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Review

Molecular and cellular genetics of non-Hodgkin lymphoma: Diagnostic and prognostic implications

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ABSTRACT

Non-Hodgkin lymphoma (NHL) is a diverse collection of malignant neoplasms with lymphoid-cell origin which includes all the malignant lymphomas that are not classified as Hodgkin lymphoma. NHL is one of the most common types of cancer diagnosed in men and women in the developed world. In the United States of America, the past few decades have seen a significant rise in the incidence of NHL and it accounts for about 4% of all cancers now. The overall survival of NHL has improved drastically over the past ten years. This can be attributed to better understanding of pathogenesis, refined classification, enhanced supportive care, and data from collaborative clinical trials. The prognosis of a newly diagnosed NHL patient depends, among other factors, on the specific subtype of lymphoma, stage of the disease, and age of the patient. Advances in the fields of molecular biology and innovations in cytogenetic techniques have led to the discovery of several oncogenic pathways involved in lymphomagenesis, which in turn has amplified the diagnostic and therapeutic approaches available for NHL. Our comprehension of the genetic features that determine the character of NHL, and ultimately guide the therapy, has undergone significant shift and it is essential that scientists as well as clinicians stay in tune with this rapidly evolving knowledge. In this review we have summarized the current concepts about cellular and molecular genetics of the common subtypes of NHL and their clinical implications.

1. Introduction

Non-Hodgkin lymphomas (NHLs) belong to a heterogeneous group of malignancies arising from B-lymphocytes, T-lymphocytes, or natural killer (NK) cells. B-cell lymphomas represent the majority (about 85%) of NHL in the western world, while T-cell lymphomas are much less common (about 15%) (Morton et al., 2006; Perry et al., 2015). Among B-cell lymphomas, diffuse large B-cell lymphoma (DLBCL) is the most prevalent subtype globally. The Surveillance, Epidemiology and End Results (SEER) program estimates that a total of 74,680 new cases of NHL will be diagnosed in the year 2018 in the United States of America (Howlader et al., 2015). Analysis of a British patient data-base found that diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and marginal zone lymphoma (MZL) together accounted for roughly three-fourths of all newly diagnosed lymphomas (Smith et al., 2015). While there is significant geographical variation in the prevalence of individual subtypes of NHL, it is indisputably a major cause of morbidity worldwide. NHL patients can present with a wide spectrum of clinical presentations depending on the subtype of lymphoma and site of disease. The preliminary steps in diagnosing NHL include obtaining a detailed medical history, performing thorough clinical examination, and conducting laboratory and radiological investigations. The next and most critical step is to establish an accurate histological diagnosis by obtaining tumor samples using an incisional, excisional or needle biopsy of the lymph node. In this review, we have highlighted the molecular and genetic features of the more commonly encountered types of NHL, as well as some less common subtypes where genetic abnormalities have been recently described.

2. Classification

The classification of NHL has undergone significant changes over the years as newer insights about cytogenetics and antigenic expression is gained. The Rappaport system was probably the earliest substantial effort to classify lymphomas and it used growth patterns (diffuse vs. nodular) and cytology (undifferentiated vs. differentiated) to define the disease (Byrne Jr, 1977). In the 1990s, the International Lymphoma Study Group decided to create a uniform classification of NHL based on biologic principles. This system came to be known as the Revised European-American Classification of Lymphoid Neoplasms (REAL) classification (Harris et al., 1994) which eventually lead to the World Health Organization (WHO) classification of tumors of the hematopoietic and lymphoid tissues produced in 2001 (revised in 2008 and 2016). The WHO classification is currently the most extensively used system around the world (Swerdlow et al., 2008; Harris et al., 1999). The 2016 revision of the WHO classification includes more than 50

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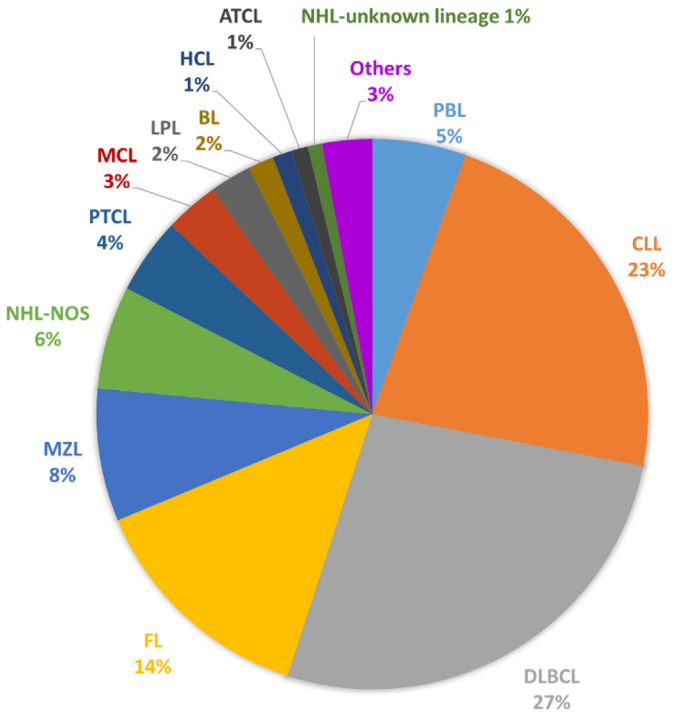

