Genetic and Epigenetic Features of Cancer Stem Cells: Implications in Lymphoma

Naavya Shrivastava

ABSTRACT

Cancer stem cells (CSCs) play a pivotal role in the initiation, progression, and relapse of various malignancies. Stem cells are widely explored yet research on the existence of lymphoma stem cells is limited and rather controversial, however the idea is not far-fetched. By linking the hematopoietic origin of lymphoma cells and strong evidence demonstrating that originating CSCs are critical in the initiation and maintenance of most cancers, this paper hypothesizes the existence of similar CSC like populations that may generate and replenish various lymphomas.

This paper first investigates the genomic and epigenomic features of cancer stem cells, and their contributions to tumour dynamics. By analysing literature on the genetic and epigenetic landscapes of these cells, I identify key mutations, regulatory mechanisms, and epigenetic modifications that drive oncogenesis, proliferation and therapy resistance.

Then, the findings are used to highlight specific genomic alterations and epigenetic patterns that distinguish putative lymphoma stem cells from bulk tumour cells in attempt to identify similarities and differences. By integrating evidence and insights into their unique capabilities for self-renewal, differentiation, evasion of treatment and relapse, this paper seeks to substantiate the existence of lymphoma stem cells, and explore how the potential of mutated B-cell lymphocytes impacts other types of lymphoma, including classic Hodgkin's lymphoma and follicular lymphoma.

This review aims to enhance our comprehension of the molecular underpinnings of lymphoma by examining the potential role of CSC- driven mechanisms. By

elucidating these processes, we can develop more effective treatment strategies, ultimately improving patient outcomes through targeted therapies.

KEYWORDS

1. Cancer stem cells (CSCs)
2. Lymphoma stem cells (LCSCs)
3. Oncogenic mutations (MYC, RAS, p53)
4. Epigenetic regulation (DNA methylation, signalling pathways)

INTRODUCTION

Lymphoma, a heterogeneous and complex hematologic malignancy, poses substantial obstacles in oncological treatment owing to its propensity for recurrence and refractoriness to conventional therapeutic modalities. The concept of cancer stem cells (CSCs) is central to these challenges, as this subpopulation of tumour cells exhibits resistance to traditional chemotherapy and radiation, and shares characteristics with stem cells, including self-renewal, differentiation, and tumorigenic potential, thereby likely contributing to cancer metastasis and relapse. [1]

Definitive proof of the existence of cancer stem cells came from studies in leukaemia, where among the complete tumour cell population only a small subset of cells could initiate, regenerate and maintain the leukaemia after transplantation into immunocompromised mice. Using similar functional approaches, a variety of cancer stem cells have been identified in an increasing number of epithelial tumours, including breast, prostate, pancreatic, head and neck carcinomas, all of which were distinguished by the expression of the cell-surface glycoprotein CD44. Another cell

surface marker, the CD133 glycoprotein, defined the tumour-initiating cells of brain and colon carcinomas. [2]

The study of lymphoma cancer stem cells (LCSCs) reveals a complex, unexplored environment where genetic and epigenetic factors regulate self-replication and differentiation. Discoveries in leukaemia and solid tumours suggest the possible the existence of lymphoma-initiating cells with stem-like, as a small subset of lymphoma cells can regenerate tumours. [3] Clinical cases also support this, such as follicular lymphoma transmission via bone marrow transplant years after donor diagnosis, highlighting their role in recurrence. [4]

Insights from B-cell somatic hypermutation and shared transcriptional programs between immune memory cells and hematopoietic stem cells (HSCs) further suggest LCSC self-renewal potential. [5] Yet, unlike HSCs leukaemia stem cells, marked by $CD34^{+}$ / $CD38^{-}$, definitive LCSC markers remain elusive. This ambiguity fuels debate: some attribute stem-cell like traits to tumour heterogeneity rather than a distinct population, while others argue that all lymphoma cells may drive progression and resistance.

In this review, I synthesize current knowledge on the genetic and epigenetic regulation of CSCs to better define the characteristics that may underlie lymphoma self-renewal, initiation, and relapse. Clarifying the existence and biology of LCSCs may inform novel therapeutic strategies to improve patient outcomes.

