The Molecular Landscape of Small Lymphocytic Lymphoma: Mechanisms and Therapeutic Approaches

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Abstract

Cancers such as Small Lymphocytic Lymphoma (SLL) and Chronic Lymphocytic Leukemia (CLL) are typically caused by a series of mutations within an individual's genome. Genes such as *TP53*, *BCL-2*, and *MYC* are crucial in the progression of not only these diseases, but others too. Therefore, in developing therapies for these disorders, it is essential to understand the mutations and interactions of these genes at the molecular level. As a result, understanding the complex mechanisms and signaling pathways that connect the genes is paramount to developing treatments. Additionally, when investigating a cancer case, the pathology behind these cancers must be accurately interpreted for a proper diagnosis. Cytokines must also be understood as they are involved in the cell signaling process. Regarding treatments, comparing the effects of different drug combinations is necessary to determine the most effective treatment regimen. In addition to drug-based treatments, immunotherapies also prove effective. Despite these advanced technologies, diagnosing cancer early on is essential, as an early diagnosis significantly improves the chances of successful treatment and survival.

Introduction

Small Lymphocytic Lymphoma (SLL) is a cancer of uncontrolled, proliferating mature B lymphocytes in the lymph nodes. T lymphocytes are also involved but are not the main source of cancerous cells. Additionally, Chronic Lymphocytic Leukemia (CLL) is the same disease as SLL. However, most cancerous cells in CLL are located in the bloodstream and bone marrow. SLL and CLL are examples of Non-Hodgkin Lymphomas (NHLs) that begin in the lymphocytes, or white blood cells (WBCs) that facilitate the body's response to infection. SLL is staged using the Lugano classification system, which takes into account the extent to which the cancer has spread within the lymph system (Table 1).

Table 1 - Lugano Classification System (adapted from Yoo 75 - 8)

Stage	Diagnostic criteria
Stage I	SLL found in one lymph node or a group of adjacent lymph nodes
Stage II	Found in at least two groups of lymph nodes on same side of the diaphragm
Stage II	Same as above with "bulky" or tumor of large size
Stage III	Found in areas of lymph node above and below the diaphragm and in the spleen
Stage IV	SLL spread widely to at least one organ outside the lymph system

Conversely, CLL is typically classified with the Rai staging system based on blood tests (Table 2).

Table 2 - Rai Staging System (adapted from Rai et al. 219 - 34)

Stage	Diagnostic criteria
Rai stage 0	High lymphocyte count (lymphocytosis); no enlargement of lymph nodes, spleen, or liver; red blood cell (RBC) and platelet counts are approximately normal
Rai stage I	Lymphocytosis; enlarged lymph nodes; no enlargement of spleen or liver; potentially slightly low RBC and platelet counts
Rai stage II	Lymphocytosis; possible enlarged lymph nodes; enlarged spleen; possibly enlarged liver; potentially slightly low RBC and platelet counts
Rai stage III	Lymphocytosis; RBC deficiency (anemia); possible enlarged lymph nodes, spleen, and liver; approximately normal platelet counts
Rai stage IV	Lymphocytosis; platelet deficiency (thrombocytopenia); possible anemia; enlarged lymph nodes, spleen, or liver

In this review, we will explore some of the genes involved in these cancers as well as the mechanisms by which they progress. Furthermore, we will discuss the structure and knockout mouse specific to each gene to understand the function of the gene itself in a broader context.

TP53: The Critical Axis and Normal Function

TP53 is a gene that encodes the tumor suppressor protein p53. It suppresses tumor development by regulating cell division, prohibiting excessive and uncontrollable cell growth. p53 is located in the cell nucleus and binds to DNA. At baseline in a healthy cell, p53 levels are kept low by the negative regulatory proteins MDM2 and MDMX, which mark p53 protein for degradation via a process called ubiquitination. However, when DNA becomes damaged by radiation, UV light, or a lack of nutrients or oxygen, p53 expression increases to determine whether the replicated DNA will be repaired or the cell will undergo apoptosis. Specifically, ubiquitination is inhibited, leading to a rapid growth of intracellular p53 levels. Then, these proteins are activated and stabilized through processes such as phosphorylation, acetylation, and methylation (Kubbutat et al. 299 - 303). If the DNA can be repaired, p53 activates specific pathways to facilitate this process. If not, stabilized p53 protein creates tetramers in the nucleus and binds to DNA to regulate gene transcription, leading to apoptosis (Williams and Schumacher 26070). Through this process, p53 prevents tumor development by regulating the quality of replicated DNA. However, if the *TP53* gene is mutated, the protein's function is compromised, and mutant DNA might continue to cause cancers such as SLL due to the absence of the regulatory protein.

p53: Structure

The structure of p53 consists of 393 amino acids including the following: an N-terminal transactivation domain (TAD), a proline-rich domain (PRD), a DNA binding domain (DBD) connected to a tetramerization domain (TET), and a C-terminal regulatory domain (CTD). The TAD contains an acidic and intrinsically disordered TAD and a proline-rich area. TADs like TAD 1 and TAD 2, both of which are contained in p53, bind to transcriptional machinery components and coactivators to promote transcriptional initiation and interact with negative regulators to end transcriptional activation (Kastenhuber and Lowe 1062 - 78). TAD can also adopt an amphipathic α-helical conformation when binding to partner proteins, such as MDMX and MDM2. The PRD contains five PXXP motifs, some of which may have a polyproline helix-like structure. However, the PRD's exact structure is unknown. The DBD structure contains an immunoglobulin-like β-sandwich, a loop-sheet-helix motif and two large loops stabilized by a tetrahedrally coordinated zinc ion. Lastly, the CTD is an intrinsically disordered region, similar to the TAD, with positively charged residues and a zinc-binding domain (Wang et al. 92).