Fig. 1. Prevalence rates of common subtypes of Non-Hodgkin Lymphoma for all age groups (SEER 2006–2015).
(DLBCL = Diffuse large B-cell lymphoma, CLL = Chronic/Small lymphocytic leukemia/lymphoma, FL = Follicular lymphoma, MZL = Marginal zone lymphoma, MCL = Mantle cell lymphoma, LPL = Lymphoplamacytic lymphoma, BL = Burkitt lymphoma, NHL-NOS = Non Hodgkin lymphoma - not otherwise specified, ATCL = Adult T-cell lymphoma, PTCL = Peripheral T-cell lymphoma, HCL = Hairy cell lymphoma, PBL = Precursor B-cell lymphoma)

defined types of NHL, including a small number of provisional entities (Swerdlow et al., 2016b). The WHO classification divides lymphomas based on the lineage from which they are derived (B, T, or NK cell) and then stratifies the subtypes within each lineage based on a combination of morphology, immunophenotype, genetic features, and clinical features. Using this principle, each NHL can be considered to be made up of clonal cells that are predominantly derived from either B-lymphocytes, T-lymphocytes or NK cells at varying stages of maturation. However, this grouping has significant overlap among subtypes, with many NHLs arising from different cells or at different stages of maturation being classified in the same category. One instance of such overlap can be seen with certain NK/T-cell lymphomas that share immunophenotypic and functional features with both NK cells and T lymphocytes (Jaffe, 1996). It is also important to mention here that some NHL subtypes do not have an identified cell of origin (like hairy cell leukemia).

For obvious clinical reasons oncologists also prefer to group NHL subtypes based on the speed of disease progression. For example, the most commonly diagnosed NHL, diffuse large B-cell lymphoma (DLBCL), is an aggressive lymphoma (Fig. 1). Indolent lymphomas represent about 40% of all newly diagnosed NHL cases with follicular lymphoma (FL) being the commonest indolent NHL (Swerdlow et al., 2008). While histological assessment of tissue sample remains the foundation of the lymphoma diagnosis (Fig. 2), pathologists around the world are increasingly relying on these newer techniques like cytogenetic testing, florescence in situ hybridization (FISH), DNA amplification, and next-generation sequencing (NGS) to complement the decision-making process. Cytogenetic and molecular genetic abnormalities are almost universal in hematological malignancies, but in contrast to the acute leukemia, mutations in lymphoma are more commonly used for prognostication rather than diagnosis. Certain recurrent mutations seen in NHL are prognostically important, and aid in selection of appropriate therapy. More importantly, as novel molecularly targeted therapies become available these genetic alterations can also become potential therapeutic targets. The survival rates of different subtypes of NHL vary significantly (Fig. 3) but the combined 5-year overall survival is estimated to be about 71% based on SEER data (Howlader et al., 2015).

3. Molecular biology and cytogenetics

Most B-cell and T-cell NHLs show clonal rearrangement of their immunoglobulin (*IG*) and T-cell receptor (*TCR*) genes respectively. Although identification of clonal rearrangements in immunoglobulin heavy chain (*IGH*), immunoglobulin kappa (*IGK*), immunoglobulin lambda (*IGL*) or T-cell receptor (*TCR*) genes is not an absolute requirement for diagnosing NHL, this information can be useful to support a diagnosis of lymphoma in challenging cases. Apart from *IG* and *TCR* genes, mutations in other proto-oncogenes, epigenetic modifiers and karyotypic abnormalities are also frequently seen in NHL. Importantly, clonal gene rearrangements can sometimes be detected in benign lymphoid proliferations as well (Van Dongen et al., 2003).

4. B-cell lymphomas

4.1. Diffuse large B-cell lymphoma (DLBCL)

Diffuse large B cell lymphoma may arise de novo or through transformation from a pre-existing low-grade B cell lymphoma. *BCL6* mutations are present in up to 40% cases of DLBCL, with mutations in 5′ noncoding region being most common (Shen et al., 1998). Mutations replacing the *BCL6* promoter with constitutively active promoters derived from other genes are also frequently seen. These genetic changes impede the negative auto-regulation by the BCL6 protein which is primarily a transcriptional repressor (Pasqualucci et al., 2003). Mutations of *TP53* and 9p21/*CDKN2A* are frequently detected in cases of histologic transformation (Lo Coco et al., 1993; Elenitoba-Johnson et al., 1998). A *BCL2* rearrangement is seen in about 20–30% of DLBCL cases and may be seen in both de novo DLBCL and transformation from follicular lymphoma.

Rearrangements of the immunoglobulin heavy and light chain genes and somatic mutations of the variable regions are seen in most patients (Klein et al., 1998). DLBCL can be divided into two major subgroups on the basis of gene expression - one with high expression of genes that are commonly seen in germinal center B-cells (GCB-type) and other group with gene expression pattern normally seen in activated peripheral B-cells (ABC type). A smaller subset of cases is unclassified, falling into neither category. Common genetic alterations seen in GCB type are *BCL2* translocation, *REL* amplification, mutations of *EZH2*, and gains of 12q12 (Huang et al., 2002; Pasqualucci and Dalla-Favera, 2015; Houldsworth et al., 2004) and those seen in ABC type are trisomy 3, gains of 3q and 18q21-q22, losses of 6q21-q22, and mutations of genes regulating the NF-κB pathway (*TRAF3*, *TRAF5*, *MAP3K7*, *TNFAIP3* and *MYD88*) (Pasqualucci and Dalla-Favera, 2015; Compagno et al., 2009). Genetic alterations that have been reported with increased frequency in unclassified cases include *BCL6* fusions, *NOTCH2* and *SPEN* mutations (Schmitz et al., 2018a). GCB type DLBCL patients have a better 5-year overall survival (OS) as compared to the ABC type (Alizadeh et al., 2000). Truncating or DNA-binding domain mutations of *TP53*, mutations of *CDNK2A*, and alterations of the NOTCH pathway have been associated with worse outcomes (Karube et al., 2017). Recent comprehensive genetic analyses have identified multiple genetic subtypes or clusters of DLBCL, defined by shared genetic changes. Schmitz et al. described four genetic subtypes: EZB, associated with *EZH2* mutations, GCB-like gene expression profiles, and a relatively favorable prognosis; BN2, associated with *BCL6* fusions, *NOTCH2* mutations, unclassified gene expression profiles, and a favorable prognosis; N1, associated with

