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Molecular Sub-typing of Diffuse Large B-cell Lymphoma

Thomas Drago

School of Medicine, Trinity College Dublin; Dublin, Ireland

ABSTRACT

Background: Diffuse large B-cell lymphoma (DLBCL) is the most common form of Non-Hodgkin Lymphoma (NHL) in adults. Affecting nearly 7 out of every 100,000 people in the United States annually, this hematogenous neoplasm is known for its aggressiveness and rapid development. Being the most common NHL, it has been divided into several subgroups based on pathogenesis and treatment methods. In particular, subtypes such as germinal center, activated B-cell-like, and primary mediastinal diffuse large B-cell lymphomas have been divided by their uniqueness of pathology at the cellular level. Knowing the numerous cytokines, inflammatory markers, and other microcellular processes that these lymphomas disrupt can help target an effective therapeutic at the disease.

Methods: Through extensive review of literature and analysis of current data, this article aims to delineate three of the main diffuse large B-cell lymphoma by highlighting key features of each disease. Online databases such as Google Scholar, PUBMED, EMBASE, and Cochrane Library were reviewed to collect information on molecular subtyping of this lymphoma.

Results: After reviewing several online resources, it is evident that diffuse large B-cell lymphoma can be broken up into three main categories. Germinal center DLBCL are predominantly a cause of mutations in the BCL-2 and BCL-6 genes which upregulate their growth, activated B-cell-like DLBCL has been shown to upreegulate NF-kB and FOXP1 genes, and primary mediastinal DLBCL upregulates both NF-kB as well as TRAF1. These specific gene mutations cause each subtype to proliferate in their own way, causing unique array of symptoms that are susceptible to distinct therapeutic regimens.

Conclusion: Dividing DLBCL into smaller subtypes based on pathogenesis and cellular disturbances can aid in the diagnosis and overall treatment in each particular disease. Knowing how each subtype affects the body can also provide promising insight on developing therapies that target the mechanisms of these subtypes. With this, future studies might be able to focus on the prevention of this deregulation and greatly reduce the morbidity of this malignancy.

Keywords: lymphoma; Non-Hodgkin Lymphoma; B-cell; malignancy; diffuse large B-cell

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1 Introduction

Lymphoid cells are structures that help mediate the body's immune response to foreign pathogens (1). Through a process called hematopoiesis, the body manufactures red blood cells for oxygen transport, platelets to assist in blood clot formation, and white blood cells to support the immune system (2). These three cell types all originate from a multipotential hematopoietic stem cell in the bone marrow that can differentiate into either a myeloid progenitor cell or a lymphoid progenitor cell. The myeloid progenitor further differentiates into platelets, red blood cells and myeloid white blood cells, whereas the lymphoid progenitor differentiates into lymphocyte white blood cells (3).

More specifically, the common lymphoid progenitor undergoes lymphopoiesis (4), allowing for two potential routes of progression. It can form a natural killer (NK) cell to assist in the innate immune system for an immediate, nonspecific response to a pathogen in the body, or it can form a lymphocyte that assists in the adaptive immune system to form a slower but more highly specific, antibody-mediated response to a pathogen (5). This lymphocyte is able to become either a T lymphocyte that interacts with an antigen presenting cell (APC) directly to form a cell-mediated response (6) or a B lymphocyte to produce antibodies that are key factors of the humoral immunity (4).