METHODS

This paper employs a literature-based review methodology to investigate the genetic and epigenetic features of cancer stem cells (CSCs) and their potential role in lymphomagenesis. Scholarly databases such as PubMed, Nature, and SpringerLink were systematically searched using combinations of keywords including “cancer stem cells,” “lymphoma stem cells,” “oncogenic mutations,” “DNA methylation,” and “signalling pathways.” Publications between 2000 and 2025 were considered, with emphasis on peer-reviewed studies elucidating mechanisms of CSC self-renewal, differentiation, and therapy resistance. Selected papers were analysed to identify recurrent oncogenic mutations, tumour suppressor inactivation, and epigenetic alterations, and to synthesize findings from lymphoma-specific case studies and comparative stem cell research. Figures were created using BioRender for conceptual visualization. This integrative analysis allowed the correlation of existing CSC frameworks with emerging evidence for lymphoma stem cell populations.

RESULTS

What are Cancer Stem Cells?

CSCs were first identified in acute myeloid Leukaemia in 1994 in which an AML-initiating cell population was identified from AML patients by transplantation into severe combined immune-deficient (SCID) mice. The leukaemia-initiating cells were identified on the basis of cell surface marker expression CD34+/CD38−. By 2003, evidence of cancer stem cells had been identified in breast cancer, brain cancer, and a variety of tumours including those in the colon, pancreas, lungs, and melanoma. [2]

This subpopulation of cells are defined by their ability to self-renew, differentiate and their resistance to conventional cancer therapies (chemotherapy and radiation therapy)

[2] They are primarily characterized by the property of unlimited self-renewal, maintenance and expansion of the undifferentiated cell pool over the lifetime of the host, and multi-lineage differentiation, which produces progeny of diverse mature phenotypes to generate and regenerate tissues. [3]

Origin and theories on the existence of CSCs

The origin and classification of CSCs remain debated, with estimates ranging from a small tumour subpopulation to as many as 25% of cancer cells exhibiting stem-like traits. Proposed origins include transformation of normal stem/progenitor cells under environmental changes, genetic or epigenetic alterations in somatic cells, and epithelial-to-mesenchymal transition (EMT) driven by transcription factors such as SNAI1/2, ZEB1/2, or TWIST1/2, which enhance invasiveness and self-renewal. [2]

CSC identification relies on surface markers, but these lack universality and may change with cancer progression, complicating characterization. [2] Some researchers even question CSC existence, arguing that xenotransplantation studies distort tumour biology, since human tumour growth depends on interactions with supporting cells absent in mice. This perspective supports a clonal evolution model, where many tumour cells—not a distinct CSC subset—sustain cancer growth. [6]