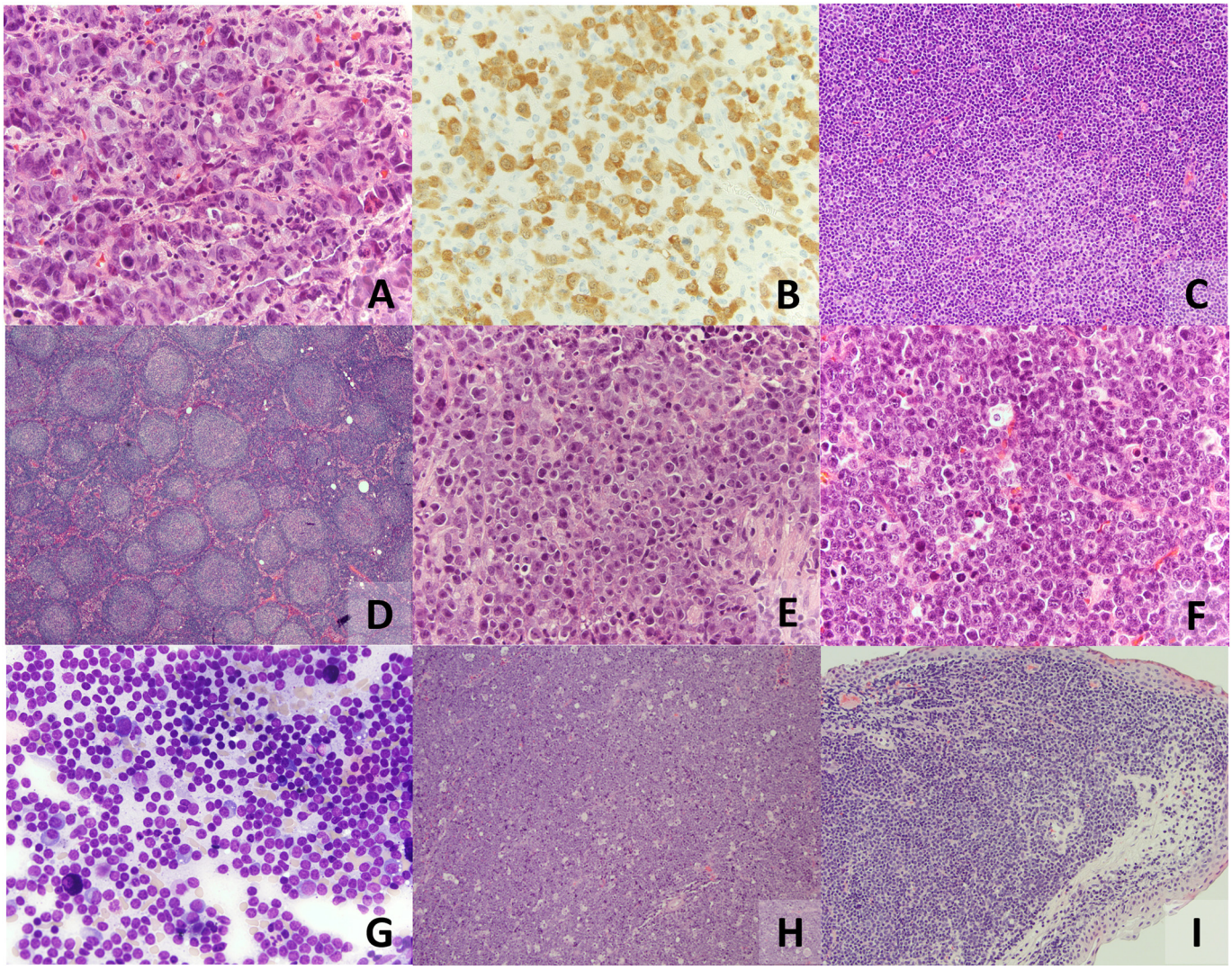

Fig. 2. Representative histology images of non-Hodgkin lymphoma subtypes: (A) Anaplastic large cell lymphoma, ALK-positive [hematoxylin and eosin(H&E), 40×] (B) Anaplastic large cell lymphoma, ALK-positive, showing the most common nuclear and cytoplasmic pattern of ALK staining by immunohistochemistry [40×] (C) Small lymphocytic lymphoma [H&E, 20×] (D) Follicular lymphoma [H&E, 4×] (E) Diffuse large B cell lymphoma [H&E, 40×] (F) High-grade B cell lymphoma with *MYC*, *BCL2* and *BCL6* rearrangements ("triple-hit" lymphoma), [H&E, 40×] (G) Lymphoplasmacytic lymphoma [Giemsa-stained bone marrow aspirate, 40×] (H) Burkitt lymphoma [H&E, 10×] (I) Extranodal marginal zone (MALT) lymphoma involving the conjunctiva [H&E, 20×].

