REVIEW ARTICLE

Molecular insights into treatment failure in Diffuse Large B Cell Lymphoma (DLBCL)

ABDULMOHSEN M ALRUWETEI
Medical Laboratories Department, College of Applied Medical Sciences, Qassim University, Qassim, Saudi Arabia
Correspondence to Abdulmohsen M Alruwetei, Email: roietaie@qu.edu.sa

ABSTRACT

Diffuse large B-cell lymphoma (DLBCL) patients have an excellent prognosis with 60% current 5-year overall survival rate, however, unacceptable large number of patients suffer from relapse or refractory (R/R) disease. Given the clinical diversity among DLBCL patients, there is an urgent need for understanding the molecular heterogeneity of the disease and its influence on patient's prognosis and the success of treatment as well as developing new treatment strategies based on the molecular defects that underpin resistance to R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) immunotherapy. The present review introduced the novel genetic classification system for DLBCL, discussed recent experimental genomic studies which employed next generation sequencing techniques aimed for identifying molecular lesions associated with treatment failure in DLBCL patients.
Keywords: DLBCL, R-CHOP, therapy failure, Genomics

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is a group of disorders characterized by malignant expansion of mature large B lymphocyte, in lymph nodes and/or other lymphoid and non-lymphoid tissues. DLBCL represents most cases of lymphoid malignancy in adults and accounts for 30–40% of all Non-Hodgkin Lymphoma (NHL) cases[1,2]. While most patients respond well to R-CHOP treatment, the response in considerable number of patients is worse. The clinical course of the disease is aggressive and could be fatal if left untreated due to fast growing tumour masses and deterioration of the patient's general condition. Most clinical centers use similar therapeutic protocols at initial for treatment of DLBCL patients and the response to treatment is rather diverse.

Historically, the initial treatment of all newly diagnosed DLBCL cases was based on using of a combined regimen of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). Further improvement to the treatment of patients has been achieved through introduction of Rituximab (R) along with the standard CHOP therapy[3,4,5]. The use of R-CHOP regimen provides durable remission in >70% of patients and is responsible for the overall 5-year survival rate of 60–70%. However, a small group of patients develop refractory disease or resistance to treatment while relapse occurs in 30-40% of patients which results in dismal prognosis[6]. Current treatment options for relapse /refractory diseases (R/R) include stem cell transplantation (SCT) and high doses of chemotherapy or experimental protocols for patients not eligible for intensive therapy or SCT[7]. Unfortunately, such strategies are not adequate and also depend on the patient's tolerance to intensive treatment approaches yet R/R patients have 3-4 months life expectancy if left untreated[6]. Improved survival of DLBCL patients demand early identification of patients at risk of treatment failure and applying alternative strategies which are able to overcome drug resistance and prevent disease recurrence. The recent advances in understanding the genomic of DLBCL disease, certainly the use of high-throughput next generation sequencing (NGS) technologies is promising to characterize the treatment failure related molecular features of DLBCL disease, which could provide rationale for targeting oncogenic alterations associated with unsuccessful treatment of the disease. This review will discuss the standard and updated prognostic features of DLBCL disease and will also discuss that most recent experimental genomic studies in the context of therapy resistance in DLBCL disease.

Classification and prognosis of DLBCL: The current knowledge about DLBCL disease acknowledge the diversity of DLBCL disease and the influence of clinical, biological and molecular features of the disease in prognosis of patients[8,9]. The WHO classification of mature lymphoid neoplasms recognizes several entities of the disease. However, the majority of DLBCL cases do not follow unique criteria for the classification and therefore are categorized as high-grade B-cell lymphoma (HGBL), not otherwise specified (NOS)[10]. Recent update to the WHO classification considers the cell-of-origin (COO) definition for distinguishing patients who stratified into the HGBL, NOS subtype[10]. The importance of COO definition in stratifying of DLBCL patients was initially recognised by Alizadeh et al. study which showed that DLBCL patients can be distinguished, based on the expression patterns of genes involved in B lymphocyte development and activation, into activated B-cell (ABC) and germinal centre B-cell (GCB) DLBCL subtypes[11]. Additional reports supported these findings and established the relevance of COO subdivision for identifying prognosis of patients[12,13,14]. Furthermore, the genetic rearrangement of MYC oncogene, which may occur either alone (single hit lymphoma, SHL) or in combination with BCL2 and/or BCL6 rearrangement (double hit lymphoma, DHL or triple hit lymphomas,

THL consecutively) represent a subentity of the HGBL, NOS subtype as such rearrangements can influence the prognosis of patients[10,15,16].