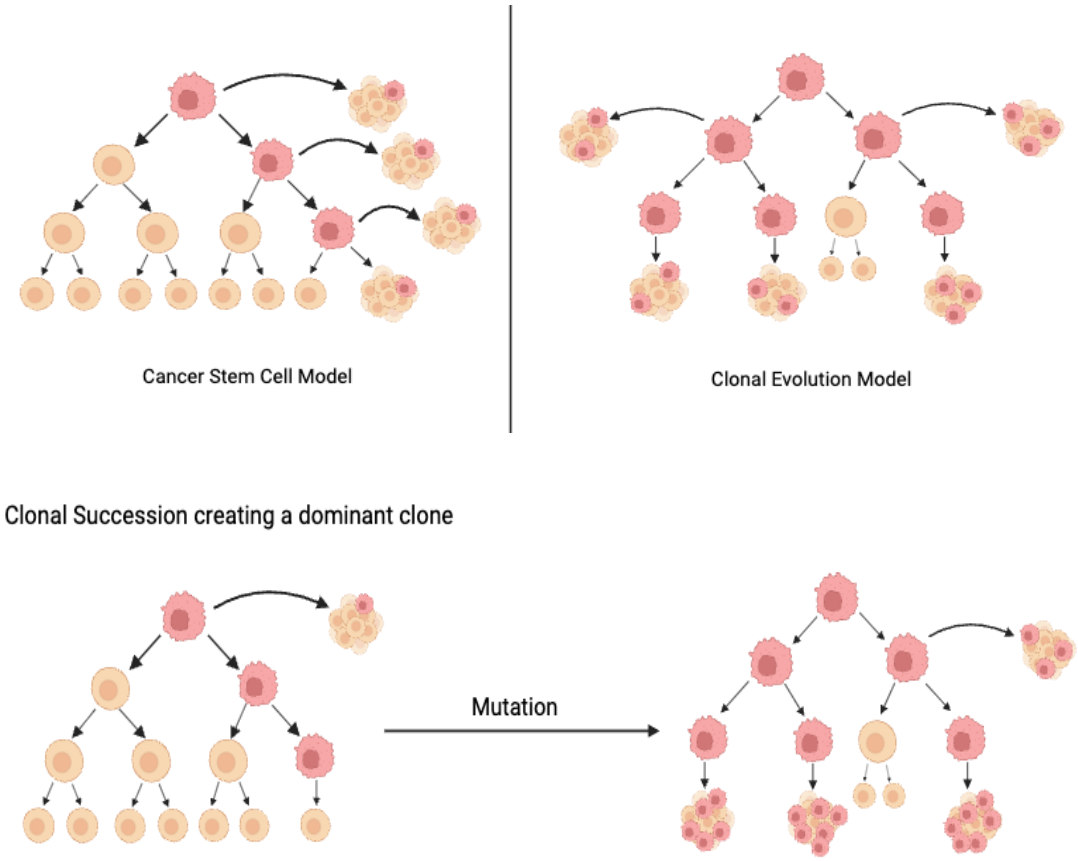

Figure 1 –Diagrammatic representation of the possible ways a cancerous tumour grows (Created in https://BioRender.com)

Genetic features of CSCs: Mutation of Oncogenes

Proto-oncogenes regulate cell growth and survival, but mutations or amplifications can convert them into oncogenes, driving uncontrolled proliferation and cancer. Activation occurs via chromosomal translocation (e.g., MYC in Burkitt's lymphoma), point mutation (e.g. codon 12 of RAS), gene amplification (e g. C-MYC in neuroblastoma), or promoter insertion, often seen in retrovirus- induced cancers. [7]

C-MYC is one of the most frequently dysregulated genes in most human cancers, either through mutations or disrupted signalling pathways. Its overexpression promotes tumorigenesis and can induce secondary mutations, such as p53 inactivation, disabling apoptosis. Additional oncogenes such as BCL2, BCL-xL, and RAS further enhance survival and proliferation. [7]

RAS, the second most mutated oncogene, integrates signals from growth factors, cytokines. adhesion molecules and stress stimuli. It encodes 3 proteins: K-Ras, N-Ras and H-Ras that are mutated in about 70% of cancers. K-Ras mutations are common in pancreatic (90%), colorectal (44%) and lung cancers(33%) ; N-Ras mutations occur in Melanoma (13%), liver (30%) and AML (30%); while H-Ras mutations are seen in bladder and kidney cancers (10%). All 3 are implicated in thyroid carcinoma. These mutations generate oncoproteins that drive metastasis and angiogenesis, partly by upregulation VEGF and suppressing thrombospondin-1. [8]

Genetic features of CSCs: Inactivation of tumour suppressor genes

Tumour-suppressor genes(TSGs) are essential for preventing cancer by limiting cell growth, promoting apoptosis, and maintaining genomic stability. The human genome contains about 6% TSGs, including 2% on the X chromosome. Inactivation typically occurs through mutations, deletions, or abnormal cell division, contrasting with the growth promoting roles of proto-oncogenes and oncogenes. [7]

The p53 gene is the most prominent TSG, acting as a transcription factor that activates growth-inhibitory and pro-apoptotic proteins in response to DNA damage. It is typically central to the G1-S checkpoint, and disabling mutations allow continued division despite DNA lesions, driving oncogenesis. [7]

ATM is another key TSG, detecting DNA damage and phosphorylating targets such as p53, BRCA-1, and CHK2 to trigger checkpoints and repair pathways. Loss of both ATM alleles causes ataxia-telangiectasia, a disorder marked by cerebellar degeneration, vascular and immune deficiency and increased susceptibility to lymphoid cancers. [7]

