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Review

The Era of Genomic Research for Lymphoma: Looking Back and Forward

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Abstract: Technological and informatics advances as well as the availability of well-annotated and reliable genomic data have ushered in the era of genomics research. We describe in this brief review how the genomics approach has impacted lymphoma research in the understanding of the pathogenesis and biology of lymphoma, in lymphoma diagnosis and in targeted therapy. Some exciting directions that could be explored in the future are also discussed.

Keywords: lymphoma; gene expression profiling; genetics; tumor microenvironment; diagnostics

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1. Introduction

Traditionally, laboratory research in cancers has been focused on hypothesis-driven investigation based on prior observations or experimental findings. With technological and informatics advances, it became possible to measure gene expression on a transcriptomic scale in the mid to late 1990s [1–4]. This raised the exciting possibility of measuring the gene expression profile of lymphomas and identifying the differences among different types of lymphomas and their putative normal counterparts, leading to a better understanding of the biology and pathogenesis of different types of lymphomas and perhaps a classification that is more biologically based. Initially, there was some skepticism regarding the accuracy and reproducibility of these global measurements and hence the usefulness of this approach [5–9]. However, with further refinement of the technology and analytical approaches and more experience gained in this type of study, it is now clear that this is a reliable, powerful approach that can lead to rapid advances in many aspects of lymphoma investigation and diagnosis [10,11].

Another major initiative starting at the beginning of this century is the sequencing of the human genome [12,13]. Only recently has the human genome sequence been completed [12], but the availability of drafts and near-complete versions has enabled and greatly enhanced various aspects of genomic research [14]. As neoplastic transformation is based on genetic alterations, it is important to identify key driver changes that contribute to the perturbation in gene expression. Moreover, with the human genome better characterized, it was possible to correct some of the annotation errors in the various array-based GEP platforms. One of the first applications of the human genome sequence was the study of genomic copy number abnormalities (gCNAs) which represented a major advance over the traditional comparative genomic hybridization [15–20]. Furthermore, as the sequence and location of the vast majority of coding genes, pseudogenes and non-coding sequences are known, it greatly facilities related genetic research that can utilize and build upon this known structural and sequence information.

The more recent development of next-generation sequencing has revolutionized genomic research and allowed individual laboratories to conduct cutting-edge research previously in the domain of genome centers. A vast array of genetic, epigenetic, transcriptomic, interactomic and other more specific investigations can be performed, frequently in collaboration with institutional core facilities. In this communication, how lymphoma

research has been impacted in this omics age will be briefly reviewed, drawing mostly from the experience of a consortium of investigators in the Lymphoma/Leukemia Molecular Profiling Project (LLMPP) and their collaborators. Potential exciting developments with major implications on future research will also be discussed.