Several genetic and cytogenetic abnormalities are characteristics of DLBCL disease, in which some are implicated in the prognosis of patients. Earlier studies have shown the prognostic significance of certain genetic abnormalities in DLBCL disease. For instance, MYC gene rearrangement which is detected in 5% to 15% of *de novo* DLBCL confer significant worse 5-year progression free survival (PFS) and overall survival (OS) compared to MYC non-rearranged patients who received standard R-CHOP regimen[17,18]. Other studies have also linked the presence of single hit BCL2 or BCL6 gene rearrangement with the prognosis of DLBCL disease although with conflicting results between studies[19-23]. DLBCL patients who harbour double hit (MYC/BCL2 or MYC/BCL6 translocations) or triple hit (MYC/BCL2/BCL6 rearrangement) lymphoma and patients with co-expression but no translocation of *MYC* and *BCL2* genes refereed to "double expressor" demonstrate inferior prognosis post R-CHOP treatment patients[15,24,25,26]. In addition, the COO classification has also been useful in stratifying patients according to their prognosis[27]. DLBCL cells of patients with ABC-subtype are characterised by mutations in the B-cell receptor (BCR) and the NF-kB pathway genes, such as CD79b, MYD88, CARD11 and TNFAIP3 or genes involved in regulation of the cell cycle such as CDKN2A/B and RB1 and patients with DLBCL-ABC subtype commonly display poor OS[28,29]. In contrast, the OS of those stratified as DLBCL-GCB subtype is better and tumour cells frequently display BCL2 and/or MYC gene rearrangements, as well as genetic lesions in the the epigenetic modifiers such as KMT2D, EP300, CREBBP, and EZH2 and PI3K/AKT signaling molecules such as PTEN, MIR17HG[29].

Excellent progress has been achieved in utilising set of common genetic alterations for identifying distinct molecular subtypes of DLBCL. In a recent study, Schmitz et al. have used the whole-exome sequencing (WES), gene copy number analysis and RNA sequencing to categorize DLBCL patients according to the molecular profiles into different subtypes with prognostic relevance. This study showed that DLBCL can be divided into four molecular subtypes denoted as MCD (co-existence of mutations in MYD88^{L265P} and CD79B mutations), BN2 (BCL6 fusions and NOTCH2 mutations), N1(NOTCH1 mutations), and EZB (EZH2 mutations and BCL2 translocations). Patients who exhibited molecular features related to BN2 and EZB subtypes demonstrated favourable survival while MCD and N1 subtypes are linked with unfavorable survival subtypes[30]. In a similar study, Chapuy et al. utilized WES and targeted sequencing of samples from DLBCL patients for comprehensive genetic analysis of DLBCL and study the prognostic relevance of molecular features which led to recognition of another distinct molecular classification model for DLBCL disease. The analysis of genetic profiles in relevance to the prognosis identified 5 risk subgroups termed as C1 (BCL6 translocations and NOTCH2 or SPEN mutations), C2 (TP53 and CDKN2A aberrations, genomic instability), C3 (PTEN, KMT2D, CREBBP, and EZH2 alterations), C4 (BCR–PI3K, NF-κB, or RAS–JAK pathway aberrations, BRAF, STAT3, CD83, CD70, and CD58 mutations) and C5 (co-existence of MYD88^{L265P} and CD79B mutations, BCL2, PIM1, and PRDM1 mutations). This model defined variable prognosis of patients within subtypes, where patients in C1 and C4 subtypes exhibit favorable outcome while C2, C3 and C5 subtypes show unfavorable outcome[31]. Subsequently, Wright et al. presented an algorithm which unified the molecular subtypes of the two initial studies and divided DLBCL patients into seven genetic subgroups with prognostic differences[32]. These studies along with other reported algorithms for molecular stratification of DLBCL patients hold the promise for developing improved predictive markers which could help in distinguishing patients according to their prognosis, provide opportunity for applying targeted therapy and /or tailoring treatment according to the biology of the disease.