NOTCH1 mutations, ABC-like gene expression profiles, and a less favorable prognosis; and MCD, associated with *MYD88* L265P and *CD79B* mutations, ABC-like gene expression profiles, and less favorable outcomes (Schmitz et al., 2018). BN2 tumors were noted to show changes associated with marginal zone lymphoma. The MCD-type tumors shared genetic changes previously described in primary extranodal large B cell lymphomas and tended to present with extranodal disease. In a study of 304 primary DLBCLs, Chapuy et al. described five genetic subsets (clusters C1-C5) (Chapuy et al., 2018). Cluster 1 was associated with *BCL6* structural variants, *NOTCH2* mutations, mutations in NF-κB pathway members *BCL10* and *TNFAIP3*, and frequent FAS mutations. These tumors were associated with favorable outcomes despite having predominantly ABC-like gene expression profiles and their genetic profiles were similar to marginal zone lymphoma. Cluster 2 tumors had frequent biallelic *TP53* inactivation by mutation and/or copy loss, loss of 9p21.13/*CDKN2A*, and loss of 13q14.2/*RB1*; this cluster included both ABC and GCB-like tumors. Cluster 3 was characterized by frequent *BCL2* mutations and structural variants, mutations in chromatin modifiers, including *EZH2* and *PTEN* alterations, and were associated with a worse prognosis, though the majority were GCB-type. Cluster 4 tumors had a favorable prognosis, were predominantly GCB-type, and had mutations in multiple linker and core histone genes, *BRAF*, *STAT3*, genes encoding immune-evasion molecules such as CD58, CD70, and CD83, and NF-κB regulators including *CARD11*. Cluster 5 tumors had a worse prognosis, tended to be ABC-type, and were characterized by gains of 18q (possibly affecting *BCL2* and *MALT1*). Similar to the MCD-type described by Schmitz et al., C5 tumors had frequent mutations in *MYD88* (L265P), *CD79B*, and other genes associated with primary extranodal tumors (Chapuy et al.; 2018).

MYC rearrangement is found in up to 10–15% cases of diffuse large B-cell lymphoma (Cigudosa et al., 1999) and about half of these patients have additional rearrangements involving the *BCL2* and/or *BCL6* genes. These patients are now classified separately as high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements and they often require more intensive chemotherapy (*R-EPOCH* instead of *R-CHOP*) as compared to most DLBCL patients (Kluin et al., 2017; Barrans et al., 2010). *MYC* rearrangements in these tumors frequently involve the IGH gene but can also involve the immunoglobulin light chain genes or a non-*IG* partner. FISH testing using both dual-fusion probes for the *MYC-IGH* rearrangement and break-apart probes for *MYC* are generally recommended to increase the sensitivity of *MYC* rearrangement detection (Swerdlow, 2014).

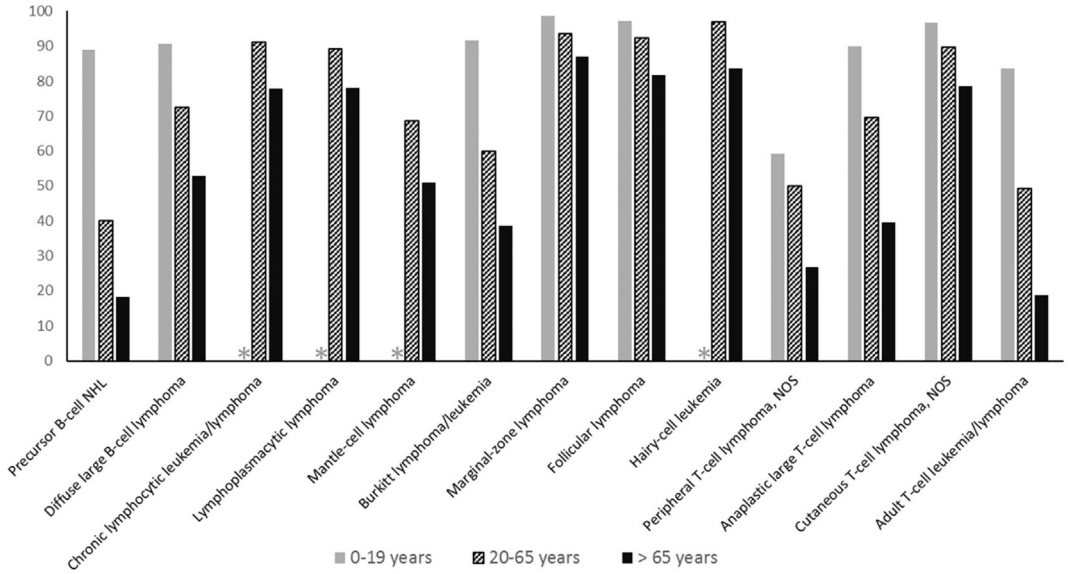

Fig. 3. Five-Year Relative Survival (percent) of common NHL types by age at diagnosis.
(Based on 2008–2014 SEER data. Asterisks represent that the number of cases in those age groups were negligible.)