2. Gene Expression Profiling (GEP) Analysis

2.1. Diffuse Large B-Cell Lymphomas (DLBCLs)

GEP performed in a microarray format was developed in the 1990s. The probes on the array may consist of cDNA fragments or oligonucleotides [21–23]. Both of these may be spotted on the array, but oligonucleotides may also be synthesized in situ [24,25]. The initial arrays were generally not transcriptome-wide, but later commercial arrays such as the Affymetrix U133 arrays are close to whole transcriptome, and commercial arrays also tend to be more reproducibly manufactured with standard operating procedures and hence more comparable among studies than institution/lab-based ones [4]. The earliest microarray analysis of lymphoma was based on a cDNA array platform and is significant in demonstrating that different lymphoid malignancies tend to form unique clusters [26] (Figure 1). Furthermore, in diffuse large B-cell lymphomas (DLBCLs), two distinct clusters could be identified with one of them expressing many germinal center (GC) B-cell associated transcripts and hence having a GC B-cell differentiation program. The other cluster did not express the GC B-cell signature but expressed many transcripts associated with in vitro B-cell activation. The former was named GC B-cell like (GCB)-DLBCL, and the latter activated B-cell like (ABC)-DLBCL, which had worse survival independent of the international prognostic index (IPI) [26]. The findings were later confirmed in a follow-up study with a larger number of cases [27]. There was a group of cases that could not be classified into these two subtypes, initially called group 3, which was not a specific entity but a rather heterogeneous group of cases including some with low tumor content that precluded classification into the GCB or ABC subgroups. These earlier studies were performed on patients treated with CHOP chemotherapy, but a subsequent study on Rituximab (R)-CHOP treated patients confirmed that the ABC group has worse outcomes, even with R-CHOP treatment [28]. Since these two subtypes of cases have been validated to be biologically distinct and have different clinical outcomes [29], attempts have been made to reproduce the GEP-based classification with immunohistochemical (IHC) stains that can be readily performed on FFPE tissue and thus are applicable to routine clinical settings. The first published one, the "Hans algorithm", divided DLBCL into GCB and non-GCB (contained mostly ABC cases) subtypes based on three immunostains (CD10, BCL6 and MUM1) with a concordance rate to GEP-classified cases of >80% and demonstrated the more favorable prognosis of the GCB subtype [30]. The reproducibility of this algorithm has been quite variable with some laboratories unable to demonstrate a prognostic difference between GCB and non-GCB types. This may be related to the differences in the staining protocol, scoring, number of patients studied and even the composition of the patient populations. Several other IHC-based classification algorithms have been proposed, but the above-mentioned factors may still be major limitations [31,32]. A more recent attempt was made to transfer the original array-based diagnostic algorithm to another simpler transcript-based platform. The original diagnostic signature was condensed to 15 parameters with the assay performed on the NanoString platform [33]. This resulted in an assay with over 90% concordance with the original diagnosis, and the platform is highly reproducible in different laboratories [33].