Molecular determinants of treatment failure in DLBCL: Despite the improvement in understanding the biology of DLBCL disease, current treatment strategies apparently do not protect DLBCL patients from developing resistance to the standard R-CHOP or relapse after treatment. Treatment failure in DLBCL disease occurs due to inability of drugs to produce profound tumour cell killing and completely eradicate cells which could sustain re-emergence of tumours[33]. Currently, with the advent in the high-throughput NGS, it is more feasible to fully characterize the whole or target regions of the genome of normal and cancerous cells. Many studies have employed whole genome or target regions of the genome sequencing of paired samples of primary diagnosis and relapse to define the relationship between relapse and diagnosis and elucidate the potential role of certain pathways in mediating resistance to R-CHOP therapy. The most recent studies intended to investigated treatment failure based on different genomic and epigenomic approaches are detailed below.

Jiang et al. 2014, analysed the VDJ rearrangement based on deep sequencing of matched diagnosis and relapse samples from 14 DLBCL patients, of which 7 pairs were also analyzed by whole exome sequencing (WES) to determine how relapse disease is genetically altered compared to that at diagnosis. The WES analysis of difference in genetic landscape between diagnosis and relapse diseases revealed that relapse cell populations gained single nucleotide variants (SNVs) in > 300 genes, of which 71 previously reported to be mutated in primary diagnosed DLBCL, such as BCL2, EP300, KMT2D, MYC, TET2 and TNFRSF14. Furthermore, relapse clones were affected by indels and deletion in CD58 or B2M genes, ARHGEF7 and PLCB2 genes, which are may affect the integrity of RAC1-mediated B-cell receptor signaling and also deletion in IL9R gene, which may affect the response of JAK-STAT signaling to IL-9. The overall finding from this study was that relapse could arise from the same origin cells of which diagnosis clones were

derived but each acquired several unique somatic mutations or it was originated from diagnosis clones with further slight divergence[34].

In aim to identify genes that may be associated with relapse, Morin et al. analyzed the difference in mutation profiles based on WES between a cohort of 25 samples derived from R/R patients and 138 samples of an independent "diagnostic" DLBCL cohort. The analysis revealed high frequency of mutations in some of the well-known DLBCL related genes such as MLL3, MPEG1, CCND3, FOXO1, STAT6, TP53, and MYC in samples of relapsed patients. Notably, mutations were also detected in MYD88 and CD79B genes that may affect sensitivity to novel therapeutics. In another experiment, the difference in mutation profiles was assessed between matched diagnosis-relapse samples of 12 DLBCL patients included in this study, based on targeted sequencing of genes that were frequently mutated in the exomes and/or had a role in diagnostic DLBCL. It was noticed that relapse disease is characterized by enriched mutations in STAT6, EZH2, FOXO1, SOCS1, KMT2D, CD79B and NFKBIE genes as compared to diagnosis samples. This study presented examples of clonal selection for mutations in several genes known as having potential roles in DLBCL relapse, rehighlighted the potential impact of genetic lesions in JAK/STAT and BCR signaling molecules[35].

In a subsequent study, Juskevicius et al. conducted comparisons of genetic mutations between samples of 20 relapsed DLBCL patients and either their respective samples at time of diagnosis or samples from 20 non-relapsed patients based on targeted NGS of 68 genes, which frequently reported as hotspots for mutations in B-cell lymphoid malignancies. The analysis of difference in genetic profiles between matched diagnosis-relapse samples showed higher frequency of mutations in *KMT2D, MEF2B, TET2, PRDM1, PTEN* and *EBF1* genes in relapse disease. Similarly, Melchardt et al. conducted targeted NGS of 104 genes known to be frequently mutated in lymphoma for samples of 28 DLBCL patients at diagnosis, relapse or refractory disease. Analysing the difference in allelic fractions between diagnosis and relapse clones revealed gain of allelic fractions in *TP53, RB1* and *EZH2* genes at relapse and subsequent back tracking of *TP53* mutation in diagnostic samples based on ultra-deep sequencing technique showed the existence of a minor clonal population with mutated *TP53* in the primary samples. Furthermore, a comparison of genetic profile between R/R samples and an independent primary cohort from the literature showed significant increase in frequency of *TP53, MCL1, ATM, FAT2, MYC, RB1* and *SMARCA4* mutations in relapse samples compared to that in the primary cohort. In a recent study, Rushton et al. reported the mutation profiles related to treatment resistance in DLBCL patients based on WES and targeted sequencing of lymphoma-associated genes using circulating tumour DNA (ctDNA) samples isolated from plasma and biopsy of 135 patients with R/R DLBCL disease. This study showed that samples of R/R patients are characterized by mutations in 6 genes; KMT2D, TP53, CREBBP, NFKBIE, FOXO1, and MS4A1. Moreover, evaluation of the difference in clonal dynamics between paired diagnosis-relapse DLBCL diseases revealed that in some cases mutations enriched in relapse represent cell populations evolved from diagnostic clones[36].