4.2. Follicular lymphoma (FL)

FL belongs to the family of B-cell neoplasms that have germinal center differentiation. Follicular lymphoma cells express CD19, CD20, CD22, BCL2, and germinal center markers, including CD10, BCL6, LMO2, and HGAL. Absence of CD10 and/or BCL2 expression may be seen, particularly in high-grade disease (Jaffe et al., 2017a). Most cases of FL show a translocation between the *BCL2* oncogene, located on the chromosome 18, and an immunoglobulin (*IG*) gene locus (Rowley, 1988; Bloomfield et al., 1983). The translocation seen most commonly is t(14;18)(q32;q21) which leads to juxtaposition of the *BCL2* gene and the *IGH* promoter sequence on chromosome 14. This leads to inappropriately high expression of the anti-apoptotic protein BCL2. Translocations such as t(2;18)(q11;q21) and t(18;22)(q21;q21) involving kappa or lambda light chain genes respectively are less common (Lin et al., 2008; Hillion et al., 1991). Many patients have additional mutations such as breaks in chromosomes 1, 2, 4, 5, 13, and 17 or trisomies affecting chromosomes X, 7, 12, and 18 (Tilly et al., 1994). Some FL patients have mutations affecting the 3q27 region, involving *BCL6*, which plays important role in normal germinal center development (Bosga-Bouwer et al., 2003). These patients generally have more aggressive course and a poorer prognosis. Studies employing deep RNA sequencing techniques suggest that up to 30% of DLBCL and 90% of FL cases carry somatic mutations in genes involved with histone modification. These include genes like *MEF2B* and *CREBBP* which contributes to histone acetylation and *KTM2D* (previously *MLL2*) that encodes a histone methyltransferase (Morin et al., 2011). Recently some studies have also shown that FL patients carry mutations in genes encoding transcription factors and proteins that are involved in epigenomic regulation (*EZH2*, *ARID1A*, *EP300*) (Morin et al., 2011; Pastore et al., 2015). These findings suggest that alterations in chromatin structure plays an important pathogenic role in FL.

4.3. Mantle cell lymphoma (MCL)

MCL is a mature B-cell lymphoma commonly seen in middle aged to elderly patients. The immunoglobulin heavy chain variable region (*IGHV)* genes are generally unmutated or minimally mutated, though mutated *IGVH* genes are present in a subset of cases (Swerdlow et al., 2017b). Mutated *IGVH* gene status has been associated with a leukemic, non-nodal presentation, and often a better prognosis (Swerdlow et al., 2017b). Over 95% of mantle cell lymphomas have a t(11;14)(q13;q32) translocation involving *CCND1* (which encodes cyclin D1) and the *IGH* gene. Rarely, variant translocations involving light chain genes have been reported. These rearrangements result in increased expression of cyclin D1 and activation of cyclin-dependent kinases (CDK4 and CDK6) which counteract RB dependent cell cycle inhibition (Musgrove et al., 2011). Secondary genetic changes like losses of 1p, 6q (*TNFAIP3*), 8p, 9p (*CDKN2A*), 9q, 11q (*ATM*), 13q, and 17p (*TP53*) as well as gains of 3q, 7p21, 8q24 (*MYC*), and 12q are frequently seen (Swerdlow et al., 2017b; Espinet et al., 2010). *TP53* mutations are found in about 20% of MCL patients. *TP53*, *CCND1*, *NOTCH1*, and *NOTCH2* mutations are associated with higher proliferative rates and worse prognosis (Eskelund et al., 2017). Fewer than 5% of mantle cell lymphomas are cyclin D1-negative and lack *CCND1-IGH* rearrangements. About half of these cases have expression of cyclin D2 or cyclin D3 (Swerdlow et al., 2017b). From a histological perspective, MCL cells are usually small to intermediate in size and have a surface expression of CD19, CD20, CD22, FMC-7, CD5, CD43, and BCL2 and nuclear expression of cyclin D1 and SOX11 in the majority of cases (Swerdlow et al., 2017b).

4.4. Marginal zone lymphoma (MZL)

According to the WHO classification of lymphoid neoplasms, MZL comprises of three distinct diseases that are believed to arise from post-germinal center marginal zone B-cells. MZLs have a characteristic immunophenotype that is positive for CD19, CD20, and CD22 and generally negative for CD5 and CD10, though occasional CD5-positive cases and rare CD10-positive cases have been described Cook et al., 2017. Marginal zone lymphomas include the nodal, extranodal and splenic subtypes, with extranodal marginal zone lymphoma (EMZL) of the mucosa-associated lymphoid tissue (MALT) being the commonest variant. Somatic mutations in the variable region of immunoglobulin genes are frequently seen in these patients which is consistent with a post-germinal center stage of B-cell development (Du et al., 1996). EMZL often arise in areas with chronic inflammation due to long-standing infectious or autoimmune disease with gastro-intestinal MALT being the most common site. Gastric MALT lymphomas arise in the setting of *Helicobacter pylori* infection and can respond to *H. pylori* eradication (Zucca and Bertoni, 2016). A number of genetic abnormalities may occur in EMZL, including translocations such as t(11;18)(q21;q21), t(14;18)(q32;q21) and t(1;14)(p22;q32) which result in