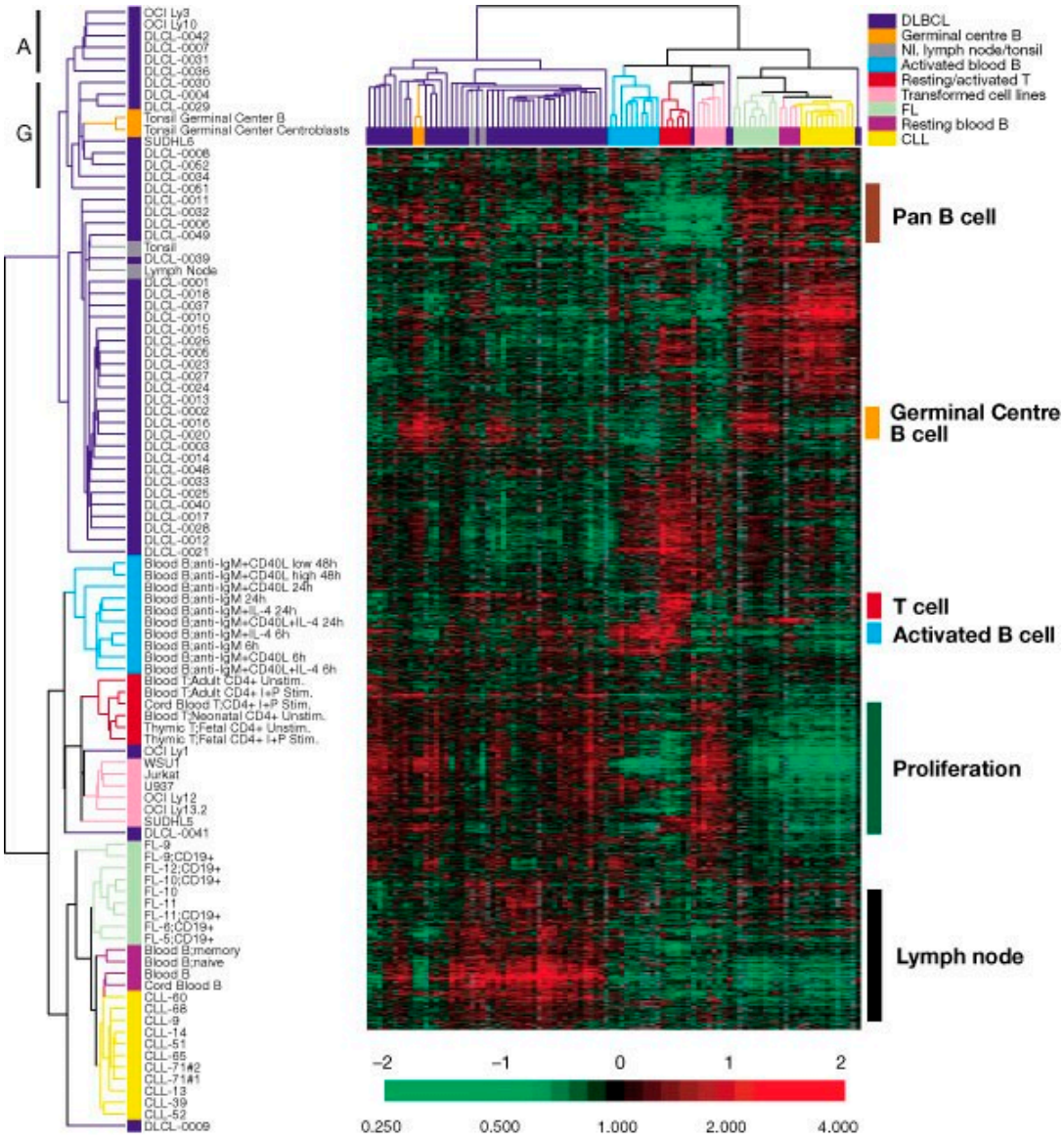

Figure 1. Hierarchical clustering of GEP data. Different lymphoid malignancies form distinct clusters based on their gene expression profile. Reproduced from Figure 1: Alizadeh AA et al. *Nature* volume 403, pages 503–511 (2000).

Several studies with global miRNA analysis demonstrated distinct miRNA signatures associated with DLBCL subtypes [34,35] and identified predictive miRNA biomarkers in DLBCL, including high expression of miR-155 and miRNA-363 [36], which is significantly associated with R-CHOP failure. miRNA-based studies are fewer than mRNA-based studies partly because of the rather late entry of miRNA into the field when many seminal studies were already reported. The advantage of using miRNA is the stability of the molecules and their good preservation in FFPE tissues.

The initial GEP studies were performed on DLBCL-NOS cases [26–28,37]. There are many other DLBCL subtypes that occur at rather low frequencies and likely have different biology and hence unique GE signatures. Some of these have been studied by GEP and demonstrated interesting findings. Among these is primary mediastinal large B-cell lymphoma (PMBL), which unexpectedly exhibited a signature similar to that of Hodgkin lymphoma (HL) cell lines [38,39]. It also characteristically had JAK/STAT pathway, IL13 and IL4, and NK-κB pathway activation [40]. Interestingly, later genetic studies also indicated overlaps of genetic alterations between these two diseases [41,42]. There is

a study that examined the presence of PMBL signature in a series of "non-mediastinal DLBCL" with GEP studies [43]. A more detailed analysis of the clinical/radiological data indicated that most of the cases with this signature had evidence of mediastinal disease and morphology compatible with PMBL, indicating that the lymphoma most likely originated from the mediastinum, but there were rare cases with no apparent mediastinal involvement, suggesting that there may be PMBL-like DLBCL without clinical and radiological evidence of mediastinal disease. Most of the other types of DLBCL studied are non-GCB tumors with similarity to the ABC subtype (such as primary CNS, testicular, CD5+ and cutaneous diffuse large B-cell lymphoma-Leg type) or with more plasmablastic features (plasmablastic lymphoma and primary effusion lymphoma) [44–52].

There have been numerous attempts at identifying prognostically important biomarkers with the current standard R-CHOP therapy independent of the IPI [53,54]. Most of the single-parameter prognosticators described have not been reproducible. TP53 mutation [55], BCL2 expression in GCB-DLBCL [56] and high BCL2 expression in the ABC-DLBCL [57,58] appeared to be associated with worse outcome. It should be noted that BCL2 expression is controlled by different mechanisms in these two types of DLBCL. BCL2 expression is mainly associated with BCL2 rearrangement in the GCB-DLBCL while in ABC-DLBCL, it is regulated by NF-κB activation and/or 18q21 gain or amplification [57]. GEP-based prognosticators have also been developed including the one published by the LLMPP group [28]. These signatures still need to be independently validated and perhaps also examined in the context of genetic profiles, as discussed later.

