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Lymphoid malignancies: many tumor types, many altered genes, many therapeutic challenges

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Review Series

The lymphoid tissues, including both the B and T cell lineages, are characterized by a unique level of biological complexity due to the anatomical organization of functionally distinct cell subpopulations and complex processes of genetic alteration required to generate immune responses. Not surprisingly, this physiological diversity and complexity is mirrored by the broad spectrum of malignancies derived from lymphocytes. The articles in this Review Series highlight recent progress in selected common lymphoid malignancies, with a focus on the genetic alterations that drive malignant transformation, including those identified by genome-wide analyses. These genetic alterations represent the basis from which cellular pathways of therapeutic relevance can be identified, studied, and eventually targeted.

Lymphoid malignancies: many tumor types, many altered genes, many therapeutic challenges

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Few other tissues in the body are characterized by the biological and functional complexity of the lymphoid system. Classically, lymphoid tissues can be divided into two types: (a) the central or primary tissues (bone marrow and thymus), in which lymphoid precursor cells mature to a stage at which they can express antigen receptors, and (b) the peripheral or secondary lymphoid tissues (lymph nodes, spleen, and mucosa-associated lymphoid tissues), in which antigen-specific responses occur. These structures enable the development of the immunoglobulin receptor–expressing B cell lineage, including naive, germinal center, memory B cells, and plasma cells, as well as the T cell receptor–expressing T cell lineage, including helper, cytotoxic, and regulatory T cell subpopulations. This range of cell types provides a simplified conceptual framework for understanding the even more complex landscape of lymphoid malignancies that includes more than 40 distinct tumor types in the most recent classification scheme, with tumors differing widely in their phenotype and clinical behavior.

The goal of this Review Series is to concisely review the pathophysiological mechanisms associated with only a subset of the most common lymphoid malignancies. Two reviews focus on malignancies derived from immature B cell and T cell precursors. Van Vlierberghe and Ferrando review the distinct subset of T cell acute lymphoblastic leukemias (T-ALLs) defined by genetic alterations such as activating mutations in *NOTCH*, deletions of the *CDKN2A* locus in chromosome 9p21, and translocations that promote aberrant expression of transcription factor oncogenes (1). Focusing on B-precursor acute lymphoblastic leukemia (B-ALL), Charles Mullighan discusses how recently discovered cryptic or submicroscopic genetic lesions cooperate with known chromosomal rearrangements and how these genetic changes defined new B-ALL subtypes (2). Several reviews in the series highlight lymphoid cancers that derive from multiple stages of lymphocyte development, including the mature compartment. Campo and colleagues describe the molecular mechanisms that drive B cell–derived mantle cell lymphoma (MCL) and new implications for patient treatment (3). Neoplastic B cells that escape normal germinal center apoptotic program contribute to follicular lymphoma (FL); Gascoyne and colleagues delineate recurrent genetic aberrations and perturbations to the microenvironment that contribute to FL pathogenesis (4). Gaidano, Foa, and I examine the genetic alterations found in chronic lymphocytic leukemia (CLL), a B cell cancer that is the most common leukemia in adults (5). Küppers et al. review the transforming events underlying Hodgkin lymphoma (HL), which derives from mature B cells and is frequently associated with changes in the NF-κB and JAK/STAT pathways (6). New high-throughput technologies have improved our understanding of peripheral T cell lymphomas (PTCLs); Pileri and Piccaluga discuss recent advances in classification and potential molecular targets with translation importance (7). Last, but not least, the article by Kuehl and Bergsagel examines a malignancy displaying the phenotype of terminally differentiated plasma cells, multiple myeloma (MM) (8). They emphasize disease pathogenesis, heterogeneity between cases and within individual cases, and animal models and genetic screens that suggest new therapeutic opportunities.

The new era of genomic analysis

Lymphoid malignancies, as with most tumor types, have a genetic origin involving genetic alterations that drive the transformation of a somatic cell clone. For at least three decades, the search for the genetic alterations associated with lymphoid malignancies has been largely based on the molecular analysis of chromosomal translocations whose associations with distinct tumor subtypes was firmly established by cytogenetic analysis. Although present in non-lymphoid tumors, chromosomal translocations represent the hallmark of lymphoid malignancies, and these translocations often represent a major pathogenetic determinant. The analysis of these genetic alterations has led to the identification of many classical proto-oncogenes, with general importance extending far beyond lymphoid biology, including the pleiotropic transcription factor gene *MYC* and the antiapoptotic gene *BCL2*. Chromosomal translocations carry great biological and diagnostic value. Many such translocations have been genetically recapitulated in mice to generate useful preclinical models of lymphoid malignancies and are the focus of intense efforts toward therapeutic targeting. However, recent technological developments in genomic analysis, including next-generation sequencing of cancer genomes, genome-wide analysis of copy number variations, and gene expression profiling have complemented classical approaches, leading to a remarkably increased pace of discovery. This research has

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shown that the total complexity of the genetic alterations associated with malignant transformation is much higher than perhaps was expected, ranging from approximately 10 to 100 alterations per case in different tumor subtypes. As always, the analysis of the genome is the starting point for understanding lymphoid malignancies, with the full sequencing of coding genomes coupled with extensive gene expression profile analysis opening a new era of functional investigations, new diagnostic approaches, and targeted therapeutic developments. This Review Series includes malignancies for which this analysis has been completed, thus allowing an initial critical discussion of the findings.

Future challenges and opportunities

The "tsunami" of new information regarding the genetic alterations involved in the development of lymphoid leukemias, lymphomas, and myeloma is likely to have a significant impact both on the pace and the nature of research. The availability of such a wealth of new information presents several important challenges and opportunities. First, it is likely that some genetic alterations may have a complex and unexpected role in tumor development. The classic distinction between mutations that are "drivers," i.e., contributing to pathogenesis, and "passengers," i.e., occurring by chance as part of basic mutation rate and thus pathogenetically irrelevant, is likely to be too schematic and may evolve into a spectrum of intermediate functional categories. Nonetheless, even the initial dissection of highly important versus less important lesions presents clear experimental challenges. Second, recurring sets of genetic alterations associated with a given malignancy need to be organized in credible and experimentally testable cellular networks that justify and explain their co-selection. Third, different genetic lesions can alternatively affect the same cellular pathway in different cases, suggesting the complexity of the genetic variations may conceivably be reduced to a less complex landscape of pathways, a notion relevant for the diagnostic context and for the selection of the most appropriate therapeutic targets. Finally, while lymphoid malignancies, like all cancers, are genetic diseases, they are also dependent on their environment for their development, survival, and dissemination. Thus, the research on the genetics of the tumor clone must also be coupled with research on its broadly defined environment. Lymphoid malignancies derived from cells with a physiological role of meeting foreign antigens or from cells dependent on continued antigen presence represent a strong paradigm for this notion. This Review Series aims to discuss these themes by framing basic research results in a clinical context and, as such, will hopefully be of interest to both experimental researchers and practicing clinicians.

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