Epigenetic features of CSCs: DNA methylation

DNA methylation, the addition of a methyl group to cytosine residues within CpG dinucleotides, is a key epigenetic modification regulating gene expression, genomic imprinting, X-chromosome inactivation, transposon silencing, and genome stability. [9] [10]

Aberrant methylation is a hallmark of cancer. Hypermethylation of promoter regions frequently silences tumour suppressor genes, suggesting that epimutations can act as oncogenic drivers. Examples include MLH1 repression, contributing to genomic instability in gastric and colon cancers; CDH1/CHH13 silencing, which promotes invasion and metastasis; and hypermethylation of DAPK1, and apoptosis regulator [9]

In lymphoma, stem cells show marked epigenetic plasticity, allowing transitions between stem-like and differentiated states, which supports therapeutic resistance. This resistance is particularly evident against hypomethylating agents. Additionally, tumour suppressor silencing has been linked H3K27me3-mediated repression, underscoring the interplay between DNA methylation and histone modification in sustaining lymphoma stem cell populations. [11]

Epigenetic features of CSCs: Signalling pathways

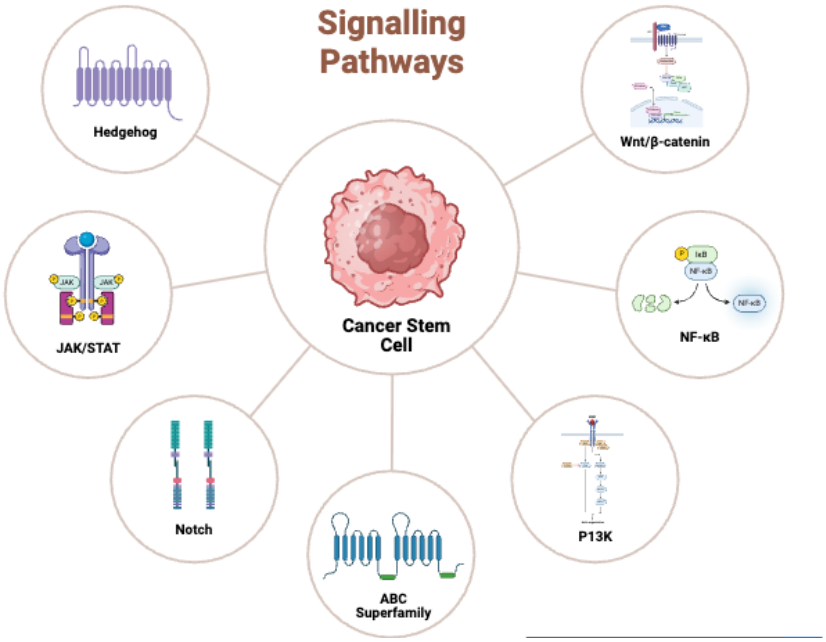

Figure 2- the main signalling pathways whose dysregulation plays a major role in CSC epigenetic environment (Created in https://BioRender.com)

Dysregulation of signalling pathways is central to CSC self-renewal and proliferation. Key pathways include PI3K/AKT, JAK/STAT, Wnt/β-catenin, Hedgehog, Notch, NF-κB, and regulators such as PTEN and Bcl-2. PI3K/AKT activation drives tumorigenesis across cancers, with PTEN and mTOR defects reported in melanoma, T-ALL, and prostate cancer. Similarly, aberrant JAK/STAT signalling promotes tumour initiation, while NF-κB dysregulation enhances survival, chemoresistance, and inflammation. Notch, Hedgehog, and Wnt pathways also maintain CSC populations, and cooperative Wnt/Notch dysregulation in lymphoma CSCs has been

shown to promote tumour growth, supported by PI3K/AKT/mTOR signalling. [12]. [13]

Clinical implications of CSCs

CSCs are emerging as critical therapeutic targets, as their resistance to Chemotherapy and radiotherapy contributes to relapse and metastasis. Current treatments often lack specificity against CSCs and damage healthy tissue, leaving residual CSCs that drive recurrence.