The above-mentioned reports described the potential link between unsuccessful therapy of DLBCL disease and an increase in tendency of mutations affecting several genes involved in cell proliferation, cell survival and tumor suppression activity in relapsed DLBCL disease. Studies have shown that MYC gene, which play an integral role in B cell development, differentiation, proliferation and survival, is frequently affected by mutations in relapse samples which in some cases appear as unique, relapse specific and target regions which promote sustaining of MYC's oncogenic function[35,36,37]. Of importance, the oncogenic phenotype of MYC gene also could enhance the chemoresistance phenotype of p53 and BCL2[38,39], which themselves are found to be prevalent in relapse disease indicating for their roles in treatment failure and driving relapse disease. High frequency of mutations in the anti-apoptotic, BCL2 gene, was observed in relapse samples of DLBCL patients in compare to their corresponding samples at diagnosis and also in samples of R/R DLBCL patients when compared to non-paired diagnosis samples[34,40-43]. Certainly, BCL2 is targeted by SNVs in regions which involve places regulate the gene expression and therefore may increase its anti-apoptotic properties[43]. These relapse-associated genetic variants potentially contribute to resistance for R-CHOP therapy in DLBCL disease. The tumor suppressor gene, TP53, is another common mutated gene in relapsed DLBCL cases[35,42,43]. The TP53 plays crucial roles in maintaining the integrity of human genome through controlling oncogene transformation, DNA repair, progression of cell cycle and induction of apoptosis[44,45]. The genetic lesions in p53 observed in relapse samples represents selection of a minor treatment-resistant subclone present at diagnosis and also the acquisition of novel mutations at relapse[42].

The studies also provided evidences that relapsed DLBCL cases are characterized by high frequency of mutations in molecules related to the JAK-STAT signaling pathway which facilitate signal transduction from cytokine and growth factor receptors and transcription activation of genes critical for cell survival, proliferation and differentiation[46]. In particular, mutations have been detected in the JAK1, STAT6, SOCS1 and PIM1 genes which is regulated by JAK-STAT signaling pathway, emphasizing the important role of active JAK-STAT signaling pathway in driving relapse in DLBCL patients[2,41,42]. Further evidences underlying the potential influence of dysregulated JAK-STAT pathway in treatment failure of DLBCL were demonstrated by studies which revealed frequent inactivation mutations affecting NFKBIE gene which encodes for IκBε protein that suppress the NF-κB–mediated transcription in DLBCL disease [35, 41]. Loss of IκBε protein will allow for NF-κB–mediated

transcription of IL-6 and IL-10 causing autocrine signaling and maintain the activity of JAK1/2 and STAT3 molecules in the JAK-STAT pathway[47,48].

The observations that relapse DLBCL disease harbor genetic alterations in molecules linked to the ability of cells to escape immune surveillance urge for their potential implication in disease recurrence. Several studies reported relapse specific variants and an increase in frequency of mutations in human leukocyte antigen (*HLA),* β*2*-microglobulin (*B2M),* which help in the surface HLA class I molecules assembly, the class II transactivator (CIITA) genes, which affect the gene expression of MHC proteins and also in CD58 genes, which encode for a cell adhesion molecule which activate T and natural killer cell for immune recognition[2,34,35,41,49,50]. Such genetic lesions may interfere with the antigen presentation and recognition of MHC proteins by the immune-effector cells which render tumor cells able to escape from immune-surveillance and may represent a strategy for maintaining the survival of relapse tumors.

