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Review

Microenvironmental abnormalities induced by viral cooperation: Impact on lymphomagenesis

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ABSTRACT

When stringent criteria have been used, the Epstein Barr virus (EBV), the Kaposi's sarcoma herpesvirus (KSHV), human immunodeficiency virus type 1 (HIV-1) and human hepatitis C virus (HCV) have been identified with sufficient evidence to be causative agents of non-Hodgkin's Lymphomas. Initially, single viral infection was considered fully responsible for the oncogenic properties of each virus, while it is now established that in many cases, multiple viral agents collaborate as cofactors in inducing lymphomas, especially in the presence of HIV-dependent immunodeficiency. Viruses cooperate by using their specific pathogenetic mechanisms in different combinations. The aim of this review is to describe the cooperation between different viruses in the development of lymphomas including the evidences supporting their pathogenetic role. Viral cooperation, a mechanism by which different viruses coinfecting human tissues have synergistic or regulatory effects on carcinogenesis, targets neoplastic B cells as well as cells of the microenvironment, such as reactive T-cells, B cells and macrophages, as well as non-immune cells such as endothelial cells, that contribute to tumor microenvironment. The most important viral genes involved in cooperation include HIV-1 *tat* and *vpu*, EBV LMP-1 and EBNA-2 and KSHV KIE2, Rta and LANA. Lymphomagenesis related to viral cooperation represents an interesting topic where microenvironmental abnormalities may be particularly relevant, particularly because antiviral targeted therapies and therapies producing the reconstitution of the immune system may constitute areas of interest aiming at improving the outcome of virus associated lymphomas. While the immune component of the lymphoma microenvironment can be easily studied by immunological and molecular techniques, the definition of the non-immune component of the lymphoma microenvironment is largely incomplete and may be the issue of future investigations. Understanding the pathogenetic role of viral infection in specific malignancies and defining microenvironmental abnormalities and mechanisms of viral carcinogenesis are important steps toward precise diagnosis and accurate treatment strategies for HIV-associated cancers.

1. Introduction

Infectious agents play an important role in the etiopathogenesis of non-Hodgkin and Hodgkin Lymphomas [1,2]. It is increasingly evident that appropriately defining appropriately infection-associated cancers is mandatory to improve cancer prevention, diagnosis and research and that characterizing these tumors with respect to genomic features is essential in order to optimize treatments. Very recently, Gopal et al. issued a prospective view on this topic and correctly claimed that pathologic and molecular identification of oncogenic viruses in tumor specimens is necessary to classify infection-related cancers [3]. However, due to the widespread diffusion of many potential oncogenic viruses infecting humans and the relatively low incidence of related cancers, establishing their effective oncogenic roles remains challenging. In fact, in reviewing the international literature on virus-associated cancers, we had previously found that many published studies do not provide enough details about the pathologic features or the molecular characteristics of the malignant specimens [4]. A portion of the studies on cancers classified as infection-related reported the detection of a virus in tumor tissue by polymerase chain reaction, without evidencing whether or not it infects the tumor cells. Only a few studies reported results obtained by in situ methods showing the virus within individual tumor cells. For these reasons, we have emphasized that strict diagnostic criteria must be used to establish associations between viruses and cancers, a strategy that could help to define

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Table 1
Virus associated lymphomas assessed by the IARC Monograph Working Group.

Pathogenetic mechanism	Viruses involved	Mechanisms of action
Direct action	EBV	Induction of growth signals Inhibition of apoptosis Genomic instability
	KSHV	Inhibition of apoptosis Genomic instability
	HTLV 1	Tax-dependent cell proliferation and transformation
Chronic antigenic stimulation/inflammation	HIV	B cell stimulation via P24 antigen, CD40L
	EBV	IL-10 production
	HCV	HCV E2 B cell stimulation and engagement of IL-2 production by T cells
	HBV	Not defined
Immunodeficiency	HIV	T helper cell depletion Treg cell depletion Cytokine dysregulation
	EBV	Impairment of T cell cytotoxic response
	KSHV	Evasion from innate and adaptive immune response

more precisely several controversial issues existing in this field [5].