2.2. Other B-Cell Lymphomas

Mantle cell lymphoma (MCL) was found to have a unique GEP that included high expression of cyclin D1 as expected, but also some transcripts not generally expressed in normal B-cells such as SOX11 [59]. Interestingly, there were some cases with strong MCL signature but lacking cyclin D1 expression and translocation. It was suspected that these cases may be initiated by translocation associated with other cyclin molecules, some of which were found to be overexpressed [60]. This is indeed the case as demonstrated by translocations involving cyclin D2 and cryptic insertion of Ig light chain enhancers near CCND2 and D3 [61]. The expression of SOX11 in classical MCL and also in these cyclin D1 negative cases makes it a useful marker for diagnosis [62]. A key prognosticator for MCL is the proliferation signature [62], and based on this finding, an assay (MCL35) has been developed using the NanoString platform that can be applied to FFPE tissues. This assay could be more objective and reproducible than the counting of Ki67 positive tumor cells in histological sections [63]. A unique group of MCL with indolent clinical course, non-nodal disease with blood involvement, small cell morphology and SOX11 negativity have been identified and under active investigation [64]. Aside from GEP studies, miRNA profiling studies also revealed a 19-miRNA classifier that was able to distinguish MCL from other B-cell lymphomas [65], and MCL patients with high expression of miRNAs from the polycistronic miR17-92 cluster and its prologues, miR-106a-363 and miR-106b-25, were associated with high proliferation gene signature and poor clinical outcome in further correlative observation [65].

Burkitt lymphoma (BL) with classical morphology, MYC rearrangement and IHC profile is generally readily distinguishable from other aggressive B-cell lymphomas [66]. There are, however, cases with more atypical features that makes it challenging to diagnose. Several groups, including LLMPP, had tried to derive a BL diagnostic signature that is highly sensitive and specific [67,68]. BL characteristically has a high MYC signature as expected, and a low level of expression of major-histocompatibility-complex class I genes and the NF-κB signature. It does express a GCB cell signature enriched in a subset of genes related to the dark zone of the GC [67,69]. The dark zone of the GC is normally largely devoid of MYC expression, but in the presence of MYC translocation, both a GC dark zone and a MYC signature are observed. However, even with GEP analysis, there are still cases that are difficult to classify. The utility of miRNA profiling has been studied, and BL also

has a unique profile that can help distinguish it from DLBCL [34]. It is unclear whether combining these signatures would improve the diagnostic performance. Interestingly, the GEP signatures of pediatric and adult BL show remarkable similarity.

2.3. Follicular Lymphoma (FL) and Transformed FL (t-FL)

FL is a GC B cell-derived lymphoma and is therefore expected to express the GC B cell signature, which is clearly the case for the major group of FL with t(14;18) [70]. Higher grade cases tended to have a higher proliferation signature [71]. For the t(14;18) negative cases, there is an enrichment of ABC-like, NF-κB, post-GCB and T-cell signature [72,73]. Proliferation and cell cycle signatures also tend to be higher, which may be related to the observation of the frequent Grade 3A morphology in this type of FL. There is further heterogeneity within the t(14;18) negative group, such as pediatric-type FL, testicular FL and primary cutaneous follicular center lymphoma, that has been described and will not be further discussed here [74]. In the study by Dave et al. on prognosticators in FL, stromal signatures appear to be predictive of outcome [75]. There are generally many FL subclones in individual patients, and the clonal composition of the biopsied LN might be quite different from other lymphoma sites. It is possible the clone(s) that ultimately determine prognosis may not be well represented in the sample studied. This may explain why no specific tumor-related signature was identified as prognostic. The host response to the FL could be more uniform, and unique stromal responses could thus be more readily identified as prognosticators [76]. In the Dave study, factors specifically predictive of transformation were not investigated [75]. However, a gene expression signature predictive of FL prognosis when treated with R-CHOP was recently generated for tumor biopsies at the time of diagnosis [77]. In addition, miRNA studies identified upregulation of miR-193a-5p, 193b* and 663 downregulation of miR-17*, -30a, -33a, -106a) in FL [78] and a miRNAs profile associated with t(14;18) negative cases [79].

