REVIEW

Infection-associated non-Hodgkin lymphomas

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Abstract

Non-Hodgkin lymphomas (NHLs) are malignant proliferations of lymphoid cells. Lymphoid cells proliferate in a physiological manner in response to antigen-dependent and antigen-independent signals. Some lymphotropic viruses, such as Epstein–Barr virus and human T-lymphotropic virus 1, as well as pathogens leading to chronic antigenic stimulation (such as *Helicobacter pylori* and hepatitis C virus), are associated with NHL. We review here some of the pathophysiological features of infection-associated NHL.

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Lymphoid cell plasticity and responsiveness

Non-Hodgkin lymphomas (NHLs) arise from malignant transformation of mature lymphocytes. The pathophysiology of NHL is complex, but major advances in the last two decades have shed light on several aspects of the mechanisms involved in lymphoid transformation, in particular in the subgroup of infection-associated lymphoma.

The incidence of NHL dramatically increased during the second half of the twentieth century, and nearly doubled between 1974 and 2009, reaching approximately 20 cases per 100 000 person-years. Although the human immunodeficiency virus (HIV) pandemic (approximately 6% of NHLs occur in HIV-infected individuals) probably had a significant impact on the epidemiology of NHL, it is not the sole factor [1].

Lymphocytes are specialized cells that respond to external stimuli (antigens) and host stimuli (receptor-mediated signalling), and acquire various effector functions that culminate in the elimination of non-self antigens (pathogens, infected and/or transformed host cells, and allogeneic cells). This property of recognizing and eliminating non-self antigens is balanced by mechanisms that enable tolerance to self antigens, in order to maintain homeostasis. Lymphocytes somatically rearrange parts of their genome (VDJ recombination of the immunoglobulin (Ig) and T-cell receptor loci), leading to the acquisition of a diverse repertoire of antigen receptors. In B-cells, Ig gene recombination occurs during the early phase of precursor B-cell development in the bone marrow. Immature B-cells bearing a surface Ig (B-cell receptor (BCR)) exit the bone marrow, and complete their maturation in peripheral lymphoid organs along two main pathways [2]. Ultimately, two B-cell subsets are recognized: marginal zone (MZ) B-cells and follicular (FO) B-cells. MZ B-cells are localized within the MZ of lymphoid organs (lymph nodes and spleen), and participate in T-cell-independent responses. FO B-cells represent the major B-cell subset, and participate in T-cell-dependent responses in germinal centres (GCs). FO B-cells undergo a second step of somatic gene rearrangement during the GC reaction. Somatic hypermutations target the

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hypervariable segments of *VH* and *VL*, which encode the Ig heavy and light chains respectively, generating antibodies with higher affinity for the antigen upon subsequent exposure. Class-switch recombination changes the constant region of the Ig, generating new isotypes with similar variable regions. As for VDJ recombination, somatic hypermutations and class-switch recombination both involve double-strand DNA breaks that are secondarily repaired. Unlike B-cells, T-cells undergo only one period of somatic VDJ recombination of the T-cell receptor locus in the thymus. Given the ability of lymphocytes to somatically rearrange their genomes, both B-cells and T-cells are intrinsically prone to genetic instability and malignant transformation. Moreover, the extended life-span of numerous lymphocyte subsets, particularly memory cells, and constant re-exposure to antigen-driven activation and proliferation increase the risk of malignant transformation.

Mechanisms of lymphoid transformation

Numerous molecular pathways are deregulated in lymphomas. Studies based on transcriptome, comparative genomic hybridization array and, more recently, whole genome sequencing of different lymphoma subtypes have characterized many recurrent genetic alterations [3]. Pathways involving cellular activation, nuclear factor-κB (NF-κB) and apoptosis can be deregulated by loss-of-function or gain-of-function mutations, gene amplifications, and/or gene translocations. Gene signatures specific to certain subtypes of NHL are now defined. The role of BCR stimulation in B-cell lymphomagenesis is supported by several lines of evidence [4]. Oncogenic mutations targeting several signalling pathways utilized by normal B-cells are found in the majority of B-cell lymphomas. NF-κB activation is central to immune activation, and its activation by several recurrent mutations is possibly the most important alteration in B-cell lymphomagenesis [5]. NF-κB is normally activated through several cell receptors on B-cells (BCRs, B-cell activating factor receptors, and Toll-like receptors). Mutations leading to constitutive NF-κB signalling are found in many different types of NHL. Interestingly, in cases where mutations in the NF-κB pathways are absent, NF-κB activation by upstream receptors is frequently detected. Normal B-cells require tonic BCR signalling for their survival. Some subsets of NHL (activated B-cell type diffuse large B-cell lymphoma (DLBCL)) rely on a so-called chronic active BCR signal for their survival. In such cases, inhibition of the BCR pathway by ibrutinib (Bruton's tyrosine kinase inhibitor) or idelalisib (phosphoinositide 3-kinase inhibitor) is effective, unless downstream mutations activating NF-κB are present (such as CARD11 mutations, which are found in approximately 10% of activated B-cell type DLBCLs) [4,6].

General mechanisms of infection-associated NHL

Direct transformation by pathogens: The case of Epstein–barr virus and human T-lymphotropic virus 1

Several NHL subtypes are associated with chronic infections. Epstein–Barr virus (EBV) was the first described human oncogenic virus [7]. Like members of the *Herpesviridae*, EBV has a lytic phase and a latent phase of infection. To establish latency, EBV specifically targets B-cells, where it is maintained indefinitely as an episome [8]. EBV-infected B-cells undergo activation and differentiation driven by the finely tuned expression of viral latent genes that hijack important cellular functions [9]. Ultimately, EBV-infected B-cells differentiate into resting memory B-cells harbouring latent EBV with very restricted gene expression [10]. The natural history of the EBV cycle in B-cells can sometimes go off-track, leading infected B-cells to proliferate under the control of viral oncogenes and progress to B-cell lymphomas [11]. Human T-lymphotropic virus 1 (HTLV-1) was the first described human oncogenic retrovirus. It is associated with adult T-cell leukaemia/lymphoma, a very aggressive form of T-cell malignancy [12]. HTLV-1-associated lymphomagenesis differs significantly form EBV-associated lymphomagenesis, but a common feature is the fact that transformed cells harbour the transforming pathogen, and oncogenesis is driven by viral factors within the transformed cells.

NHL and HIV

Infection with HIV constitutes one of the most important risk factors for lymphomas [1]. However, HIV is not directly oncogenic. The majority of lymphomas occurring in HIV-infected patients are derived from B-cells. HIV does not, however, infect B-cells. The mechanisms of lymphoid transformation during HIV infection involve distinct pathways [13]. HIV infection facilitates active chronic infection by other known direct oncogenic pathogens, such as EBV and human herpesvirus 8. Immunosuppression associated with HIV may contribute to virus-induced lymphomagenesis by these pathogens through deregulation of their gene expression programmes. HIV infection also leads to a state of chronic stimulation of the immune system, which favours the occurrence of oncogenic mutations in lymphocytes. The latter may