When these stringent criteria have been used, the Epstein Barr virus (EBV) and Kaposi's sarcoma-associated herpesvirus (KSHV) have been identified with sufficient evidence to be causative agents of NHL, and EBV has been consistently related to different forms of lymphoma [2]. For other viruses evidence is still present, but more limited or indirect, such as for HIV-1, Hepatitis Viruses B and C [2,4,6]. Three general pathogenetic mechanisms of viral-associated lymphomagenesis have been identified: first, some viruses, such as EBV and KSHV, directly infect and transform lymphocytes; second, viral antigenic products or soluble factors induce chronic B cell activation and promote cellular transformation; and third, prolonged immunodeficiency, as produced by HIV-1, facilitates viral evasion of immune response, thus resulting in the emergence of neoplastic clones [7,8] (Table 1).

Initially, after the detection of viral products within neoplastic cells, a single viral infection was considered fully responsible for the oncogenic properties, while it is now established that in many cases, multiple viral agents cooperate as cofactors in inducing lymphomas, especially when herpesviral infections occur in the presence of HIV-1 dependent immunodeficiency. As single tumor-promoting agents, EBV and KSHV use a wide set of genes that are involved in oncogenesis without the need to cooperate with genes of other viruses. These genes include EBV EBNAs, LMPs, BARF, and KSHV vFLIP and LANAs [9,10]. In some cases viruses act synergistically to promote lymphomagenesis; these cooperation mechanisms are sustained by a more limited set of viral genes that may target the same signaling pathway or interfere with the replication of coinfecting viruses.

Viruses cooperate by using all the above-mentioned pathogenetic mechanisms in different combinations. The cooperation between KSHV and HIV deeply influences the risk for development of KSHV-induced malignancies, i.e. KS, primary effusion lymphoma (PEL), and multicentric Castleman's disease (MCD). Although these disease entities display distinct features, KSHV-associated MCD is a tangle of these different entities, which are usually associated with HIV and KSHV infection [11]. In fact, MCD has become increasingly relevant in recent years thanks to its association with HIV and KSHV coinfections. Furthermore, while initially the major aspects of virus dependent lymphomagenesis were concentrated on the direct transforming activities of viral products on neoplastic cells, there is now increasing evidence that the tumor microenvironment plays an essential role in the development of lymphoid malignancies [12].

The aim of this review is to describe how different viruses cooperate in the development of lymphomas, including the evidence supporting their pathogenetic role, such as the techniques used to demonstrate the presence of multiple viruses within the same neoplastic cell and the description of the direct (i.e., transforming ability) and indirect (i.e. immunosuppression and impact on the microenvironment) mechanistic events that are involved in lymphomagenesis.

Finally, the therapeutic implications of viral cooperation mechanisms will be also discussed.

2. Viral cooperation

In the scientific literature, viral cooperation has been used to describe different phenomena. For example, in their articles, Shirogane et al. [13,14] defined "cooperation" as a mechanism for viral evolution, in which two viral genomes produce a new phenotype through a cooperative interaction between variant proteins (heterooligomer formation). This type of cooperation may be subject to positive selection even at a low multiplicity of infection, thus providing an advantage of this new viral phenotype over the wild type.

In this review that describes viral lymphomagenesis, we define viral cooperation as a mechanism by which different viruses coinfecting human tissues have synergistic or regulatory effects on carcinogenesis.

Herpesviruses, once they have infected B lymphocytes, promote a lytic infection that may be followed by the establishment of latency; on the basis of local or generalized factors (i.e. the presence of immunological defects), EBV has the special characteristic to establish three different types of latency (types I, II and III) that are represented in the various types of lymphomas [8]. Although the genes that are particularly expressed during latency are considered essential for the transforming activity of the virus, there is increasing evidence that the expression of lytic cycle genes may also have oncogenic consequences [15]. This observation is particularly relevant for the scope of this review since, in the majority of the cases, viral cooperation influences the balance between the lytic and latent phases of the viral cycle or is able to modify signaling pathways. Indirect mechanisms of cooperation, particularly for HIV, are instead related to the ability to promote immune dysregulation. In fact, the mechanism of viral cooperation is very important in HIV-infected subjects, where a high degree of immunodeficiency and/or inflammation is associated with the possibility of being infected with multiple oncogenic viruses.

Finally, it is worth noting that cooperation in lymphomagenesis is not limited to viruses, but is a general mechanism that also

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