, epithelial cancers associated with EBV infection include NPC and a subset of gastric and lymphoepithelioma-like carcinomas. In all cases of endemic BL and NPC, early onset PTLD, and PCNSL, the virus is consistently found within the neoplastic cells; conversely, only subsets of classical HL, NHL, gastric and the lymphoepithelioma-like carcinomas show evidence of EBV infection.

The EBV genome is composed of double-stranded DNA of approximately 180 kb, encoding more than 80 viral products. It is enclosed in an icosahedral nucleocapsid, surrounded by the viral tegument and a nuclear membrane-derived lipid envelope. Major targets for EBV infection are B lymphocytes and epithelial cells, though a few other cell types are rarely reported to be infected as well [7]. Box 1 summarizes the main features of EBV infection in humans and the viral life cycle.

Cancer Biology: A Brief Overview

The assessment of possible effects of infection by a given agent in cancer progression is only possible with appropriate endpoints for analysis. Based on studies of chemically-induced malignant tumors, the prevailing model for the natural history of cancer encompasses three consecutive stages: initiation, promotion, and progression [8]. Initiation is characterized by the earlier, nonlethal, genomic insult occurring in a given cell population. During promotion, initiated cells are chronically stimulated to proliferate, at the same time that they accumulate new genetic and epigenetic lesions. In this stochastic model, the accumulation of DNA lesions in a given cell lineage eventually gives rise to a transformed cell clone, which shows properties of malignant behavior. Cancer progression takes place when transformed cells colonize their original tissue site *in vivo*, and it is characterized by augmented tumor heterogeneity and biological aggressiveness, as evidenced by local invasion and distant dissemination [9,10].

The tissue microenvironment has a key role in all stages of carcinogenesis, and it is crucial for cancer progression because malignant colonization relies on trophic signals for the neoplastic cells to survive and proliferate – even though these cells generate some signaling themselves.