2.4. Peripheral T-Cell Lymphoma (PTCL)

PTCL constitutes only ~10–15% of all non-Hodgkin's lymphoma (NHL) in Western countries [80,81]. The current World Health Organization (WHO) classification recognizes many distinct PTCL subtypes, including angioimmunoblastic T-cell lymphoma (AITL), anaplastic large cell lymphoma (ALCL), adult T-cell leukemia/lymphoma (ATLL) and extra-nodal NK/T-cell lymphoma of nasal type (ENKTL) [74] as well as additional rare PTCLs that are mostly extra-nodal lymphomas [74]. Even for expert hematopathologists, the diagnosis and subtyping of PTCL is challenging [74,82], and 30–50% of PTCL cases are not classifiable with current approaches and are categorized as PTCL, not otherwise specified (PTCL-NOS) [74]. Thus, PTCL-NOS represents the most common group of PTCL with a broad morphological and immunophenotypic spectrum that does not correspond to any of the distinct T-cell entities in the WHO classification [83,84].

The study and understanding of the biology of PTCL has lagged behind that of their B-cell counterpart partly because of the relative rarity of PTCL [85]. A number of GEP studies have been reported for PTCL, but the number of cases is generally small and conclusions from these studies need to be validated [86–92]. Through extensive international collaborations, it was possible to perform several larger GEP studies on PTCL that led to the definition of robust molecular signatures for major subtypes of PTCL [93–95]. It validated previous reports suggesting a link between AITL and TFH cells [90,92]. Importantly, two novel biological and prognostic subgroups within PTCL-NOS with distinct GEP signatures were identified [95]. One subgroup, representing about a third of PTCL-NOS, is characterized by high expression of GATA3 and its target genes. GATA3 is the master transcriptional regulator in TH2 cell differentiation and regulates interleukin-4 (IL-4), IL-5 and IL-13 expression [96]. The other subgroup, representing about half of PTCL-NOS, has high expression of *TBX21* and its target genes. *TBX21* is a master regulator of TH1 cell differentiation and regulates the expression of IFNγ [97]. The "high GATA3" subgroup (designated as PTCL-GATA3) had poorer clinical outcomes, supported by an independent

study [98]. The PTCL-GATA3 group had higher MYC and proliferation signatures, whereas NF-κB targets were enriched in the TBX21 subgroup. Further examination of the "TBX21" subgroup (designated as PTCL-TBX21) identifies a subset with a high cytotoxic signature including the expression of CD8 and cytotoxic molecules such as perforin, granzyme B, TIA1 and others. These cases have a poorer clinical outcome than the rest of the PTCL-TBX21 subgroup and may represent a separate cytotoxic subgroup of PTCL [94,95]. While these studies suggest the "cell-of-origin" of different subgroups of PTCL, it is unclear whether the tumors are derived from a certain subtype of T cells, or whether different genetic changes initiating/promoting the transformation may favor the polarization of the lymphocytes to a certain lineage. It is also uncertain how stable are the phenotypes and whether further genetic changes or the cytokine environment may re-polarize the cells either partially or completely due to the plasticity of T-cell differentiation [99]. There are little data on relapsed PTCL to address some of these questions.

While activation of distinct oncogenic pathways in these subgroups [94,95,100] and the observed clinical differences support the validity of the classification, recent genetic analysis including high-resolution genomic copy number abnormalities (gCNA) [101], and mutational analysis and even miRNA analysis [102], provided further evidence that PTCL-GATA3 and -TBX21 subgroups represent distinct diseases and exploit distinct genetic pathways for tumorigenesis [101], which will be elaborated on further in later sections.

Attempts have been made to use routine IHC assays to help to separate these two subtypes of PTCL, and it is possible to have a good concordance of around 80% with molecular classification using four immunostains (GATA3, CCR4, TBX21 and CXCR12) [103]. As IHC staining and scoring may not be readily standardized, a more objective and quantitative assay with high reproducibility is preferred. An assay based on the previous microarray data and adapted to the NanoString platform has been recently developed that can be performed using FFPE tissues and thus could be utilized in routinely processed biopsy materials [104]. This assay could benefit the classification of PTCL in clinical practice as well as in clinical trials for accurate stratification of patients.