Perhaps the molecular mechanisms underlying relapse do not fully explained by genetic lesions, it has been postulated that epigenetic regulations might also coordinate in deriving chemoresistance of tumours. It has been demonstrated that mechanisms by which DLBCL disease return may include perturbations of molecules linked to the epigenetic process and changes in epigenetic status. The epigenetic modifications involve histones methylation via histone methyltransferases (HMTs) and acetylation via histone acetyltransferases (HATs) enzymes. Interestingly, frequent mutations in HMT genes including EZH2, KTM2D as well as HAT genes such as CREBBP and EP300, were observed in relapse disease, highlighting the possible roles of such genetic features in driving relapse. The EZH2 gene lesions in DLBCL mostly are gain of function type which enhance the EZH2 catalysis of H3K27me3, leading to the suppression of gene transcription and such events were found to be enriched in relapse relative to their corresponding diagnosis samples and also in R/R DLBCL cohorts as compared to independent diagnosis cohort[31,43,41,35,31]. Somatic mutations in KMT2D gene inactivate KMT2D gene which result in abrogation of KMT2D mediated H3K4me1 and H3K4me2 leading to an impairment in the activity of transcriptional enhancers. Intriguingly, mutations in KMT2D gene were reported as highly frequent lesions in DLBCL at relapse. Likewise, somatic mutations of the HAT proteins, CREBBP and EP300, which encode CBP and p300, impair H3K18 and H3K27 acetylation which in turn disrupt activity of certain enhancers for gene transcriptions. The genomic disruption of CREBBP and EP300 were found to be mostly maintained between diagnosis and relapse while higher frequency was detected at relapse in some DLBCL cases, indicating that clones harboring such lesions were implicated in disease recurrence. Other epigenetic regulators such as TET2 and BRD4 have also been reported to be common in relapse disease. The genetic abnormalities in epigenetic modulators could be accused for their role in DLBCL treatment failure due to their ability to alter the regulation of integral proteins linked with drug resistance. For instance, KMT2D acts as a TP53 coactivator in induction of DNA damage mediated p53 response. Moreover, loss of CBP/p300 function could also result in transcriptional defect of P53, and also being linked with glucocorticoid resistance in other types of hematological malignancies.

CONCLUSION:

DLBCL disease is characterized by remarkable molecular heterogeneity which highly influence patient prognosis. The current picture of DLBCL patient outcome after R-CHOP resistance demand increasing efforts for improving survival of patients. The present review provides insights into recent studies that attempted to explore genomics and epigenetics alterations related to therapy failure in DLBCL. Perhaps the findings from these studies will contribute greatly in understanding the heterogeneity of the disease and revealing real drivers of chemotherapy-resistance and relapse in DLBCL.

Conflicts of Interest: The author declares no conflicts of interest regarding the publication of this paper

REFRENCES

1. Liu, Y. and S.K. Barta, Diffuse large B-cell lymphoma: 2019 update on diagnosis, risk stratification, and treatment. Am J Hematol, 2019. **94**(5): p. 604-616.
2. Isaev, K., et al., Molecular Attributes Underlying Central Nervous System and Systemic Relapse in Diffuse Large B-cell Lymphoma. Haematologica, 2020.
3. Coiffier, B., et al., Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood, 2010. **116**(12): p. 2040-5.
4. Fu, K., et al., Addition of rituximab to standard chemotherapy improves the survival of both the germinal center B-cell-like and non-germinal center B-cell-like subtypes of diffuse large B-cell lymphoma. J Clin Oncol, 2008. **26**(28): p. 4587-94.
5. Poeschel, V., et al., Four versus six cycles of CHOP chemotherapy in combination with six applications of rituximab in patients with aggressive B-cell lymphoma with favourable prognosis (FLYER): a randomised, phase 3, non-inferiority trial. Lancet, 2019. **394**(10216): p. 2271-2281.
6. Raut, L.S. and P.P. Chakrabarti, Management of relapsed-refractory diffuse large B cell lymphoma. South Asian journal of cancer, 2014. **3**(1): p. 66-70.
7. Sukswai, N., et al., Diffuse large B-cell lymphoma variants: an update. Pathology, 2019.
8. Li, S., K.H. Young, and L.J. Medeiros, Diffuse large B-cell lymphoma. Pathology, 2018. **50**(1): p. 74-87.
9. Guo, L., et al., Molecular heterogeneity in diffuse large B-cell lymphoma and its implications in clinical diagnosis and treatment. Biochim Biophys Acta Rev Cancer, 2018. **1869**(2): p. 85-96.
10. Swerdlow, S.H., et al., The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood, 2016. **127**(20): p. 2375-2390.
11. Alizadeh, A.A., et al., Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature, 2000. **403**(6769): p. 503-11.
12. Rosenwald, A., et al., The Use of Molecular Profiling to Predict Survival after Chemotherapy for Diffuse Large-B-Cell Lymphoma. New England Journal of Medicine, 2002. **346**(25): p. 1937-1947.
13. Scott, D.W., et al., Determining cell-of-origin subtypes of diffuse large B-cell lymphoma using gene expression in formalin-fixed paraffin-embedded tissue. Blood, 2014. **123**(8): p. 1214-7.
14. Jais, J.-P., et al., Reliable subtype classification of diffuse large B-cell lymphoma samples from GELA LNH2003 trials using the