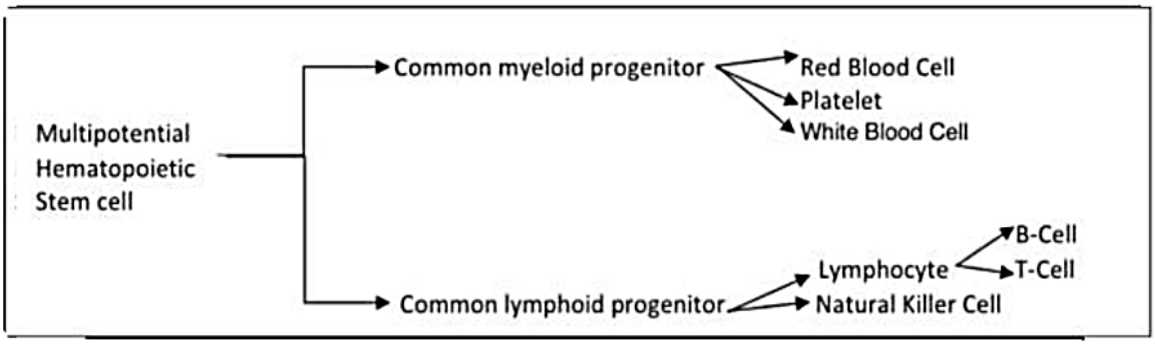

Chart 1: Flow chart of multipotential hematopoietic stem cell progressing to red blood cell, platelet, white blood cell, and B/T cell[7].

B-lymphocyte maturation is a complex process that consists of several highly-regulated stages in order to properly carry out the humoral immune response. Immature B cells are first synthesized in the bone marrow, a primary hematopoietic tissue site, and are then sent out into the circulation until they reach secondary lymphoid organs such as lymph nodes or the spleen. There, they reside predominantly in the follicular (mantle) layer of these secondary lymph organs and undergo further maturation processes (8).

While maturing in the follicular layer, the B-lymphocytes wait for full activation via antigen stimulation of a pathogen from an APC in the mantle zone. Once activated, they move to the germinal center of the secondary lymph organs to complete their maturation process. In the germinal center, the mature B-cells undergo somatic hypermutation and class switching to differentiate into memory cells and activated plasma cells. These two processes in the germinal center are what give rise to the

unique antibody produced by the plasma cell that is specific for the pathogen presented to them by the APC.

The activated plasma cell will then return to the bone marrow and begin the antibody- specific humoral response to attack the invading pathogen by releasing immunoglobulins (Ig)(8), while the memory cells remain idle in the lymphoid organs to assist in a swifter immune response from the same pathogen in future infections(9). The immunoglobulins, also known as antibodies, produced by the plasma cells aid in a pathogen's destruction and clearance from the body (10).

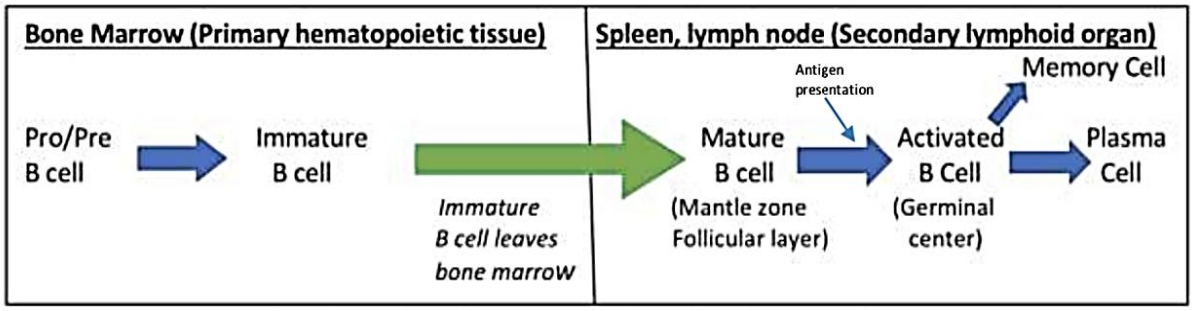

Chart 2: This flow chart depicts the normal maturation process of B-cells within the body.

As highly-regulated as B-cell maturation is, this process is susceptible to mutations or defects that can lead to countless downstream consequences. Mainly, several forms of leukemias and lymphomas can arise from a disruption in the B-cell maturation process. Acute lymphoblastic leukemia (ALL) has mutations of immature B-cell precursors in the bone marrow, chronic lymphocytic leukemia (CLL) has mutations of mature B-cells in the bone marrow, and Hodgkin and Non-Hodgkin lymphomas (NHL) have mutations of mature B-cells inside the secondary lymph nodes (11).