Novel strategies now aim to target CSCs directly or disrupt their supportive microenvironments. Therapeutic targets include ABC transporters, anti-apoptotic and detoxifying enzymes, DNA repair machinery and oncogenic signalling cascades. [11] CSCs also evade immune detection by upregulating PD-L1, suppressing antigen presentation, and interacting with tumour-associated macrophages to maintain an immunosuppressive niche. [14]

Surface markers provide additional targets: for instance high CD133 expression correlates with poor prognosis in colon, prostate, and head and neck cancers, suggesting CD133-directed therapies may be effective. In mature B-cell malignancies, stromal cells in bone marrow and lymphoid organs create protective niches that promote CSC survival, proliferation and drug resistance.

The defining properties of CSCs remains their ability to regenerate tumours resembling the original. However, translation into clinical therapy is limited by the

inconsistent correlation between CSC frequency and patient outcomes. Despite these challenges, CSCs remain central to recurrence and therapy resistance.[12]

Lymphoma Stem Cells

Lymphoma stem cells are a rather grey area- evidence regarding their existence is limited and whether they actually exist in itself is quite controversial. While leukaemia-originating stem cells are critical in the initiation and maintenance of leukaemia, the existence of similar cell populations that may generate lymphomas such as B-cell or classic Hodgkin's lymphoma upon mutation remains uncertain. [3] This part of the paper aims to synthesize the limited research on the lymphoma progenitor cells as well as see the other possible ways by which lymphoma relapses if not by stem cells.

Self-renewal in memory T cells and Memory B-cells

Self-renewal is the process by which a daughter cell identical to its parent is produced, enabling certain cells to maintain their population throughout an organism's lifetime. Long-term hematopoietic stem cells (LT-HSCs) are the best studied example, as they are multipotent and can both differentiate into mature blood cells and self-renew indefinitely.[15]

However, self-renewal in the hematopoietic system is not confined to stem cells. Antigen-specific memory B and T cells have also been observed to self-renew in over long periods. These mature cells reacquire long-term self-renewal capacity through differentiation following immunostimulation, such as infection. Upon antigenic exposure, naive lymphocytes undergo rapid clonal expansion and differentiation. In T

cells, this produces effector cells capable of combating foreign pathogens. Most effector T cells undergo apoptosis after pathogen clearance, but a small subset persists, forming a long-lived memory T cell pool. [15]

B cell responses to antigenic challenge generate short-lived plasma cells and germinal centre B cells, which undergo somatic hypermutation and Ig isotype switching. Plasma cells remain quiescent yet secrete antigen-specific antibodies indefinitely, independent of re-exposure. In contrast, memory B cells self-renew slowly and, upon re-exposure, rapidly differentiate into plasma and germinal centre B cells for another round of affinity maturation. Thus, LT-HSCs, memory B and T cells maintain themselves through self-renewal while retaining differentiation potential. [15]

Despite this shared property, overlap in self- renewal pathways between memory cells and HSCs is limited. Because HSCs are indispensable for survival, they rely on redundant pathways, only some of which are used in memory lymphocytes. For example, both memory T cells and LT-HSCs express TNF receptor II (p74R) and TNF receptor-associated factor 1 (Traf-1), which inhibit apoptosis through intracellular signalling. Both also share members of the RAS-MAPK pathway, which regulates proliferation, apoptosis, and differentiation. Likewise, the memory B cells and LT-HSCs express transcripts such as TCF4 and TCF12, downstream of β-catenin signalling, a pathway central to self-renewal across stem cell systems. [15]

Recent studies confirm that both TCF4 and TCF12 are transcriptionally activated by β-catenin in B-cell lymphoma stem cells. In addition, Traf-1 and TNFR2 signalling promotes their survival via NF-KB activation. A cooperative loop between

MAPK/ERK and Wnt/β-catenin pathways was also identified, sustaining the stemness gene network in aggressive B-cell lymphomas. [16]

Mutations in these receptor proteins or RAS genes may therefore drive the emergence of cancerous stem cells. Similarly, β-catenin overexpression, frequently observed in cancers, promotes uncontrolled differentiation and self-renewal. These findings link the CSC-like properties of memory B and T cells to the existence and persistence of B-cell lymphoma stem cells.