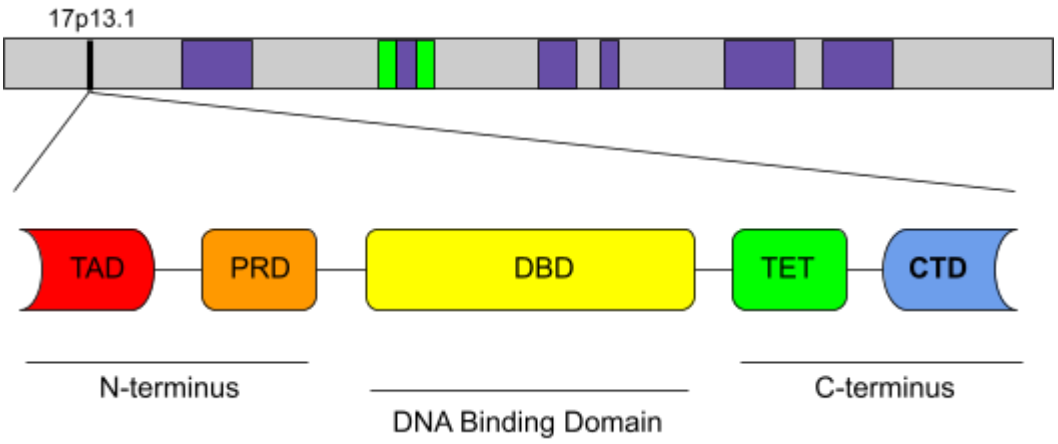


Fig. 1 - Domain architecture schematic for p53 (adapted from Babamohamadi et al. 903075)

TP53: Knockout Mouse

Several research groups have investigated the impact of deactivating the *TP53* gene in mice. Knockout mice with a deactivated *TP53* gene were found on average to develop a tumor in 4.5 months and later die within the next 1.5 months. In contrast, half of the control mice, which were heterozygous, developed tumors within 18 months and were able to live for an additional 12 months (Donehower 269 - 78). Therefore, the inhibition of the *TP53* gene demonstrates that in the absence of a tumor suppressor, a tumor can develop four times as quickly. Furthermore, this highlights why tumors must be diagnosed early to prevent damage to an individual's health.

TP53: MicroRNAs and Mutations

Typically, the cause of cancer is linked to alterations in the genetic code of genes such as *TP53* at the molecular level. The molecular mechanisms underlying p53 and cancer development involve microRNA (miRNA) molecules and their interactions with T lymphocytes. A

microRNA is an endogenous single-stranded RNA molecule that binds to complementary sequences of target mRNAs. This process leads to mRNA suppression of translation. For example, miR-34a is a miRNA that is transactivated by p53 targeting oncogenes FOXP1 and BCL-2. The *TP53* gene induces expression of miR-34a through direct binding to its promoter. When miR-34a is underexpressed, the results include diffuse large B-cell lymphomas (Xu-Monette et al. 3668 - 83). Another miRNA is miR-21 which is regulated by the transcription factor FOXP3 which governs the function of T regulatory cells. Also, miR-21 displays anti-apoptotic properties in malignant T cells. Specifically, miR-21 mutations prevent it from inhibiting the development of cancer which leads to the inability to conduct apoptosis. However, it is currently unknown which specific cells express and which mechanisms regulate miR-21. Similar to the effects observed with miR-21, mutations in miR-155 yield comparable outcomes. miR-155 is expressed when the protein STAT5 is activated, which contributes to the proliferation of malignant T cells (Lindahl et al. 45730 - 44). In total, these pathways contribute to the proliferation of malignant lymphocytes and the development of SLL.

BCL-2: The Critical Axis and Normal Function

While p53 plays a significant role in SLL, its polygenic nature means other genes contribute substantially to the condition. Another gene is *BCL-2* (B-cell leukemia/lymphoma 2 protein) which promotes the survival of cells. *BCL-2* does not increase the rate at which cells divide; rather, it prevents apoptosis. If cell death does not occur, cancer may result. On the other hand, other genes, such as *TP53*, are pro-apoptotic as they promote programmed cell death. This function is activated as a result of harmful events inside or outside the cell, which leads to one of the homologous proteins, BAX (BCL-2–associated X protein), being activated and undergoing structural changes, membrane insertion, and oligomerization. Another protein similar to BAX is BAK (BCL-2 homologues antagonist/killer), which mediates apoptosis. It forms a structure like a channel in the outer membrane of the mitochondria and a mitochondrial protein known as cytochrome c leaves the mitochondria to activate a caspase and apoptosis. However, the BCL-2 proteins also inhibit those that are pro-apoptotic (Klanova and Klener 938). Therefore, cancer progression is determined by the combination of these opposing proteins.

BCL-2: Structure

The structure of BCL-2 is composed of two central hydrophobic helices packed against four amphipathic α-helices. The surface of the protein includes a hydrophobic groove, which is responsible for anti-apoptotic activity. Additionally, BCL-2 is composed of four conserved domains: BH1, BH2, BH3, and BH4. A transmembrane domain is also included which is crucial in regulating apoptosis (Petros et al. 3012 - 7). These details are visually illustrated in **Fig. 2**.

BCL-2: Knockout Mouse

Knockout mice with a *BCL-2* deactivation typically exhibit growth retardation, lymphoid apoptosis, and earlier mortality. This deficiency also disrupted embryogenesis which led to cranial and facial abnormalities in the mice (Veis et al. 229 - 40). Therefore, the deactivation of *BCL-2* is shown to reduce cellular life expectancy due to evidence of disturbed cell growth and physical changes in mice anatomy.