Diffuse large B-cell lymphoma (DLBCL) is a form of NHL and is the most common lymphoid malignancy in adults (12), constituting up to 40% of cases globally (13). This malignancy has three main subtypes: germinal center B-cell-like (GCB) DLBCL, activated B- cell-like (ABC) DLBCL, and primary mediastinal B-cell lymphoma (PMBL). Classifying each subtype into its own form of cancer involves analyzing the unique pathogenesis, genetic mutations and overall oncogenic pathways of all three subtypes of DLBCL (10). Dividing these pathologies into distinct subtypes through identification of their pathomnemonic abnormalities can aid in identification early in the disease process. This could lead to a more focused therapeutic approach for each subtype and better prognosis for diagnosed patients.

	HODGKIN LYMPHOMA	**NON-HODGKIN LYMPHOMA**
Description	Germinal center proliferation	Monoclonal B/T cell proliferation
Lymphadenopathy	Contiguous	Noncontiguous
Symptoms	Non-Hodgkin symptoms PLUS pruritus	Painless lymphadenopathy, B symptoms (fever, night sweats, weight loss)
Risks	EBV	EBV, HIV
Forms	Nodular sclerosis; mixed cellularity; lymphocyte predominant; lymphocyte depleted	Burkitt's; follicular; diffuse large cell; mantle cell
Treatment	Radiation; chemotherapy	Radiation; chemotherapy
Complications	Immunocompromised	Tumor lysis syndrome; immunocompromised

Table 1: This chart highlights the main differences between Hodgkin and Non-Hodgkin lymphomas[14].

2 Germinal Center B-cell-like DLBCL

The pathogenesis of GCB DLBCL has been highlighted as a separate oncogenic mechanism from the other forms of DLBCL through use of gene expression profiling (9). This unique subtype of DLBCL tends to arise from normal germinal center B cells in secondary lymph nodes and is equipped with a number of distinguishing features that separates it from the other subtypes (15).

A gene translocation between chromosome 14 (antibody heavy chain locus) and chromosome 18 (BCL-2 locus) is present in 45% of GCB DLBCL, but has not been found in ABC or PMBL (16). This translocation calls for an overexpression of the BCL-2 protein that prevents cytochrome C release from the inner mitochondrial membrane, thereby inhibiting the apoptotic caspase cascade (16). Along with preventing apoptosis, GCB DLBCL also expresses an overamplification of the oncogenic mir-17-92 microRNA (16) and the deletion of tumor suppressor phosphatase and tension homolog (PTEN) that are unique to this subtype (17). These abnormalities cause an increase in B cell proliferation and further inhibition of apoptosis (18).

GCB DLBCL is also capable of blocking B-cell differentiation within the germinal center during rapid cell division and activation processes of somatic hypermutation via translocation of the BCL-6 gene. This gene is involved in a number of cellular processes that are responsible for B-cell differentiation into plasma cells and proliferation during somatic hypermutation. By blocking expression of a cell cycle inhibitor p27KIP1 and inhibiting cellular senescence, which prevents a cell from dividing, the BCL-6 gene plays a very important role in B-cell proliferation in the germinal center (19). With a translocation of this gene coupled with an overexpression of the BCL-2 gene, the B-cell is prone to unchecked and uninhibited growth that can lead to malignancy.

Given these unique genetic abnormalities in GCB DLBCL, pharmacological therapeutics have been aimed at targeting these upregulated, anti-apoptotic BCL-2 and BCL-6 genes in combination with a number of other therapeutics in order to maximize chances of upregulated proliferation inhibition. Specifically, monoclonal antibodies such as rituximab can directly initiate apoptosis in targeted cells by regulating BCL-2 overexpression via blockade of CD20 on the surface of B-cells, and direct BCL-2 inhibitors such as oblimersen sodium can directly target BCL-2 mRNA (20).