Similar to B-cell lymphomas, GEP generates data that can be used for biological pathway and signature analysis, some of which could be correlated with clinical outcome or suggest response to targeted therapy. Thus, in ENKTCL, there is evidence for the activation of the aurora kinase A (AURKA) pathway and potential efficacy of a AURKAi [93,105,106]. A more extensive in vitro drug screening study independently confirmed that AURKAi was active against NK-lymphoma cell lines [107]. High NF-κB activation has been associated with worse prognosis in ALCL [108], while in AITL, a high B-cell signature is associated with better prognosis and a high macrophage/dendritic cell signature was associated with poorer outcome [94,95]. In the TBX21 PTCL, there is an inverse correlation between B-cell and cytotoxic signature and high B-cell signature is associated with better prognosis [95] while the reverse is true for the cytotoxic signature.

3. Global Genetic Analysis

The International Human Genome Sequencing Consortium announced on 14 April 2003, the successful completion of the Human Genome Project, and the sequence was published next year in *Nature* [13,109,110]. While the human genome was not completely sequenced and assembled until recently [12], the publication was an important landmark that ushered in the era of large-scale genomic research. The initial and subsequent cumulative published data on the human genome provide the information that has enabled numerous investigations to move forward. Subsequent development of massive parallel sequencing technology allows next generation sequencing (NGS) to be done in many facilities outside of the genome centers and further enables the rapid growth of genome-based research.

3.1. The Study of Genomic Copy Number Abnormalities (gCNAs)

One of the first applications in lymphoma research based on human genomic data is the study of genomic copy number abnormalities (gCNAs) that could be done using

either SNP arrays or oligonucleotide arrays. A study by Lenz et al. on DLBCL revealed the common gCNAs and highlighted the different profiles between GCB and ABC DLBCL [111]. The simultaneous availability of GEP data further facilitated the identification of the potential driver genes associated with each of the gCNAs [111] such as *PRDM1* in 6q21 deletion, *BCL2, MALT1* and *TCF4* in 18q21 gain/amplification [112], *c-REL* and *BCL11A* in 2p14-16 gain/amplification. The selective requirement of a potential candidate genes to specific molecular subgroups could also be shown experimentally by the selective cytotoxic effect of knocking down of *SPIB* [19q telomeric gain/amp] [111] in ABC-DLBCL cell lines but not to GCB-DLBCL cell lines. Additionally, certain gCNAs or combinations appeared to be associated with prognosis as exemplified by the association with poor prognosis in ABC-DLBCL with del 9p21 (*CDKN2A and 2B*) and trisomy-3 [111]. Some common translocations also have differential distribution in the subtypes of DLBCL, such as the almost exclusive presence of *BCL2* translocation in GCB-DLCBL [113], and the more frequent *BCL6* translocation in ABC-DLBCL [114]. Methylation analysis also demonstrated distinct abnormal profiles in these two subtypes [115].

Several genome-wide DNA copy number studies on MCL identified recurrent deletions of tumor-suppressor genes, including TP53 (17p21), ATM (11q), RB1 (13q14.2) and CDKN2A, CDKN2B, MTAP (9p21.3), which provided insights into various deregulated pathways such as DNA damage repair (ATM) and cell cycle (TP53, RB1 and CDKN2A, CDKN2B) [116–118]. Somatic mutation and deletions/hypermethylation of TNFAIP3 (6q23.3) leading to NF-κB pathway activation have been observed [119,120]. Similarly, methylation analysis revealed a hypo-methylated genome in MCL; however, a subset of tumors with extensive CpG methylation, as well as an increased proliferation signature, were associated with poor prognosis [121]. Targeting the epigenome or specific aberrantly expressed genes (such as CD37) could be novel therapeutic options in MCL [122].

The genomic alteration in BL is generally much less complex compared with DLBCL, with far fewer numbers of gCNAs. In addition to the t(8;14) translocation or variant t(8;22) or t(2;8) translocations, BLs show recurrent gains involving a small locus in 13q31.3 encoding the miR17-92 cluster, recurrent gains of 1q localized to a minimal common region at 1q21.1 and 1q31.3, and frequent loss of 17p [123,124]; however, other observations are less consistent among studies [125,126]. Genomic aberrations (e.g., del13q14, del17p, gain8q24, and gain18q21) and effectors of chronic BCR– > NF-κB signaling were more associated with adult-mBL, and gain/amplification of MIR17HG and its paralogue are particularly frequent (present in 50%). BLs may be associated with EBV infection, particularly in those arising in endemic regions (>90%); recent studies have demonstrated differences in GEP as well as genetic landscape in EBV+ cases [127,128], notably the higher mutation burden due to increased AICDA activities but lower frequency of mutation in TP53, USP7 and TCF3/ID3 [129].