Lymph2Cx gene expression assay. Haematologica, 2017. **102**(10): p. e404-e406.
15. Rosenthal, A. and A. Younes, High grade B-cell lymphoma with rearrangements of MYC and BCL2 and/or BCL6: Double hit and triple hit lymphomas and double expressing lymphoma. Blood Rev, 2017. **31**(2): p. 37-42.
16. Aukema, S.M., et al., Double-hit B-cell lymphomas. Blood, 2011. **117**(8): p. 2319-31.
17. Savage, K.J., et al., MYC gene rearrangements are associated with a poor prognosis in diffuse large B-cell lymphoma patients treated with R-CHOP chemotherapy. Blood, 2009. **114**(17): p. 3533-7.
18. Barrans, S., et al., Rearrangement of MYC is associated with poor prognosis in patients with diffuse large B-cell lymphoma treated in the era of rituximab. J Clin Oncol, 2010. **28**(20): p. 3360-5.
19. Kramer, M.H.H., et al., Clinical Relevance of BCL2, BCL6, and MYC Rearrangements in Diffuse Large B-Cell Lymphoma. Blood, 1998. **92**(9): p. 3152-3162.
20. van Imhoff, G.W., et al., Prognostic impact of germinal center-associated proteins and chromosomal breakpoints in poor-risk diffuse large B-cell lymphoma. J Clin Oncol, 2006. **24**(25): p. 4135-42.
21. Copie-Bergman, C., et al., Immuno-fluorescence in situ hybridization index predicts survival in patients with diffuse large B-cell lymphoma treated with R-CHOP: a GELA study. J Clin Oncol, 2009. **27**(33): p. 5573-9.
22. Offit, K., et al., Rearrangement of the bcl-6 Gene as a Prognostic Marker in Diffuse Large-Cell Lymphoma. New England Journal of Medicine, 1994. **331**(2): p. 74-80.
23. Barrans, S.L., et al., Rearrangement of the BCL6 locus at 3q27 is an independent poor prognostic factor in nodal diffuse large B-cell lymphoma. Br J Haematol, 2002. **117**(2): p. 322-32.
24. Sarkozy, C., A. Traverse-Glehen, and B. Coiffier, Double-hit and double-protein-expression lymphomas: aggressive and refractory lymphomas. Lancet Oncol, 2015. **16**(15): p. e555-e567.
25. Johnson, N.A., et al., Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol, 2012. **30**(28): p. 3452-9.
26. Sesques, P. and N.A. Johnson, Approach to the diagnosis and treatment of high-grade B-cell lymphomas with MYC and BCL2 and/or BCL6 rearrangements. Blood, 2017. **129**(3): p. 280-288.
27. Scott, D.W., Cell-of-Origin in Diffuse Large B-Cell Lymphoma: Are the Assays Ready for the Clinic? American Society of Clinical Oncology Educational Book, 2015(35): p. e458-e466.
28. Davis, R.E., et al., Chronic active B-cell-receptor signalling in diffuse large B-cell lymphoma. Nature, 2010. **463**(7277): p. 88-92.
29. Sehn, L.H. and R.D. Gascoyne, Diffuse large B-cell lymphoma: optimizing outcome in the context of clinical and biologic heterogeneity. Blood, 2015. **125**(1): p. 22-32.
30. Schmitz, R., et al., Genetics and Pathogenesis of Diffuse Large B-Cell Lymphoma. N Engl J Med, 2018. **378**(15): p. 1396-1407.
31. Chapuy, B., et al., Molecular subtypes of diffuse large B cell lymphoma are associated with distinct pathogenic mechanisms and outcomes. Nat Med, 2018. **24**(5): p. 679-690.