Additionally, previous experimental studies have highlighted the effects of targeting the cells of origin (COO) of bone marrow involvement in GCB DLBCL patients with a treatment regimen of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R- CHOP) (21). When compared to ABC DLBCL, GCB DLBCL had a more favorable outcome with this form of treatment and is considered the standard care for most patients (22). Although similar to GCB DLBCL, ABC DLBCL has several unique characteristics of its own and is separated from the other subtypes through distinct oncogenic hallmarks.

DLBCL Subtype	Hallmark Pathologies	Chemotherapies	Therapeutic MOA
Germinal Center B-cell-like DLBCL	- BCL-2 & BCL-6 upregulation - Cell-cycle inhibitor p27KIP1 deactivation - mir-17-92 microRNA oncogene cluster activation	A. Rituximab B. R-CHOP C. Oblimersen	A. CD20 receptor inhibition; initiate apoptosis via BCL-2 blockade B. Target cells of origin in bone marrow C. Direct BCL-2 inhibition
Activated B-cell- like DLBCL	- NF-κB, MYD88 & FOXP1 upregulation	A. Fostamatinib B. Bortezomib	A. Spleen tyrosine kinase inhibitor B. Proteosome inhibitor
Primary Mediastinal B-cell Lymphoma	-TRAF1, c-REL, NF-κB upregulation	A. Rituximab B. Bortezomib C. R-CHOP (adults) D. EPOCH-R (pediatrics)	A. CD20 receptor inhibition; initiate apoptosis via BCL-2 blockade B. Proteosome inhibitor C. Target cells of origin in bone marrow D. c-MYC, BCL-2 inhibition

Table 2. This chart depicts the three main subtypes of DLBCL, their pathologies, the treatment methods of choice and the mechanisms behind the chemotherapeutics.

3 Activated B-cell-like DLBCL

Mutations affecting post germinal center B-cells that prevent differentiation into plasma cells are the main cause of malignancy in ABC DLBCL (15). More specifically, ABC DLBCL has an upregulated activation of both nuclear factor kappa-light-chain-enhancer (NF-κB)(23) as well as fork head box P1 (FOXP1) that cause the most clear indication of the malignancy(24). In these patients, NF-κB upregulation leads to chronic B-cell receptor (BCR) signaling activation which leads to an increase in intracellular signaling and proliferation (25).

Overabundance of NF-κB is mainly caused by a pathologic increase in the myeloid differentiation primary response gene 88 (MYD88), which also increases the intracellular janus kinase-signal transducer and activator of transcription proteins (JAK-STAT) pathway and type I interferon (IFN) signaling. JAK-STAT is a chain of interactions that are involved in immunity, cell division, cell death and tumor formation. If disrupted, this pathway can lead to uncontrolled cellular proliferation and growth

(26). Type I IFNs are a form of cytokine that are disrupted in ABC DLBCL. The loss of these cytokines is linked to a loss of tumor necrosis factor (TNF) and interleukin (IL) 10(27), which both lead to proliferation of the malignancy.

Uninhibited FOXP1 gene is essential for the cell-line survival of ABC DLBCL cells via repression of apoptosis (24). This transcription gene leads to direct activation of c-MYC (24), which drives multiple synthetic functions needed for rapid cellular growth and division as well as inhibits genes with antiproliferative properties (28). One of the genes this transcription factor indirectly antagonizes is BCL-6(28), a pathomnemonic hallmark of GCB DLBCL shown to be increased in that subtype.

Along with differences in BCL-6, ABC remains distinct from GCB DLBCL due to lack of overamplification of the BCL-2 gene, its absence of oncogenic mir-17-92 microRNA cluster, and its retention of the tumor suppressor PTEN gene. Pharmacologically, ABC DLBCL is treated much more effectively with spleen tyrosine kinase (SYK) inhibitors such as fostamatinib (29). These downregulate the BCR signaling pathway that is seen to be overactive in ABC DLBCL but not in GCB DLBCL. Also, proteosome inhibitors such as bortezomib inhibit the NF-κB pathway that are much more effective for ABC than GCB DLBCL (20). Given the evident contrast between ABC and GCB DLBCL, PMBL is the last subtype of DLBCL that is pathologically similar yet oncogenically distinct from the other subtypes.

