ISSN 2744-1636
Bioengineering Studies *Review Article*
Vol. 3, No. 2, December 2022, pp.44-47
https://doi.org/10.37868/bes.v3i2.id240

Review on lymphoma and deregulated signaling pathways

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Abstract
Since the incidence of cancer is increasing worldwide, there is an urgent need for more successful therapies. Here, we focused on a literature review regarding lymphoma and deregulated pathways that are hallmarks of lymphoma development. Among others, PI3K/AKT, NF-κB and JAK/STAT pathways are the most common deregulated ones. These signaling pathways are crucial for numerous cellular processes and possible deregulation can mainly lead to uncontrolled cell division and inhibition of apoptosis. A literature review was performed by using databases including PubMed, PubMed Central and Google Scholar from where the most recent and valuable studies were selected.

Keywords: Cancer, Hematological Malignancies, Lymphoma, DLBCL, T-cell Lymphoma, Signaling Pathways.

1. Introduction

Cancer is a significant health concern and one of the leading reasons for mortality in the world. The worldwide problem of cancer is predicted to grow in the upcoming years [1]. The incidence of cancer is increasing rapidly, the main reason being changes in our lifestyle, behavior, and continuous exposure to various cancer-causing substances [2]. Despite huge effort and progress in cancer research and development of new anticancer treatments, a major problem in achieving a complete cure for cancer is the resistance that body develops to these treatments [3]. Carcinogenesis is a term that refers to the development of cancer, including alterations at genetic, epigenetic and cellular levels [4]. Carcinogenesis is responsible for deregulated cell proliferation, resulting in formation of local or even metastatic cancer [5]. The aim of this study was to select and filter relevant studies regarding lymphoma using various databases.

2. Materials and Methods

The search for keywords including hematological malignancies, lymphoma, lymphoma subtypes, signaling pathways, diffuse large B-cell lymphoma, and T-cell lymphoma was performed using databases such as Google Scholar, PubMed, PubMed Central and others. Further, most recent studies were selected, together with some older ones which have valuable information regarding searched keywords.

3. Hematological Malignancies

Hematological malignancies refer to malignant blood neoplasms [6]. They can be categorized into two groups including lymphoid and myeloid [7]. As a result, neoplasms that arise from the myeloid lineage have prefix *mye-* including myeloid, myelogenous and myeloproliferative, while neoplasms that arise from the lymphoid lineage have prefix *lymph-* including lymphoid, lymphocytic, lymphoblastic and lymphoproliferative [8].
Acute leukemia can emerge from either lymphoid or myeloid progenitor cells that are accumulating in bone marrow further spreading to other tissues via bloodstream [9]. The main subtypes are acute myelogenous leukemia (AML) and acute lymphoblastic leukemia (ALL) [10]. Disorder known as a chronic myeloproliferative, refer to neoplasms of myeloid lineage that are characterized by proliferation of either mature

myeloid cells or hematopoietic cells. The main subtypes are essential thrombocythemia, primary myelofibrosis, chronic myeloid leukemia and others [11].

Myelodysplastic syndrome is characterized as failure of bone marrow function and can affect patients with high number of myeloblasts further increasing the possibility of acute myelogenous leukemia development [12, 13].

Lymphoma can originate from various stages of lymphocyte differentiation and it's categorized into Hodgkin and non-Hodgkin lymphoma. Non-Hodgkin's subtype is more common, accounting for nearly 90% of all lymphoma cases, with the aggressive diffuse large B-cell lymphoma being the most prevalent [8, 14].

4. Signaling Pathways in Lymphoma

The malignant lymphomas represent a group of more than 30 unique types of diseases that arise from a clonal proliferation of lymphocytes and have a distinct natural history [15]. Generally, lymphomas are classified as Hodgkin (HL) and non-Hodgkin lymphoma (NHL). The incidence and mortality for Hodgkin and non-Hodgkin lymphoma are increasing worldwide. According to GLOBCAN worldwide 2020 statistics, there were more than 83 000 cases and 23 000 deaths due to Hodgkin lymphoma, while more than 544 000 cases and 259 000 deaths were reported due to non-Hodgkin lymphoma [16].

Diffuse Large B-cell lymphoma (DLBCL) is prevalent form of non-Hodgkin's lymphoma. DLBCL is categorized into two primary groups: germinal center B-cell (GCB) and activated B-cell (ABC) DLBCL [17]. Hallmarks of DLCBL pathogenesis are dysregulations of the nuclear factor-kappa B (NF-κB) and phosphatidylinositol 3 kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signaling pathways [18-20].

Cutaneous T-cell lymphoma (CTCL) arises secondary to dysregulation of cancer-testis genes and B lymphoid tyrosine kinase and Jak-3/STAT and NOTCH1 signaling pathways. However, some reports suggest an association between chronic cutaneous inflammation and infectious etiology and CTCL development [21].

The incidence of T-cell lymphoma is influenced by age, geographic location and ethnic variability. Incidence data collected from different population-based registries of the SEER (Surveillance, Epidemiology, and End Results) Program between 2000 and 2018 showed that incidence of T-cell lymphoma increased in the US [1] and in Europe [22].