BCL-2: Mutations and their Consequences

The primary mutations in the *BCL-2* gene causing SLL include the frequent

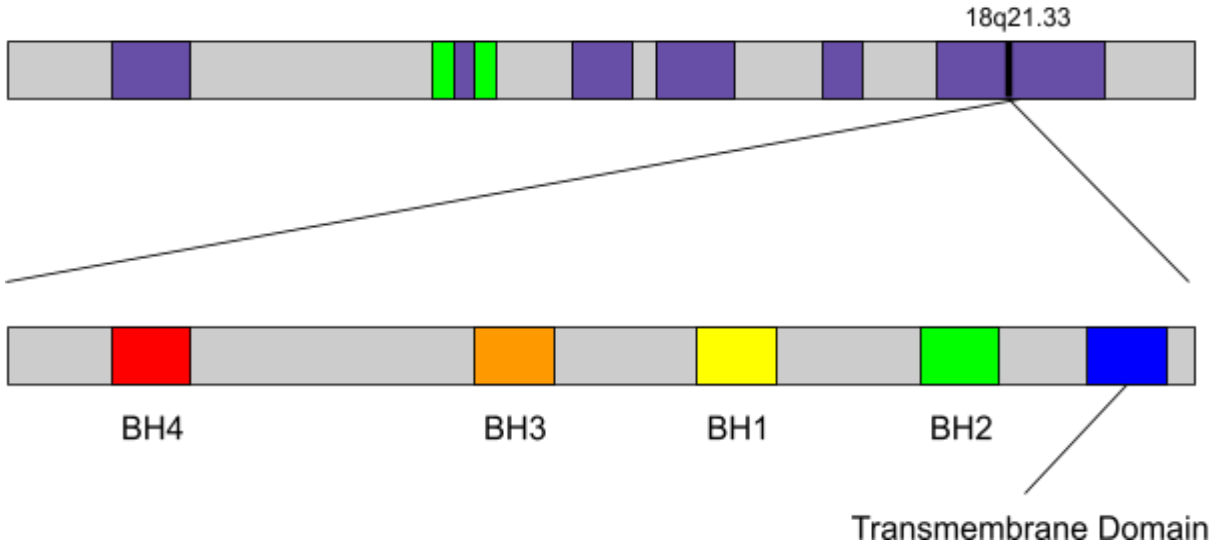


Fig. 2 - Domain architecture schematic for BCL-2 (adapted from Karst and Li 318 - 30)

overexpression of B-cell leukemia/lymphoma-2 (BCL-2/BCL2), myeloid cell leukemia-1 (MCL-1/MCL1), and B-cell lymphoma-extra large (BCL-XL/BCL2L1). These abnormalities play a vital role in lymphoma pathogenesis, drug resistance, and the progression of disease (Klanova and Klener 938). Different abnormalities exist for different cancer subtypes, in some cases, leading to similar outcomes due to identical issues. Among NHL subtypes, gene translocation and loss of chromosomal regions are common. Overall, these mutations lead to a vast increase in cell life span, with cancer being the consequence.

In studying the oncology behind B Non-Hodgkin Lymphomas (B-NHLs), a type of NHL which begins in B lymphocytes, BCL-2 presence is known as BCL-2 positivity. Measuring the extent of this gene expression may be associated with phenotypes such as in SLL. Differing levels of BCL-2 positivity may also be found across subtypes of B-NHL. For example, diffuse large B cell lymphoma (DLBCL) has a BCL-2 positivity around 49% - 67% being overexpressed by *BCL-2* translocation and amplification (Scott et al. 2848 - 56; Hu et al. 4021 - 31; Sehn et al. 131 - 3; Bolen et al. 2298 - 2307). In follicular lymphoma (FL), BCL-2 positivity is typically at least 90%, which is caused by a *BCL-2* translocation (Leich et al. 826 - 34; Bende et al. 18 - 29; Guo et al. 148 - 52). BCL-2 is positive in mantle cell lymphoma (MCL) caused by the loss of the chromosomal region 13q14.3 or gains in the region 18q21, with the former being more than twice as common as the latter (Guo et al. 148 - 52; Davids et al. 826 - 33; Tagawa et al. 1348 - 58). Similarly, in SLL and CLL, *BCL-2* is highly expressed in most cases due to the loss of the 13q14.3 region, BCL-2 hypomethylation, and translocation between chromosomes 11 and 14 (Majid et al. 874 - 7; Calin et al. 15524 - 9; Hanada et al. 1820 - 8). Translocation of the *BCL-2* gene is a common mechanism underlying the causes of some B-NHL subtypes. In other cases, *BCL-2* may not be as positively expressed. This information is summarized in **Table 3**.

Table 3 - BCL-2 positivity levels and mechanisms of overexpression in B-NHL subtypes

B - NHL subtype	BCL-2 Positivity	BCL-2 Mechanism of Overexpression
DLBCL	49% - 67%	*BCL-2* translocation *BCL-2* amplification
FL	> 90%	*BCL-2* translocation
MCL	BCL-2 positive	Loss of 13q14.3 (55% of cases) Gain of 18q21 (20% of cases)
SLL/CLL	BCL-2 positive (highly expressed in most cases)	Loss of 13q14.3 *BCL-2* hypomethylation *BCL-2* translocation

MYC: The Critical Axis and Normal Function

The *MYC* gene is an oncogene and a transcription factor which possesses a variety of functions influencing cellular activities such as the cell cycle, hematopoiesis, and responding to damaged DNA. There are multiple different types of the *MYC* gene, but in this review, we will focus on *c-MYC*. Since *c-MYC* is multifunctional, it is regulated to various extents as well. If *c-MYC* is deregulated, cellular activities such as the cell cycle and DNA repair are not properly regulated, potentially leading to cancer (Ahmadi et al. 121). This is comparable to p53 as when the *TP53* gene is mutated, damaged DNA is not repaired, which may become a cause of cancer due to unfixed genomic alterations. In cell cycle regulation, the *c-MYC* gene plays a role in the cell entering the G1 phase. During G1, the cell grows in size, produces mRNA, and prepares for cell replication. c-MYC is needed in order for the cell to be able to progress into the next stage of cell replication which is the S phase where cellular DNA is replicated. For instance, positive regulators of c-MYC include the kinases ERK, CDK2, and Src (Sears et al. 2501 - 14).

On the other hand, negative regulators include ubiquitin ligases such as Fbw7 (Welcker and Clurman 83 - 93). Collectively, these regulators and many others, influence the level of *c-MYC* gene expression during the cell cycle. If the effects of the negative regulators outweigh those of the positive regulators, *c-MYC* is deregulated and cancers such as SLL and CLL may result. In the DNA damage response, c-MYC plays a role in the expression of NBS1, a protein which influences the expression of the protein kinase ATM. Both NBS1 and ATM are involved in the DNA damage response and repair (Guerra et al. 8924). Downstream, ATM influences p53 which ultimately decides whether the cell is to undergo apoptosis or the DNA will be repaired. Deregulation of *c-MYC* disrupts the coordinated function of ATM and NBS1 in conjunction with p53, thereby impairing the initiation of DNA damage repair or apoptosis in response to genomic damage. Thus, malignant cells may form with mutated DNA resulting in cancer. In initiating apoptosis, c-MYC is involved in the intrinsic and the extrinsic pathways. The intrinsic pathway is initiated by cellular stresses such as DNA damage and hypoxia (Candé et al. 4727 - 34).