Medical cases: Functional Evidence

Aberrant Somatic hypermutation and Hodgkin's lymphoma:

During T-cell–dependent immune responses, antigen-activated B cells undergo clonal expansion in germinal centres, where the immunoglobulin variable (IGV) region genes are subject to somatic hypermutation (SHM). This process introduces nucleotide substitutions that can generate higher-affinity variants, which are then selected to become memory B cells or plasma cells. [5]

In diffuse large B-cell lymphomas (DLBCLs), SHM malfunctions in over 50% of cases, affecting both immunocompetent and immunocompromised hosts. As a consequence, proto-oncogenes such as PIM1, c-MYC, RhoH/TTF, and PAX5, are aberrantly mutated, with some loci also undergoing chromosomal via SHM induced DNA double-strand breaks. Such events may contribute to the emergence of CSCs. [5]

Hodgkin lymphoma, comprising nodular lymphocyte-predominant (NLPHL) and

classic Hodgkin lymphoma (cHL), also originates from germinal centre B cells that may acquire self-renewal properties, at different differentiation stages. [5] Studies show that aberrant SHM targets proto-oncogenes in 80% of NLPHLs and 55% of cHL cases, mirroring the mutational spectrum of IGV genes. Mutations typically involve single nucleotide substitutions, with occasional deletions and insertions, and extend to tumour suppressor genes such as SOCS1 in about 40% of primary cHL cases.[10]

Epigenetic alterations further support CSC-like properties in cHL. Methylation studies of B-cell–specific genes in cHL-derived cell lines and primary HRS cells both reveal monoallelic and mixed methylation states. Genes such as CD79B show ongoing methylation, while SYK is consistently hypermethylated, suggesting selective pressure. Importantly, BOB.1/OBF.1, a transcriptional coactivator of immunoglobulin genes, is consistently silenced, potentially bypassing the need for BCR signalling and conferring a survival advantage. These findings, highlight the role of systematic epigenetic regulation in cHL pathogenesis, contrasting the oncogenic mutations or translocations typical of other B-cell malignancies. [10]

Together, mutations in proto-oncogenes, alterations in tumour suppressor genes, and widespread epigenetic modifications strongly support the existence of CSC-like progenitor cells in Hodgkin's lymphoma.

Follicular lymphoma case:

In 1992, a 32 year old man was treated for acute myeloid leukaemia with an allogeneic bone marrow from his father and remained in remission. [4] Three years later, the patient's father was diagnosed with stage IV follicular lymphoma that

progressed to DLBCL and died in 1998 despite chemotherapy. In 2003, the patient developed bulky retroperitoneal lymphadenopathy, biopsy confirmed follicular lymphoma. [4]

Molecular analyses showed that the patient's lymphoma was donor derived. Both lymphomas carried the identical BCL2/IGH fusion site, and IGH monoclonality analysis revealed 5 subclones from the donor's tumour (VH3-74 with 97% homology) and subclones from the recipients tumour (VH1-69 with 97–98% homology). These findings indicated post-germinal centre origin. [4]

Further research in FL demonstrate that one-third of BCL2-IGH occur at later V-D-J recombination stages, often involving pre-B or immature B cells. FL cells also consistently show SHM of both IGH alleles, suggesting that immortalized B cells with BCL2 overexpression continue to transit through the germinal centre. [3]

Overall this case supports the concept that both donor and recipient lymphomas arose from the same neoplastic progenitors transmitted during the transplantation, highlighting the existence of lymphoma progenitor cells with the ability to differentiate and self-renew. [4]