Class I PI3K heterodimers consist of two types of subunits including catalytic subunits (p110α) and regulatory subunits (p85α). PI3K is activated when it is bound via scaffold proteins to the plasma membrane, which occurs in response to different extracellular signals. Upon activation, the catalytic subunit p110α of PI3K transforms the liquid substrate, phosphatidylinositol-4,5-bisphosphate (PIP2), into phosphatidylinositol -3,4,5-triphosphate (PIP3). As a consequence serine/threonine kinase AKT/protein kinase B (PKB) gets phosphorylated at two specific amino acid residues Ser473 and Thr308, further promoting growth and cell survival [24, 25].

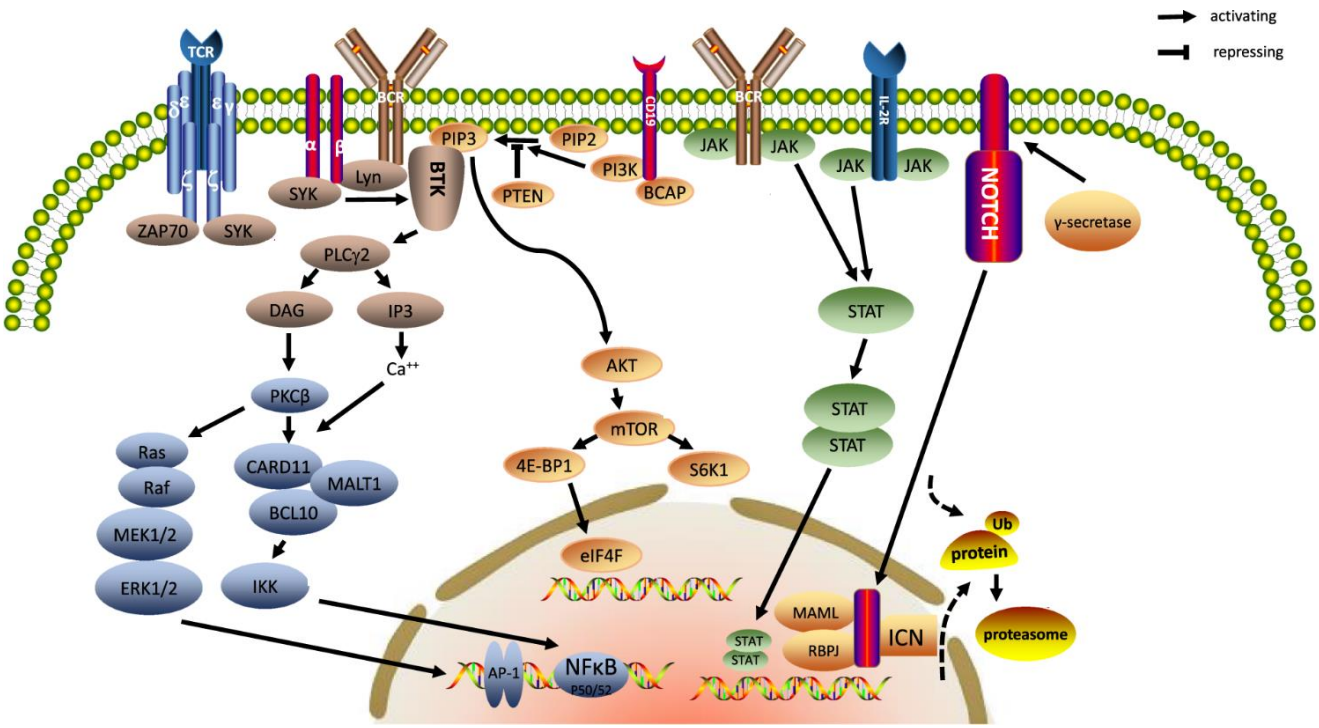

Figure 1. Mechanisms of commonly deregulated signaling pathways [23].

The activation of NF-κB transcription factors is triggered by external and internal stimuli including growth factors, cytokines, ionizing radiation, DNA damage and others. These signals initiate activation of IκB kinase (IKK) further leading to translocation of NF-κB dimers into the nucleus and transcription of genes responsible for wide range of cellular functions, as seen in Figure 1 [26, 27].

STAT transcription factors consist of N-terminal DNA binding domain, C-terminal domain and SH2 domain which plays an important role in association with phosphorylated tyrosine residue of the receptor. Once STAT transcription factor binds to the receptor, JAK phosphorylates the C-terminal domain of STAT3 causing it to disintegrate from the receptor. Then, spontaneous formation of dimers of phosphorylated STAT3 monomers and translocation into the nucleus occur, further activating genes responsible for numerous cellular responses [28, 29].

As a conclusion, this review consolidates published studies on lymphoma and most common deregulated signaling pathways in certain lymphoma subtypes. These pathways are often constitutively activated upon different stimuli. It is crucial for further progression in cancer treatment to evaluate new possible targets for inhibition of above mentioned signaling pathways.

Declaration of competing interest

The author declare that he has no known financial or non-financial competing interests in any material discussed in this paper.

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