In contrast, the extrinsic pathway is activated by the binding of the death ligand to death receptors on the cell surface. Death receptors are a type of tumor necrosis factor receptor family which are responsible for the activation of the signaling cascade and initiation of apoptosis

(Lavrik et al. 265 - 7). *c-MYC* deregulation prohibits it from responding to cellular stressors or ligand binding. The signaling cascade will not activate and apoptosis will not be initiated, resulting in cancers such as SLL and CLL. In all, these failures collectively have the same outcome which demonstrates the multiple levels of *c-MYC* gene regulation and their effects.

c-MYC: Structure

The structure of c-MYC consists of an N-terminal transactivation domain (TAD) which includes conserved transcriptional regulation elements known as MYC boxes (MB), a central region, and a C-terminus region with a basic helix–loop–helix leucine zipper domain (bHLHLZ) (Conacci-Sorrell et al. 014357). The transcription and stability of c-MYC depend on the TAD, making it crucial for the gene in its role as a transcription factor. c-MYC transformation depends on the bHLHLZ region, which is why it is the most studied region structurally. This region is also crucial in the design of drugs to inhibit c-MYC (Draeger and Mullen 1785 - 93). The central region contains a protein sequence known as PEST containing the amino acids proline (P), glutamic acid (E), serine (S), and threonine (T) (Kurland and Tansey 3624 - 9). In **Fig. 3**, there are two nuclear localization sequences (NLS) or amino acid sequences that function as indicators for the c-MYC protein transport into the cell nucleus (Rosales et al. 1953).

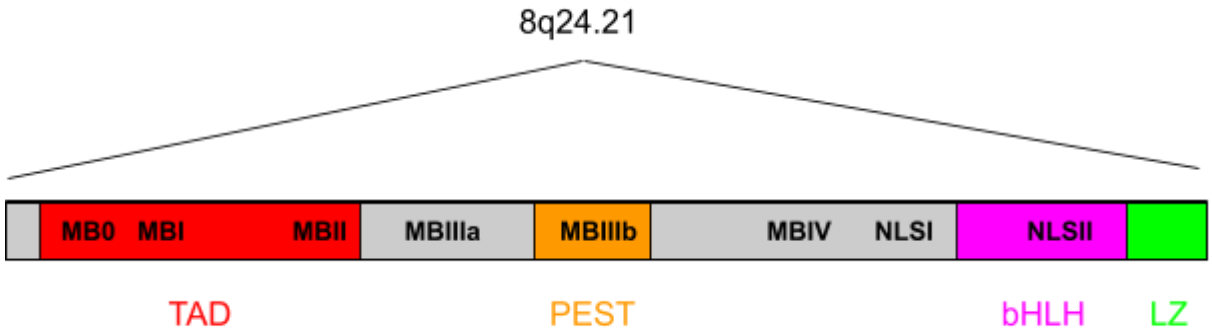


Fig. 3 - Domain architecture schematic for c-MYC (adapted from Soucek et al. 1038)
The Soucek group demonstrated that the c-MYC protein is divided into the TAD with c-MYC boxes MB0, MBI, and MBII, the protein sequence PEST with c-MYC box MBIIIb, and the bHLHLZ region with nuclear localization sequence NLSII.

MYC: Knockout Mouse

Knockout mice with haploinsufficiency (a phenomenon when one functional copy of a gene is insufficient to create a normal phenotype) and a deactivated *MYC* gene after birth were found to live considerably longer than the wild-type mice, exhibit premature aging, and experience a reduced incidence of cancer. The deactivation of *MYC* also facilitated a reduction in mitochondrial and ribosomal structural and functional strength, the creation of reactive oxygen species, and cellular deterioration (Prochownik and Wang 1244321). This is unique compared to the findings of deactivating *TP53* and *BCL-2* as those studies found that deactivating those genes decreased the lifespan of the mice. In contrast, deactivating the *MYC* gene benefits the

mice more than it harms them. This is due to reduced cell proliferation from the *MYC* deactivation which reduces the incidence of cancer.

c-MYC: Mutations and their Consequences

In a study of 750 patients, a variety of gene variants were identified in association with the diffuse large B cell lymphoma phenotype, including one example, SLL. Most of the gene variants in the population were single-nucleotide substitutions, one example being single-nucleotide variations (SNVs). The SNVs were later classified as either germline single-nucleotide polymorphisms (SNPs) or somatic mutations. In the c-MYC coding sequence, fourteen SNPs were identified, with two of the most prevalent being rs4645959 and rs2070582. When SNPs were excluded, c-MYC mutations were found in 250 patients with DLBCL. These mutations were primarily found in the 5'UTR (untranslated region) and coding sequence regions, whereas mutations in the 3'UTR regions were less frequent. In the two groups in the study, the MUT-MYC (mutant) and the WT-MYC (wildtype), the main clinical difference was that MUT-MYC patients with DLBCL originating within the germinal area of the lymph nodes (GCB DLBCL) had a higher frequency of primary nodal origin (lymph nodes) instead of the lymphatic system (extranodal). On the molecular scale, the mutant group experienced more c-MYC 5'UTR mutations ($P < 0.0001$) and CD10 ($P = 0.0052$) and PI3K expression ($P = 0.048$). Another finding found that the mutant group had more frequent *c-MYC* rearrangements compared to the wildtype group ($P = 0.011$) (Xu-Monette et al. 3593 - 605). These are several examples of the most common mutations in individuals with a mutated *c-MYC* gene in DLBCL cases like SLL.