activation of NF-κB through the BCL10/MALT1 signaling complex (Du, 2016). The commonest cytogenetic abnormality in EMZL is t(11;18)(q21;q21) (*BIRC3-MALT1*) which is associated with resistance to *H. pylori* eradication when it occurs in gastric lesions (Zucca and Bertoni, 2016). A less common translocation t(3;14)(p14.1;q32) fuses the *FOXP1* gene to the *IGH* gene (*IGH-FOXP1*) causing increased nuclear levels of the FOXP1 transcription factor (Wlodarska et al., 2005). It is generally seen in ocular adnexa, thyroid, and skin lesions. Other genetic aberrations include *TNFAIP3* gene deletion on chromosome 6q23 (seen in 15–30% of cases), *MYD88* mutations (seen in 6–10%) and trisomies of chromosomes 3 and 18 (Johansson et al., 2016). Splenic marginal zone lymphoma and nodal marginal zone lymphoma are much less common compared to EMZL. Deletion of chromosome 7q, gain of 3q, and mutations of *NOTCH2* and *KLF2* are frequently seen in splenic marginal zone lymphoma (Pyris et al., 2017). Gains of chromosomes 3 or 18 and deletion of 6q23 are often seen in nodal marginal zone lymphoma.

4.5. Burkitt lymphoma (BL)

Burkitt lymphoma is an aggressive, highly proliferative B cell lymphoma that usually expresses germinal center markers (CD10 and BCL6), CD19, CD20, CD22, and surface immunoglobulin (Leoncini et al., 2017). The pathognomonic mutation seen in BL is a translocation between the *c-MYC* oncogene (8q24) and one of the immunoglobulin (*IG*) genes. The *c-MYC* gene encodes for a transcription factor (MYC protein) which is multifunctional phosphoprotein that can activate or enhance expression of multiple genes. This in turn can alter the overall behavior of the cell by regulating cell cycle progression, apoptosis and cellular transformation. The majority of the patients have involvement of the *IGH* gene on chromosome 14 or t(8;14)(q24;q32) (Dalla-Favera et al., 1982). Translocations affecting the kappa and lambda light chain genes, namely t(2;8)(p12;q24) or t(8;22)(q24;q11), are seen in a minority of cases. The location of *MYC* breakpoints can be variable depending on the type of *IG* partner. FISH testing for using both *MYC-IGH* and *MYC* break apart probes may increase the sensitivity of *MYC* rearrangement detection; however, in up to 10% of BL, a *MYC* rearrangement may not be identifiable by routine diagnostic methods. In these cases, a diagnosis of BL can still be made if the morphologic and immunophenotypic criteria are met, the clinical picture is appropriate, and other types of high-grade B cell lymphoma have been excluded (Leoncini et al., 2017).

BL exists in three distinct but well recognized forms: the endemic form which affects children in equatorial Africa, the sporadic form which is commonly seen in western world, and the immunodeficiency-associated BL. Patients with sporadic or immunodeficiency associated BL tend to have the breakpoints within or nearby *MYC* whereas endemic BL patients can have more widely spread distribution of their breakpoints making them difficult to diagnose in some break-apart FISH assays (Pelicci et al., 1986). Another region frequently carrying mutation in BL patients is the 5′ noncoding region of the *BCL6* gene (like DLBCL) (Capello et al., 1997). Studies using next-generation sequencing have also found that mutations in the transcription factors *TCF3* and *ID3* (a negative regulator of *TCF3*) in BL patients (Schmitz et al., 2014). Epstein-Barr virus (EBV) genomes can be isolated in many HIV-associated BL cases (Hamilton-Dutoit et al., 1991).

4.6. Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)

CLL is the most common adult leukemia in Western countries (Campo et al., 2017; Rai and Jain, 2016). The malignant cells in CLL are derived from small mature B lymphocytes and express CD5, CD19, CD20, CD23, CD43, and CD200. Expression of CD20 and surface immunoglobulins are relatively weak and FMC-7 expression is generally absent (Campo et al., 2017). Expression of ZAP-70, CD49d, or CD38 is associated with a poor prognosis (Campo et al., 2017). Cytologically and molecularly there is no difference between CLL and SLL since the same neoplastic cell population is present in both. The disease is called CLL if there are greater than 5×10 malignant cells in circulation, SLL if there is nodal/tissue involvement with fewer than 5×10 /L circulating malignant cells, and monoclonal B-cell lymphocytosis (MBL) if there are fewer than 5×10 /L circulating neoplastic cells in the absence of lymph node/tissue involvement (Hallek et al., 2008). MBL patients with $< 0.5 \times 10$ /L circulating clonal cells (low-count MBL) generally remain in stable disease state, whereas high-count MBL patients have a higher risk of progression to overt CLL (Campo et al., 2017; Fazi et al., 2011).

Although CLL does not have a pathognomonic mutation, cytogenetic abnormalities are commonly present. The region most frequently involved is chromosome 13q14.3 and it typically contains deletions of microRNAs 16–1 and 15a, which are negative regulators of *BCL2* gene (Hsi, 2012). Isolated deletion of 13q is generally associated with a good prognosis except when present in ≥80% of cells (Campo et al., 2017). Trisomy 12 is seen in up to 20% of CLL cases and is associated with atypical cytological features (Hsi, 2012). Deletion of chromosome 11q22–23, which involves the *ATM* gene, is also frequently seen and often presents with prominent lymphadenopathy and poor outcome (Puiggros et al., 2014). Other predictors of poor response to fludarabine-containing chemotherapy and worse overall prognosis are deletion of 17p13 and mutations involving *TP53* gene (Rai and Jain, 2016). The mutational status of the immunoglobulin heavy chain variable region (*IGHV*) genes also has prognostic importance in CLL. Patients carrying un-mutated *IGHV* genes (at least 98% homology with germline) have a worse prognosis as compared to those with mutated *IGHV* genes (Hamblin et al., 1999). An association has been found between un-mutated *IGHV* status and surface expression of Zap-70 and CD38 (Wiestner et al., 2003). A subset of *IGHV3–21* expressing patients tend to have adverse prognosis, regardless of *IGHV* mutational status (Ghia et al., 2008). Other genetic features associated with aggressive disease include mutations affecting the *NOTCH1* and *SF3B1* genes (Rossi et al., 2013).