32. Wright, G.W., et al., A Probabilistic Classification Tool for Genetic Subtypes of Diffuse Large B Cell Lymphoma with Therapeutic Implications. Cancer Cell, 2020. **37**(4): p. 551-568.e14.
33. Coiffier, B. and C. Sarkozy, Diffuse large B-cell lymphoma: R-CHOP failure-what to do? Hematology. American Society of Hematology. Education Program, 2016. **2016**(1): p. 366-378.
34. Jiang, Y., et al., Deep sequencing reveals clonal evolution patterns and mutation events associated with relapse in B-cell lymphomas. Genome biology, 2014. **15**(8): p. 432-432.
35. Morin, R.D., et al., Genetic Landscapes of Relapsed and Refractory Diffuse Large B-Cell Lymphomas. Clin Cancer Res, 2016. **22**(9): p. 2290-300.
36. Rushton, C., et al., IDENTIFYING MUTATIONS ENRICHED IN RELAPSED-REFRACTORY DLBCL TO DERIVE GENETIC FACTORS UNDERLYING TREATMENT RESISTANCE. Hematological Oncology, 2019. **37**(S2): p. 35-36.
37. Dang, C.V., MYC on the path to cancer. Cell, 2012. **149**(1): p. 22-35.
38. McMahon, S.B., MYC and the control of apoptosis. Cold Spring Harbor perspectives in medicine, 2014. **4**(7): p. a014407-a014407.
39. Eischen, C.M., et al., Disruption of the ARF-Mdm2-p53 tumor suppressor pathway in Myc-induced lymphomagenesis. Genes & development, 1999. **13**(20): p. 2658-2669.
40. Juskevicius, D., et al., Distinct genetic evolution patterns of relapsing diffuse large B-cell lymphoma revealed by genome-wide copy number aberration and targeted sequencing analysis. Leukemia, 2016. **30**(12): p. 2385-2395.
41. Rushton, C.K., et al., Genetic and evolutionary patterns of treatment resistance in relapsed B-cell lymphoma. Blood Advances, 2020. **4**(13): p. 2886-2898.
42. Melchardt, T., et al., Clonal evolution in relapsed and refractory diffuse large B-cell lymphoma is characterized by high dynamics of subclones. Oncotarget, 2016. **7**(32): p. 51494-51502.
43. Greenawalt, D.M., et al., Comparative analysis of primary versus relapse/refractory DLBCL identifies shifts in mutation spectrum. Oncotarget, 2017. **8**(59): p. 99237-99244.
44. Levine, A.J., P53 and The Immune Response: 40 Years of Exploration-A Plan for the Future. Int J Mol Sci, 2020. **21**(2).
45. Vogelstein, B., D. Lane, and A.J. Levine, Surfing the p53 network. Nature, 2000. **408**(6810): p. 307-10.
46. Rawlings, J.S., K.M. Rosler, and D.A. Harrison, The JAK/STAT signaling pathway. Journal of Cell Science, 2004. **117**(8): p. 1281.
47. Lam, L.T., et al., Cooperative signaling through the signal transducer and activator of transcription 3 and nuclear factor-{kappa}B pathways in subtypes of diffuse large B-cell lymphoma. Blood, 2008. **111**(7): p. 3701-13.
48. Lu, L., et al., Gene regulation and suppression of type I interferon signaling by STAT3 in diffuse large B cell lymphoma. Proc Natl Acad Sci U S A, 2018. **115**(3): p. E498-e505.
49. Klemm, S.L., Z. Shipony, and W.J. Greenleaf, Chromatin accessibility and the regulatory epigenome. Nature Reviews Genetics, 2019. **20**(4): p. 207-220.
50. Mareschal, S., et al., Whole exome sequencing of relapsed/refractory patients expands the repertoire of somatic mutations in diffuse large B-cell lymphoma. Genes Chromosomes Cancer, 2016. **55**(3): p. 251-67.