The p53–BCL-2–c-MYC Connection

The three genes discussed can be integrated into a unified model that represents the progression of cancer at a genetic level. First, when *c-MYC* is deregulated, p53-dependent apoptosis is promoted as well as the p53-independent activation of the BH3-only protein Bim (pro-apoptotic). Second, to promote tumor development, targeted inactivation of the p53 or the Bim pathway in B cells that express c-MYC is sufficient (Egle et al. 6164 - 9; Schmitt et al. 2670 - 7). Likewise, tumor-derived c-MYC mutants that exhibit weakened Bim activation but normal increases in p53 levels are capable of creating tumors (Hemann et al. 807 - 11). Therefore, p53-independent and dependent signals act together to promote apoptosis. These signals combined must outweigh the opposing antiapoptotic BCL-2 group, as the inactivation of one of the pro-apoptotic effectors may drop the system below the firing threshold required for apoptosis which may lead to cancer such as SLL and CLL (Hemann and Lowe 1256 - 9).
Note: Puma, Noxa, and Bax are pro-apoptotic proteins known for their roles in the cell signaling pathway that regulates apoptosis. This information is visualized in **Fig. 4**.

The Pathology and Cytokines of SLL and CLL

Pathology is the study of disease which concerns its causes and its effects. A pathologist establishes a diagnosis of SLL or CLL through examination of a tissue biopsy or blood stain.

To begin, we will compare the appearance of normal and cancerous lymph node tissue (SLL) to understand the differences in the tissue specifically that warrant an SLL diagnosis. In a normal lymph node tissue under a microscope, several components must be distinctly visible including the capsule (connective tissue surrounding the node), cortex (outer region of the node), and medulla (internal part of the node). Furthermore, in a normal lymph node, (Fig. 5) there can be expected a variety of cells such as lymphocytes and plasma cells. On the other

hand, a tissue with SLL would exhibit the destruction of normal lymphoid tissue by small lymphocytes which contain irregularly condensed chromatin and round and relatively similar-looking nuclei (Fenu and Rosenthal 32010762). Additionally, paler centers of proliferation are scattered in different areas in the tissue and the cells are characterized as being a more uniform population of B lymphocytes. These differences are visually demonstrated in **Fig. 5** (retrieved from Sangle and Pernick (a) and Kajtar (b)).

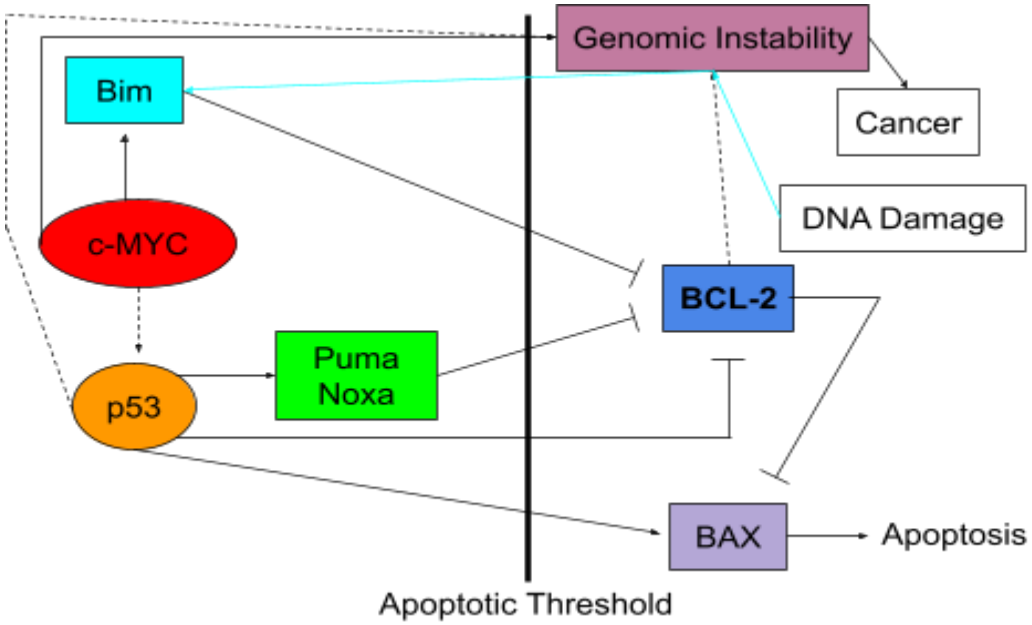
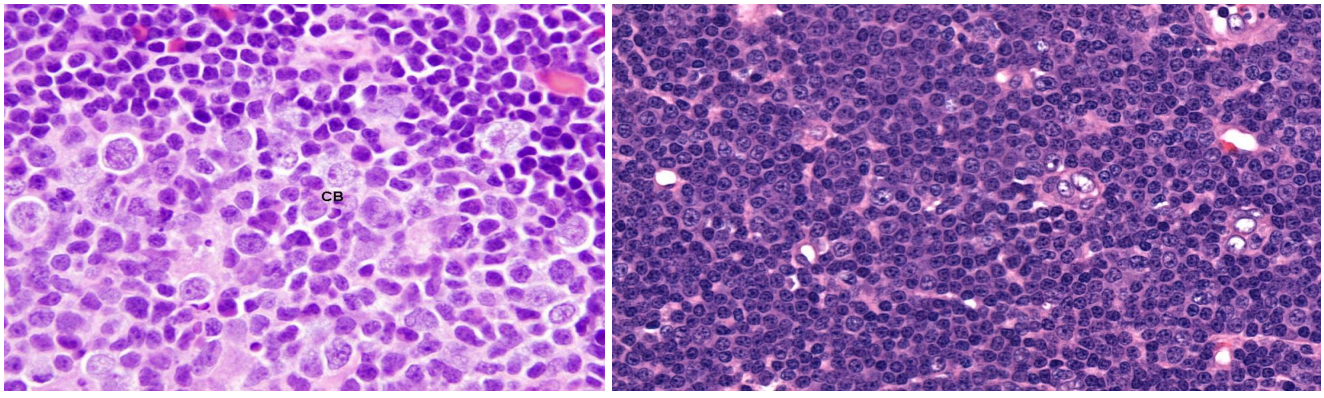


Fig. 4 - The c-MYC, p53, and BCL-2 pathway in apoptosis (adapted from Hemann and Lowe 1256 - 9)
Hemann and Lowe identified proteins that inhibit or activate one other, ultimately leading to cancer or apoptosis.