4.7. Hairy cell leukemia (HCL)

Hairy cell leukemia is a type of B-cell neoplasm in which the malignant cells have distinctive hair-like cytoplasmic projections. It is a rare lymphoma characterized by infiltrates of atypical, mature lymphocytes involving the blood, bone marrow, and spleen. These lymphoma cells express B-cell markers like CD19, CD20, and CD22. They also express CD11c, CD25, CD103, CD123, CD200, TRAP, TBX21, and annexin A1 (Foucar and Stein, 2017). Immunohistochemical staining shows presence of cyclin D1 in the absence of a *CCND1* gene rearrangement (Bosch et al., 1995). The gene expression profile of HCL is related more to memory B-cells than naïve B-cells. There is down-regulation of CCR7 and CXCR5 chemokine receptors which are involved in homing to lymph nodes and entry into lymphoid follicles (Basso et al., 2004). V600E mutation in the *BRAF* gene is seen almost universally and causes constitutive activation of the MAP kinase signaling pathway (Tiacci et al., 2011). This mutation can be detected and quantified by a variety of molecular methods such as PCR and next-generation sequencing. Antibodies that target the V600E mutation have been developed can be utilized as immunohistochemistry tool for diagnostic studies and response monitoring (Andrulis et al., 2012).

4.8. Lymphoplasmacytic lymphoma (LPL)

Lymphoplasmacytic lymphoma, previously called lymphoplamacytoid lymphoma, is a rare, low grade mature B-cell neoplasm. Waldenstrom macroglobulinemia, a cancer associated syndrome with presence of IgM para-protein in blood is almost always a manifestation of LPL (Owen et al., 2001). The neoplastic cells seen in LPL are generally a mixture of small lymphocytes, plasmacytoid lymphocytes, and

plasma cells. Expression of B-cell markers like CD19, CD20, CD22, and CD79a is seen on the lymphoid cells, usually without co-expression of CD5 or CD10 (Swerdlow et al., 2017a). The plasma cell component expresses CD19 and CD138, and is often CD45 positive too (Morice et al., 2009). The bone marrow is usually involved, whereas involvement of the lymph nodes and spleen is less common. Many recurrent mutations are seen in LPL with the most common being the *MYD88* L265P mutation (over 90% cases) followed by *CXCR4* and *ARID1A* mutations (Swerdlow et al., 2017a). Testing for *MYD88* mutation can be used to confirm the diagnosis since it is rare in other small B-cell lymphomas. Mutations of the *CXCR4* gene are associated with more aggressive disease and resistance to ibrutinib (Cao et al., 2015). While uncommon, LPL can progress to large B-cell lymphoma and such cases are generally associated with *TP53* mutation (Swerdlow et al., 2017a).

5. T-cell lymphomas

T-cell lymphomas (TCL) are a heterogeneous group of lymphomas which constitute less than 15% of all NHL in western countries. Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) and anaplastic large cell lymphoma (ALCL) are among the most common types of T-cell lymphomas (Jaffe et al., 2017b). With increased use of gene expression profiling many new cancer-driving mutations have recently been discovered. This has broadened our understanding of the role that transcription factors (like *GATA*) play in normal and aberrant differentiation of helper T lymphocytes into TH1 and TH2 cells (Iqbal et al., 2014).

5.1. Anaplastic large cell lymphoma (ALK^+ and ALK^- ALCL)

ALCL is divided into two subtypes ALK^+ ALCL, which constitutively expresses ALK tyrosine kinase, and ALK^- ALCL which has similar morphologic and immunophenotypic features but lacks ALK expression. Expression of ALK is generally determined by immunohistochemistry and cytogenetic tests are not needed. The malignant cells in ALK^+ ALCL express CD30 and are often positive for one or more T-cell markers like CD2, CD4 and CD5. CD3 expression is generally absent but cytotoxic T-cell markers may be present. One feature considered somewhat characteristic of ALK^+ ALCL is the presence of “hallmark cells” with abundant cytoplasm and horseshoe or kidney-bean-shaped nuclei. *TCR* gene rearrangement is seen is present in about 90% of anaplastic large cell lymphomas irrespective of expression of T-cell markers (Foss et al., 1996). As the name suggests, ALK^+ ALCLs have rearrangements involving the anaplastic lymphoma kinase (*ALK*) gene on chromosome 2p23 (Van der Krogt et al., 2017). *ALK* is a regulator of cell growth, cell proliferation and apoptosis and plays vital roles in multiple pathways including RAS-MAPK, PI3K-AKT, mTOR, SHH, STAT3, and others (Hallberg and Palmer, 2013). The most common translocation partner, seen in up to 80% of cases, is *NPM1* (chromosome 5q35) followed by *TPM3* (chromosome 1q21) (Van der Krogt et al., 2017). Many other translocation partners like *ATIC* (2q35), *TFG* (3q12.2), *TRAF1* (9q33.2), *CLTC* (17q23.1), *ALO17/RNF213* (17q25.3), *TPM4* (19p13.12), *MYH9* (22q12.3), and *MSN* (Xq12) have been recognized (Van der Krogt et al., 2017; Hallberg and Palmer, 2013). The most common *NPM1-ALK* translocation results in nuclear and cytoplasmic ALK staining by immunohistochemistry, while other translocations result in cytoplasmic or membranous staining. Gene expression profiling has revealed a common gene signature for ALK^+ and ALK^- ALCL that allows their distinction from PTCL-NOS. A common ALCL signature is the presence of *TNFRSF8* (CD30), *BATF*, *TMOD1*, and *p53* transcriptional targets, with downregulation of genes associated with T-cell receptor signaling (Iqbal et al., 2014). Other genes that are overexpressed in ALK^+ ALCL include genes involved in ALK signaling, *BCL6*, *CEBPB*, *PTPN1*, and *SERPINA* (Lamant et al., 2007).