4 Primary Mediastinal B-cell Lymphoma

This last molecular subtype of DLBCL is unique in that it mainly arises from thymic B-cells (16). Clinically, PMBL presents differently from both ABC and GCB DLBCL in that it mainly affects younger individuals (median age 33) when compared to the median age of the other subtypes (median age over 60). It also intervenes extensively from the mediastinum into other thoracic structures, which is atypical of NHL in general. NHL malignancies tend to involve extra thoracic sites that PMBL lymphomas do not tend to affect. In this sense, PMBL has more of a clinical presentation of Hodgkin lymphoma than that of NHL (16).

PMBL is also particularly clinically similar to nodular sclerosing Hodgkin lymphoma, a form of lymphoma that typically affects young women. These two forms of malignancy both present with histologically prominent sclerosis primarily in the mediastinum, and possess evidence of thymic remnants upon pathological examination (16).

Through gene expression profiling, it was made evident that PMBL is genotypically more similar to Hodgkin lymphoma as well as clinically, possessing over one third of genes characteristically expressed in Hodgkin lymphoma lines. Some of these features are pathomnemonic Reed Sternberg cells, which are multilobated nuclei (30), constitutive activation of JAK-STAT, and a gain of function in the 9p24 chromosomal region (31). The amplification of this particular chromosome can lead to an increase of oncogene expression that have a prominent role in tumorigenesis (32).

Genetic testing has also revealed that TNF-receptor-associated- factor 1 (TRAF1) and nuclear c-REL are unique to the profile of PMBL (30) when compared to the other subtypes of DLBCL. TRAF1 mutations have specific associations with increased signal transduction of the MAPK and NF-κB pathways, as well as inhibitor-of-apoptosis proteins (IAPs) that are distinct to PMBL (33). The nuclear

c-REL is a protooncogene that aids in the NF-κB activation and also has a prominent role in lymphopoiesis (34).

Similar to ABC DLBCL, the PMB Lover expression of the NF-κB pathway (18) can lead to pharmaceutical chemotherapy treatments that are aimed at inhibiting this pathway. Thus, a downregulation of NF-κB can have positive therapeutic effects in these patients. Bortezomib is a particularly useful chemotherapeutic as it is a proteosome inhibitor that ultimately inactivates NF-κB(36).

Along with NF-κB downregulation, R-CHOP administration has been shown to treat PMBL effectively via the blockage of the CD20 protein and cells of origin in bone marrow (21). In pediatric patients, however, a regimen known as EPOCH-R is given in a dose-adjusting manner based on patient blood tests and includes administration of etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (21). Several studies have shown positive results when highlighting the use of this treatment in the management of PMBL, and some have even began showing the therapeutic effects of this regimen in adults (32). Regardless of age, this therapy mainly targets patients with c-MYC and BCL-2-rearrangements (32).

5 Conclusion

Diffuse large B-cell lymphoma is the most common form of Non-Hodgkin lymphoma worldwide. The pathogenesis of this malignancy affects several phases of the B-cell maturation process, allowing for unique oncogenic variations and clinically independent subtypes. Each disrupted phase of the maturation process leads to its own distinct subtype, resulting in unique symptoms, genomic abnormalities, chemotherapy receptiveness and overall mortality.

Being the most common form of Non-Hodgkin lymphoma, diffuse large B-cell lymphoma comes with a wide array of cellular disruptions that greatly affect the overall malignant effect of the disease. Dividing this neoplasm into specific subtypes by molecular classification systems is showing to be an effective way to target the pathological causative agents in each subtype and manage them accordingly through proper chemotherapeutics. As research and genetic testing progress further, the prognoses of each DLBCL subtype can continue to become more promising. Future experiments continuing to focus on these molecular mechanisms of each subtype and reduce the pathogenic agents can have a substantial impact towards the overall management of this malignancy.

6 Conflict of interest

Drago does not provide any conflicts of interest.

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