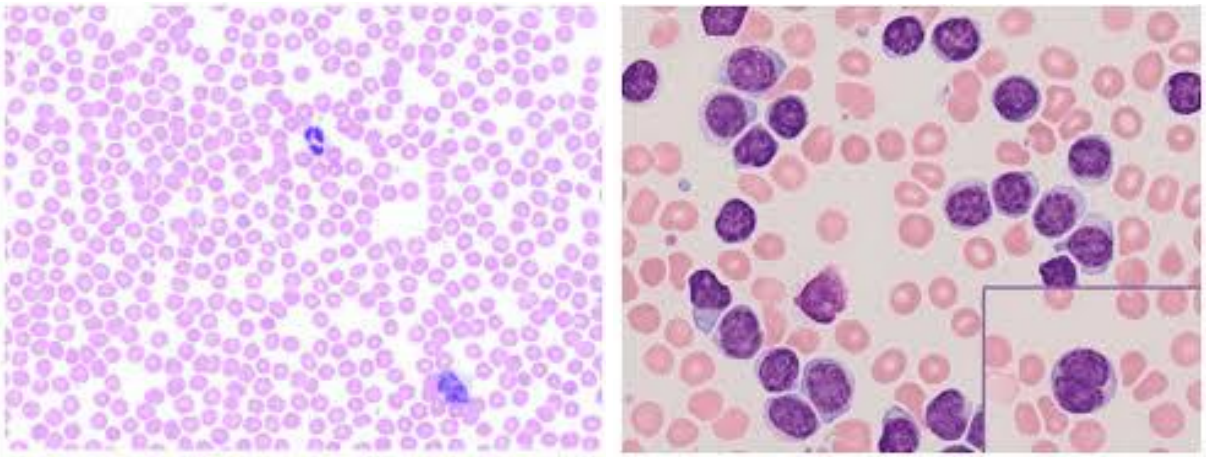


a b

Fig. 5 - Histological slide images of lymph node tissues

a. Normal (retrieved from Sangle and Pernick)
b. Cancerous; SLL (retrieved from Kajtar)

When considering the histology of CLL, a sample of the patient's blood must be analyzed as it is a blood disorder and does not concern tissues. A normal blood smear would be characterized as having relatively uniform RBCs in size and shape as well as a pale center. WBCs should also be present in normal amounts and appear mature without abnormalities. Last, there should not be any smudge cells present. In contrast, a peripheral blood smear of a patient with CLL would include small and mature lymphocytes with darkly stained nuclei, but in greater numbers due to the presence of cancer. Condensed chromatin and smudge cells, which are more fragile than normal lymphocytes, should also be present (Hallek et al. 2745 - 60; Nowakowski et al. 449 - 53). These details are illustrated in the images shown in **Fig. 6** (retrieved from Kachur and Rosen (a) and McCall et al. (b)).



a b

Fig. 6 - Hematological slide images of peripheral blood smears
a. Normal (retrieved from Kachur and Rosen 33889717)
b. Cancerous; CLL (retrieved from McCall et al. 9185432)

Cytokines are signaling proteins involved in the process of cell-to-cell communication, and are especially vital in the immune system. Cytokines are either up-or downregulated in SLL and CLL. Some examples of overexpressed cytokines compared to the healthy control group without SLL include: β2M, I-309, IL-5, IL-10, IL-16, IL-28A, and MCP-1. In contrast, instances of underexpressed cytokines compared to the control include the following: Fractalkine, IFN-γ, IL-17, IL-23, IL-33, TGF-α, and VEGF (Karmali et al. 161 - 70). Despite the expression patterns being mixed, an overall increase in Th2 cytokines and a decrease in Th1 and Th17 cytokines is observed. This abnormal combination of cytokine levels mediates the inflammatory response, which facilitates cancer development. The data is summarized in **Table 4**.

The Influence of Drugs on SLL and CLL Recovery

A variety of drugs and procedures are being developed to treat patients with SLL and CLL. Combinations of drugs and other treatments may also be utilized in other NHL subtypes. The data presented in the following paragraphs is summarized in **Table 5**.

Table 4 - Over and Underexpressed cytokines in SLL

Overexpressed cytokines	P for means	Underexpressed cytokines	P for means
β2M	< 0.001	Fractalkine	= 0.006
I-309	= 0.008	IFN-γ	= 0.003
IL-5	= 0.001	IL-17	= 0.009
IL-10	= 0.001	IL-23	= 0.02
IL-16	< 0.001	IL-33	= 0.008
IL-28A	= 0.001	TGF-α	< 0.001
MCP-1	< 0.001	VEGF	= 0.008

For example, R-CHOP stands for rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, which is a treatment regimen that uses the five mentioned drugs to treat different NHL subtypes. One study found that four cycles of R-CHOP with two additional doses of rituximab had a 94% rate of progression-free survival (PFS) of three years. This was compared to six cycles of R-CHOP, which had a 96% rate of PFS of three years. Cycles were repeated every 21 days with a total sample size of 588 patients. These findings were not statistically significant however so the difference observed between these two treatment options is likely attributable to chance (Poeschel et al. 2271 - 81). Due to the heterogeneous responses to the drugs, further interrogation of these trials is warranted based on the results.

Another study utilized DA-EPOCH-R, which stands for dose-adjusted etoposide, vincristine, doxorubicin with cyclophosphamide, prednisone, and rituximab, which is another treatment regimen used to treat NHL. Six cycles of DA-EPOCH-R were found to have a two-year PFS rate of 79%. This was compared to six cycles of R-CHOP, which was found to have a 76% rate of two-year PFS (P = 0.65). All cycles were repeated every 21 days with 491 patients. Like the previous study, these results were not statistically significant either (Bartlett et al. 1790 - 9). This indicates little to no statistical difference between the rates of PFS of the two treatment methods, which warrants further work on these treatment techniques.

A further example of a drug used to treat cancer is Obinutuzumab, which is a prescription medicine and also a monoclonal antibody. When studied in combination, the Obinutuzumab and 6 or 8 cycles of CHOP produced a three-year PFS rate of 70%. This was compared to a 67% rate of three-year PFS with 6 or 8 cycles of just R-CHOP (P = 0.39). The cycles were repeated every 21 days across a sample of 1,418 patients. Ultimately, this difference was also not statistically significant (Vitolo et al. 3529 - 37). Therefore, there exists relative similarity between these treatment methods and further research should be done to determine a more effective treatment.