ALK^- ALCL generally affects an older patient population and is associated with a worse prognosis than ALK^+ ALCL, although this could be confounded by the varied age distributions. Some ALK^- ALCL patients have activating mutations of *JAK1* and/or *STAT3*, or fusions involving transcriptional regulators and tyrosine kinases *(NFKB1-ROS1*, *NCOR2-ROS1*, or *NFKB1-TYK2)* (Crescenzo et al., 2015). Losses of *TP53* and *PRDM1/BLIMP1* are frequently seen and are associated with poor outcomes. Other genetic abnormalities include translocations involving *DUSP22* gene on chromosome 6p25.3 and *FRA7H* fragile site on chromosome 7q32.3 (Castellar et al., 2014). *DUSP22* rearrangements have been associated with a more favorable prognosis, with 5-year OS rates similar to ALK^+ ALCL (Castellar et al., 2014). The molecular signature of ALK- TCL includes overexpression of *CCR7*, *CNTFR*, *IL22*, and *IL21* (Lamant et al., 2007). The t(6;7)(p25.3;q32.3) translocation results in downregulation of *DUSP22* expression and increased expression of microRNAs in the *MIR29* cluster (Zeng and Feldman, 2016). Rearrangements involving the *TP63* gene is found in a proportion of ALK^- ALCL patients, along with inv(3) (q26q28), resulting in a *TBL1XR1-TP63* fusion (Zeng and Feldman, 2016). These patients tend to have particularly poor prognosis. Another more recently described entity is breast implant-associated anaplastic large cell lymphoma, a rare lymphoproliferative disorder that involves a peri-implant seroma, with or without invasion of the fibrous capsule around the implant. The disease is generally limited, and responds to removal of implant and capsule. The morphologic and immunophenotypic features are similar to ALK- ALCL. Mutations in *JAK1* and *STAT3* genes have been described (Matutes, 2018).

5.2. Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)

PTCL-NOS is a heterogeneous group of mature T-cell neoplasms that is seen predominantly in the adult population and has an aggressive course (Pileri et al., 2017). These patients can be broadly divided into two subgroups with distinct genetic features. One subset has increased expression of *GATA3* and its target genes (*CCR4, IL18RA, CXCR7, IK*), while the other subset has increased expression of *TBX21* (*T-bet*). High expression of *GATA3* has been associated with adverse prognosis (Iqbal et al., 2014). There are no disease defining mutations or rearrangements for PTCL-NOS but patients often have complex karyotypes and can have gains in 7q, 8q, 17q, and 22q, and losses in 4q, 5q, 6q, 9p, 10q, and 12q (Nelson et al., 2008). Complex abnormal karyotypes are common in PTCL-NOS. Rearrangements of *VAV1* gene, which plays a role in T-cell receptor signaling, have also been described in some cases (Boddicker et al., 2016).

6. Conclusion

Non-Hodgkin lymphoma is a group of heterogeneous neoplasms that affects patients irrespective of age, race and geographical location. Our comprehension of the genetic changes that initiate malignant transformation in lymphoma cells has significantly enhanced in the past few years. In this review we have summarized the key genetic and molecular features seen in common subtypes of NHL. Advancements in biomedical tools and techniques are expected to unravel newer intracellular signaling pathways which will further enrich our understanding of the pathogenesis of NHL in coming years. Increasing familiarity of molecular and cellular genetics will in turn, lead to better risk assessment and classification of newly diagnosed and relapsed NHL patients. It is important to correlate the newly found knowledge of cytogenetics and molecular genetics with morbidity and outcome statistics to extract meaningful information for clinical application. Another important area that can see significant progress is the development of targeted therapies. Deciphering of pathogenetic pathways and discovery of novel molecular targets will allow scientist to design precise immunotherapeutic approaches and small-molecules with targeted cytotoxicity against specific subtypes of lymphomas. Agents like Rituximab, Nivolumab and Axicabtagene ciloleucel (Yescarta) have demonstrated that goal-driven research aimed at unique genetic and cellular features

of lymphoma can be translated to noteworthy gains in the overall outcomes of patients. It is expected that the progress in molecular and cytogenetic characterization of Non-Hodgkin lymphoma will continue at a rapid pace in coming decades and will significantly refine the classification, prognostication and therapeutics of this disease.

Summary statement

Our comprehension of genetic features that determine the character and prognosis of non-Hodgkin lymphoma (NHL) has undergone significant shift in recent years and it is essential that scientists as well as clinicians stay in tune with this rapidly evolving knowledge. In this review we have summarized the current concepts about cellular and molecular genetics of the common subtypes of NHL and their clinical implications.

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