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Perspective

Critically dysregulated signaling pathways and clinical utility of the pathway biomarkers in lymphoid malignancies

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Abstract

Accumulating evidence confirmed that many dysregulated signaling pathways and aberrant genetic alterations contribute to the oncogenesis and heterogeneity of lymphoid malignancies. Therapeutically targeting dysregulating signaling pathways and their hidden oncogenic biomarkers are becoming available, but did not show desired therapeutic effect in current clinical practice. It is meaningful to further understand the underlying mechanisms of the dysregulated signaling pathways and to address the potential utility of pathway-related biomarkers. To precisely identify the dysregulation of signaling pathways and the "driver" oncogenic biomarkers, as well as to develop reliable and reproducible risk-stratification based on biomarkers will be challenging. Nevertheless, pathway-based targeted therapy will raise the hope to improve the outcomes of the patients with lymphoid malignancies, especially with aggressive types, and the efficient utility of pathway-related biomarkers in diagnosis, prognosis, prediction of lymphoid malignancies may also be able to power precision medicine.

Keywords: Lymphoma; Signaling pathway; Biomarker; Therapeutic target

Introduction

Lymphoid malignancies are known for a wide variety of types and molecular and clinical heterogeneity. Increasing evidence supported that many dysregulated oncogenic signaling pathways and aberrant genetic alterations have contributed to the oncogenesis and heterogeneity.[1,2] The most frequently dysregulated signaling pathways involved in lymphoid malignancies include B-cell receptor (BCR) pathway, nuclear factor-kappa B (NF-κB) pathway, phosphoinositide-3-kinase/v-akt murine thymoma viral oncogene homolog/mechanistic target of rapamycin (PI3K/AKT/mTOR) pathway, the Janus kinase/signal transducer and activator

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of transcription (JAK/STAT) pathway, apoptosis pathway, and programmed death-1/programmed death-ligands (PD-1/PD-Ls) pathway.

In the current era of precision medicine, therapeutically targeting dysregulated signaling pathways and their hidden oncogenic biomarkers are becoming hot topics in the field of cancer research and translational medicine worldwide. Meanwhile, progress has been made in risk-stratification of patients based on the targeted biomarkers, accordingly providing optimal intervention for different risk groups. Many preclinical and clinical trials demonstrated that targeted therapies have clinical activity against a broad spectrum of lymphoid malignancies.[3,4]

In this review, to comprehensively understand the detailed mechanisms underlying the development of lymphoid malignancies and the potential of targeted therapy, we summarized several key dysregulated signaling pathways involved in oncogenesis and heterogeneity of lymphoid malignancies. The utility of pathway-related biomarkers for diagnostic, predictive, and therapeutic usage is also included.

BCR signaling pathway

BCR is a transmembrane receptor whose membrane-bound immunoglobulin can bind to extracellular antigen. Correspondingly, immunoglobulin-linked heterodimer of cluster of differentiation (CD) 79A/CD79B can deliver the antigen stimulatory signals from outside to inside the cell. Following a series of molecules activation, BCR signaling and its downstream signaling cascades consequently control precise function of normal B cells.[5]

In the three BCR signaling pathways (Fig. 1), the chronic active BCR signaling pathway is classical and antigen-dependent. With the antigen-mediated BCR clustering towards cell membrane, the cytoplasmic tail of BCR, especially immune receptor tyrosine-based activation motifs (ITAM) domain of CD79A and CD79B, becomes phosphorylated by Src family members. Being subsequently recruited and activated by phosphorylated ITAM, spleen associated tyrosine kinase (SYK) thereby activates downstream signals including PI3K/AKT/mTOR signaling, mitogen-activated protein kinase (MAPK) signaling, NF-κB signaling, and nuclear factor of activated T cells (NF-AT) signaling through phosphorylating bruton tyrosine kinase (BTK) and B-cell linker (BLNK). As linker molecules, AKT and BTK are key components to deliver multiple signals.[2,6]

The tonic BCR signaling pathway and autonomous BCR signaling pathway exist, depending on the interaction between BCR and Lyn/SYK or the two neighboring BCRs rather than external antigenic stimulation.[6]

Normal BCR signaling has been proven to be functional in B-cell proliferation, survival, apoptosis, and differentiation; aberrantly activated BCR pathway is related to oncogenesis of several types of B-cell hematologic malignancies, especially in chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), active B-cell-like diffuse large B-cell lymphoma (ABC-DLBCL), and mucosa associated lymphoid tissue (MALT) lymphoma.[2,7] Furthermore, several key components in these pathways are potential therapeutic targets or diagnostic biomarkers.

CD79A/B

CD79A, a transmembrane protein with a cytoplasmic ITAM, forms a CD79A/B heterodimer with CD79B, which is required for the BCR aggregation to induce signal-initiating. In about 20% of ABC-DLBCL cases, CD79A and CD79B mutations can be observed, suggesting their oncogenic roles in dysregulation of BCR signaling pathway in specific ABC subtype.[7]

BTK

BTK is fundamental to the function of BCR signaling pathway and its downstream signaling. As a member of Tec family, BTK is by far the most studied cytoplasmic tyrosine kinase. It is restrictedly expressed in B cells and plays an important role in the differentiation and activation of B cells.[8] It is also related to immune function, transcription regulation, and apoptosis modulation due to its function in Toll-like receptor (TLR) pathway and cytokine receptor signaling pathway.[9] In BCR signaling pathway, BTK is responsible for receiving signals from SYK and transducing signals to initiate downstream signaling pathway.[10]

Given the key function of BTK in BCR pathway and downstream NF-κB pathway, an inhibitor against BTK, ibrutinib, showed encouraging efficacy on patients with untreated and relapsed/refractory CLL, ABC-DLBCL, follicular lymphoma (FL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), and lymphoplasmacytic lymphoma (LPL). The inhibition against BTK induces downstream kinase inactivation and cell apoptosis through binding to BTK at the C481 residue irreversibly.[11,12]