In addition to the above discussed combination drug therapies, Venetoclax is a biological small molecular inhibitor designed to target BCL-2. Mechanistically, Venetoclax targets the BH-3 domain of BCL-2 (Perini et al. 66; Itchaki and Brown 270 - 87). Venetoclax functions in a similar

manner to BH-3 which fits perfectly into the space of the BCL-2 molecule where BH-3 binds. Proteins known as BIM actively promote apoptosis which attach to the BCL-2 protein. Consequently, the presence of proteins known as BH-3 only proteins also initiate apoptosis. The proteins can activate other proteins such as BAX and BAK which are responsible for inducing apoptosis. BH-3 only proteins can also prohibit proteins that attempt to prevent apoptosis, like MCL-1. Therefore, Venetoclax can release proteins that trigger apoptosis and prevent tumor development (Mihalyova et al. 10 - 25; Smith et al. 2150 - 63; Merino et al. 879 - 91). A study's findings also demonstrated that in cells with T-cell acute lymphoblastic leukemia (T-ALL), cells treated with Venetoclax showed a considerable increase in apoptosis compared to the control group ($P < 0.05$). The same was observed in cells with B-cell acute lymphoblastic leukemia (B-ALL) treated with Venetoclax ($P < 0.05$) (Tari et al. 229 - 41).

Table 5 - Comparing rates of PFS among different treatment regimens

Treatment comparison	Rate of 2- or 3-year PFS	Statistical Significance
R-CHOP x 4 (+2 additional rituximab) R-CHOP x 6	3 year PFS 94% 3 year PFS 96%	No - neither treatment is inferior to the other
DA-EPOCH-R x 6 R-CHOP x 6	2 year PFS 79% 2 year PFS 76%	No - neither treatment is inferior to the other
Obinutuzumab + CHOP x 6 - 8 R-CHOP x 6 - 8	3 year PFS 70% 3 year PFS 67%	No - neither treatment is inferior to the other

The Influence of Immunotherapies on SLL and CLL Recovery

In addition to the wide range of prescription medicines available for SLL and CLL treatment, immunotherapies are also available to treat these medical conditions should the previous options be insufficient to resolve the issue. Some examples are chimeric antigen receptor (CAR) T-cell therapy and immune checkpoint inhibitors.

CAR T-cell therapy involves collecting T lymphocytes from the patient, and genetically altering them to express a chimeric antigen receptor (referred to as CAR) that targets a specific cancer protein on cancerous cells. Then the modified cells are returned into the patient and used to fight the cancer. The anatomy of the CAR contains an antigen recognition domain targeting a specific antigen, a hinge connecting the recognition site to the transmembrane domain, and an intracellular domain with a CD3z chain vital for the signaling of the T cell receptor (Brentjens et al. 279 - 86; Geldres et al. 3 - 9; Brudno and Kochenderfer 31 - 46; Kochenderfer et al. 689 - 702; Sadelain 3392 - 400). One target for treating lymphomas is the type 1 transmembrane glycoprotein CD19. It is expressed on the surface of B lymphocytes as well as on newly transformed cancer cells, like in B-NHL, in more than 95% of cases (Ramos et al. 112 - 8; Bailly et al. 505 - 17). Thus, CD19 is a viable target for treating these lymphomas.

Despite the potential effectiveness of CAR T-cell therapy, several risks are associated with this technique. For example, cytokine release syndrome (CRS), a systemic inflammatory response, is the most frequent adverse effect. The exact mechanism by which this occurs is not entirely understood, although it is related to the release of inflammatory cytokines (Gauthier and Turtle 50 - 2). The main symptoms include fever, fatigue, rigors, or anorexia, which may be

followed by tachycardia, hypoxia, neurological changes, and more (Riches and Gribben 207 - 35). Another obstacle is immune effector cell-associated neurotoxicity syndrome (ICANS), a side effect characterized by inflammation found in the brain. Again, the mechanisms by which this occurs are not entirely understood, but some theories claim it may be associated with CNS T-cell trafficking, greater vascular permeability, and a disruption in the blood-brain barrier (Lee et al. 517 - 28). Symptoms of this include headaches, focal deficits, confusion, seizures, and hallucinations (Gust et al. 1404 - 19; Wang et al. 896 - 925). A third challenge is infection. The therapy weakens the patient's immune system, resulting in a depletion of B lymphocytes, which can lead to diseases such as adenovirus, cytomegalovirus (CMV), Epstein–Barr virus (EBV), and human herpesvirus 6 (HHV6) (Ostojska et al. 1595; Liu et al. 126 - 9).

In contrast to CAR T-cell therapy, immune checkpoint inhibitors block proteins known as checkpoints that regulate the immune response to cancer cells. Cancer cells may exploit these checkpoints to avoid destruction. One example of an immune checkpoint inhibitor is Bruton's Tyrosine Kinase (BTK). BTK has been identified as a part of the B-cell receptor (BCR) signaling pathway and is necessary for normal B-cell development (Singh et al. 57; Hendriks et al. 219 - 32). Some examples of BTK inhibitors specifically for the treatment of SLL and CLL include ibrutinib and acalabrutinib. These inhibitors deactivate BTK by binding to Cys481 on the ATP-binding region of BTK, which inactivates the BTK enzyme and disrupts BCR signaling. This signaling disruption can then prevent the disease progression (Singh et al. 57; Palma et al. 686768).

There are a variety of adverse effects, many of which are shared among three immune checkpoint inhibitors: ibrutinib, acalabrutinib, and zanubrutinib. The most common effects include diarrhea, arthralgia, hypertension, atrial fibrillation, UTI, dyspepsia, headache, cough, and bleeding (Byrd et al. 3441 - 52). **Table 6** compares CAR T-cell therapy to immune checkpoint inhibitors based on their operational mechanisms and adverse effects.