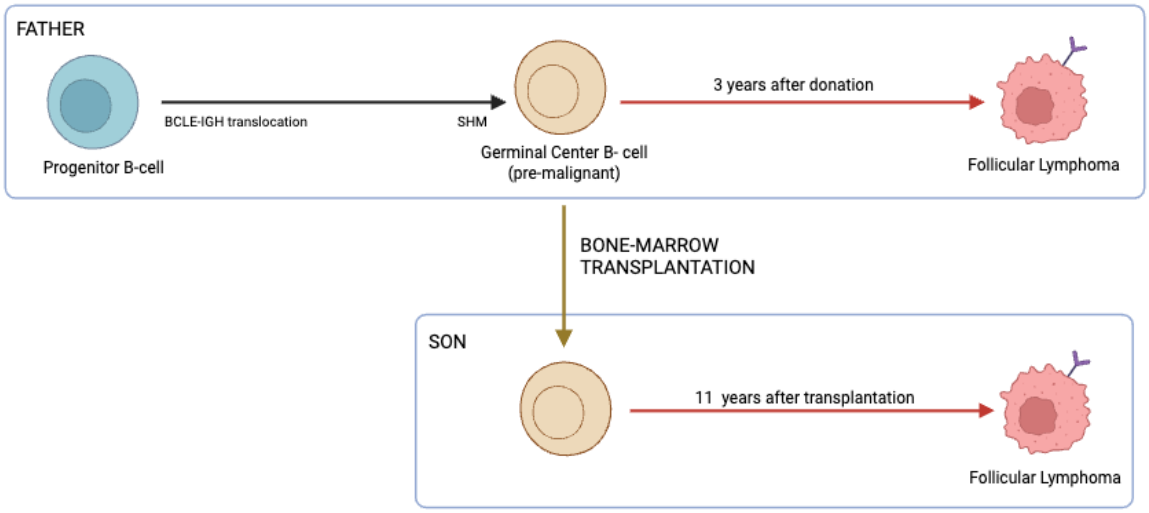

Figure 3- diagrammatic representation of the process by which follicular lymphoma was developed in the patient.(Created in https://BioRender.com)

DISCUSSION

The findings of this review highlight striking parallels between established cancer stem cell models and the cellular dynamics observed in lymphomas. The mutational landscape of lymphoma, particularly involving MYC, RAS, and p53, mirrors genetic disruptions that confer stemness and survival advantages in solid and hematologic malignancies. These mutations, coupled with hypermethylation-induced silencing of tumour suppressors such as CD79B and SYK, suggest that lymphoma cells may acquire self-renewal capacity through both genetic and epigenetic reprogramming. Importantly, the dysregulation of signalling pathways including PI3K/AKT, Wnt/β-catenin, and NF-κB underscores a conserved molecular circuitry driving the persistence of CSC-like populations across cancer types.

The functional overlap between long-term hematopoietic stem cells, memory lymphocytes, and lymphoma progenitors further supports this hypothesis. Studies demonstrating β-catenin–mediated activation of TCF4 and TCF12 in B-cell lymphoma stem cells suggest that mechanisms originally evolved for immune memory are being co-opted for oncogenic self-renewal. This reactivation of developmental signalling cascades in mature lymphocytes could explain the recurrence and clonal evolution characteristic of lymphomas. Moreover, clinical cases such as donor-derived follicular lymphoma provide compelling evidence for the transfer and regeneration of malignant progenitors, revealing that lymphoma-initiating cells possess true stem-like potential.

Nonetheless, the concept of lymphoma stem cells remains controversial. Alternative models propose that tumour heterogeneity and microenvironmental pressures, not discrete stem cell populations, govern relapse and resistance. Indeed, the plasticity of lymphoma cells, capable of transitioning between stem-like and differentiated states, blurs the boundary between CSC-driven and stochastic growth models. The absence of definitive surface markers also hampers the isolation and validation of LCSCs, making it difficult to confirm their existence experimentally.

Future research should focus on delineating these putative LCSC populations through single-cell sequencing, lineage tracing, and functional assays that integrate epigenomic and transcriptomic profiling. Understanding the precise balance between genetic mutations, epigenetic flexibility, and microenvironmental influence will be essential to developing CSC-directed therapies. Ultimately, elucidating the mechanisms of lymphoma self-renewal may bridge current gaps between theoretical

CSC biology and translational oncology, paving the way for targeted strategies that prevent relapse and improve patient survival.

CONCLUSION

Overall, CSCs are characterized by mutations in proto-oncogenes such as RAS and MYC, inactivation of tumour suppressors like p53, and epigenetic alterations including DNA methylation and dysregulated signalling pathways, which collectively drive self-renewal, therapy resistance, and metastasis. While lymphoma stem cells remain poorly defined, evidence from aberrant B-cell somatic hypermutation, recurrent MYC, RAS, and p53 mutations, and methylation patterns suggests parallels with CSC biology in Hodgkin and non-Hodgkin lymphomas. Moreover, donor-derived follicular lymphoma cases highlight the role of progenitor cells in initiation, persistence, and relapse, supporting the possibility of stem-like populations underpinning lymphoma progression.

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