Table 6 - The operational mechanisms and risks of CAR T-cell therapy and immune checkpoint inhibitors

Type of therapy	**CAR T-cell therapy**	**Immune checkpoint inhibitors**
Operational mechanism	Genetically altering T-lymphocytes	Blocking checkpoints that regulate immune response
Risks/adverse effects	Fever, fatigue, anorexia, tachycardia, hypoxia, neurological changes, cytokine release syndrome, headaches, seizures, hallucinations, neurological toxicity (eg. ICANS), adenovirus, CMV, EBV, HHV6	Diarrhea, nausea, bleeding, fatigue, cough, neutropenia, hypertension, atrial fibrillation, headache, muscle spasms, urinary tract infection

Cancer Diagnostics

Even though research efforts towards developing drugs are taking shape and are successful to an extent, diagnosing a patient with cancer as accurately and early as possible gives the best chance to healthcare professionals in treating the disease effectively.

One group of tests that can be done to diagnose a patient early on with CLL is a blood test. Notable in this group are the complete blood count (CBC) and the peripheral blood smear. First, the CBC test measures the amount of WBCs, RBCs, and platelets in the bloodstream. This is also done with a differential which counts the types of WBCs in the sample. When a blood-related issue is suspected, these tests are among the first to be done. Individuals with CLL exhibit lymphocytosis, characterized by an excessive number of lymphocytes. However, other tests should be done for improved accuracy as CLL patients may also display low levels of RBCs and platelets. Second, the peripheral blood smear consists of a microscopic analysis of the blood sample. In CLL, the blood smear may show numerous smudge cells, or abnormally shaped or damaged lymphocytes (Hallek et al. 2745 - 60; Nowakowski et al. 449 - 53).

Biopsies are another method to detect an early onset of cancer. In a biopsy procedure, a sample of tissue is removed for microscopic analysis to diagnose or monitor a disease. For example, a lymph node biopsy involves removing a portion of the lymph node to be tested for leukemia cells. This method is typically utilized when blood tests are insufficient to make the diagnosis or when the doctor wants to know if the leukemia has progressed into a more aggressive cancer. If these methods are combined and still insufficient for diagnosis, a bone marrow aspiration and biopsy are performed together. In the bone marrow aspiration, a hollow needle is inserted into the bone marrow of the hip bone, and a syringe suctions a small quantity of liquid bone marrow. The biopsy is performed by taking a small piece of bone and marrow using a larger needle that is inserted into the bone (Hallek et al. 2745 - 60).

These blood tests and biopsies are viewed microscopically by a pathologist, hematologist, or oncologist. Pathologists specialize in examining specimens to study diseases. Hematologists specialize in the detection and treatment of blood-related disorders. Oncologists specialize in the detection and treatment of cancer.

Flow cytometry and immunohistochemistry are two other tests used to classify cancer cells based on the antigens (tags) on their surfaces. This is known as immunophenotyping. Both tests involve treating samples of cells with antibodies, which are proteins that bind to specific antigens. Flow cytometry categorizes the treated cells using a machine that analyzes their physical and chemical features with the aid of a laser (Hallek et al. 2745 - 60). On the other hand, in immunohistochemistry, treated cells are viewed under a microscope to determine if antibodies are bound to antigens on the cell surfaces (DiGiuseppe and Borowitz 6 - 10).

Chromosome, molecular, and genetic tests are also used to understand the causes of cancer phenotypes. For example, in cytogenetics, cells are grown in a laboratory for several days before their chromosomes are analyzed microscopically. Another assay is fluorescent in situ hybridization, which uses fluorescent dyes that bind to regions of specific chromosomes. This technique is typically faster than cytogenetics because cells do not need to be grown. These tests usually look for alterations in an individual's genome. For instance, a section of a chromosome may be missing (deletion), an extra copy of a chromosome may be present (trisomy), or genetic material is swapped between two chromosomes (translocation). Some examples of genomic alterations in CLL include del(11p) or del(17p), which are deletions (Molica et al. 1177 - 85). Regarding molecular tests, common proteins analyzed include immunoglobulins. These antibodies aid the body in fighting infections and are composed of light

and heavy chains. The immunoglobulin heavy chain variable region genes, IGHV or IgVH, and whether they are mutated, can provide insight into the aggressiveness of CLL (Thompson et al. 303 - 9). As previously mentioned, mutations in the *TP53* gene may also provide insight into the severity of not only CLL, but also other cancers.

Some blood-based tests that can be applied with the help of biomarkers to detect cancer are circulating tumor DNA (ctDNA) and circulating tumor cells (CTC). ctDNA is composed of DNA derived from tumor and normal cells in extracellular bodily fluids. The biomarker can be used to assess the molecular basis of the tumor and predict the patient's future cancer progression (Mithraprabhu and Spencer 129 - 45). In comparison, CTCs are released from tumors and are moved through the body via the circulatory system or lymphatic vessels. Afterwards, they may settle and form micrometastases (small, undetectable clusters of cancer cells) under the right conditions. This information may also describe the tumor's molecular landscape, assisting in cancer diagnosis (Vidlarova et al. 3902).

Conclusion: Future Perspectives

The variability in the statistical significance of treatment outcomes across different therapeutic agents for NHL underscores the uneven progress in drug development within this field. While some therapies demonstrate clear clinical benefit, others yield more modest or uncertain improvements. However, this must be understood in the context that immense time and effort are invested in developing new treatments for these cancers, and not all of them will yield a notable improvement compared to other similar drugs or courses of medication. Importantly, identifying and addressing limitations in new treatments remains a critical component of the drug development process. Lessons learned from suboptimal outcomes are invaluable in guiding future research directions and refining treatment strategies to enhance efficacy and patient care.

Researchers funded by the National Cancer Institute are currently advancing knowledge about lymphomas. Some current treatment techniques include chemotherapy, radiation therapy, targeted therapy, and immunotherapy to treat all kinds of NHL cancers, including SLL and CLL. Another treatment influences the signaling pathways, such as the B-cell receptor pathway, which regulates NHL. To treat SLL, a new drug, ibrutinib (Imbruvica), has been approved to shut down the pathway. As technology advances, we will undoubtedly see more advanced and effective methods of treating various cancers. Despite this, it is still paramount to maintain a healthy lifestyle as cancer prevention is more beneficial for any individual, regardless of whether or not they have cancer. Ultimately, the combination of proactive health decisions and a detailed understanding of biological science seems to be the foundation for effective cancer management.

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