FL is associated with recurrent genetic alterations including chromosomal gains (7, 12, 18 and X) and deletions (6q and 1p) [130–134] and further refined to genetic loci del of 1p36.33-p36.31, 6q23.3-q24.1 and 10q23.1-q25.1 and gains of 2p16.1-p15, 8q24.13-q24.3 and 12q12-q13.13 with higher resolution techniques [135]. The transformation to aggressive lymphoma [136] is rarely associated with c-*MYC* rearrangement [136], but no specific changes are unique to transformation, although some genetic changes have been reported to be associated with transformation, including mutation of *p53* [137] and *BCL2* [138] and homozygous *9p21* deletions [139], and gains of 3q27.3-q28, 6p12-p21 and 17q21.33 [140]. Overall, genetic abnormalities associated with transformation impair immune surveillance, activate the NF-κB pathway and deregulate the cell cycle and B-cell transcription factors [135,141]. Of special interest are mutations and CNAs affecting S1P-activated pathways, which likely regulate lymphoma cell migration and survival outside of follicles [141]. Global methylation profiling of sequential FL and transformed-FL biopsies revealed a hypermethylated genome common to FL, and an over-representation of genes targeted for epigenetic repression by PRC2 within the hypermethylated gene set. Along with the

similarity in hypermethylation pattern between paired biopsies, this suggested that the widespread methylation observed may represent an early event in lymphomagenesis [142].

3.2. Mutation Analysis: Example on DLBCL

Several driver mutations were identified before the era of NGS in DLBCL, such as *CD79b* affecting BCR signaling [143], *CARD11* activating the NF-κB pathway, TNFAIP3 mutation or loss dysregulating NF-κB and *MYD88* linking IL1/TLR pathway to NF-κB activation [144–147]. These mutations are far more common in the ABC-DLBCL, supporting the previous GEP finding of the importance of BCR signaling and NK-kB activation in this subtype of DLBCL [29]. Subsequent application of NGS in the study mutations in lymphoma leads to an explosive growth in mutations identified and the construction of the genomic landscape of several types of lymphoma including DLBCL [148–151], MCL [117,120,152], FL [153,154], BL [155,156] and marginal zone lymphomas [157–161]. As DLBCL is the most common lymphoma, it has also been most extensively studied, and genomic subgroups have been delineated. Using consensus clustering, Chapuy et al. [151] identified five genomics clusters based on mutation and gCNA analyses, and these clusters have biological and clinical implications. Schmitz et al. [150], using a different approach, identified four genetic subgroups, and three of these appear to overlap with three of the clusters reported by Chapuy et al. [151] (Table 1). These studies indicated there are genetic subgroups of DLBCL that could be robustly defined, and they could further refine the GCB vs. ABC distinction. In a subsequent analysis, Wright et al. [162] re-affirmed the previous findings by Schmitz et al. and reported an additional subgroup associated with TP53 abnormalities and another a small subgroup called ST2 that has a similar profile to T-cell rich B-cell lymphoma or DLBCL transformed from LPHL [163,164]. Whether ST2 tumors are de novo DLBCL or represent un-recognized transformation of LPHL is unclear. While mutation and gCNA data are critical in the defining of these genetic subgroups of DLBCL, other genetic information is also important such as BCL2, BCL6 or MYC rearrangement. Some of the genetic abnormalities may suggest the potential usefulness of targeted agents as pointed out by Wright et al. [162]. For example, DLBCL in the MCD group typically have mutations affecting MYD88 and CD79B and are associated with high response rate to ibrutinib. However, despite the apparent match of a putative driver mutation to a targeted drug, the effectiveness of the agent still needs to be determined by rigorous pre-clinical studies followed by well-designed clinical trials.

Table 1. Comparison of two genetic classification schemes for DLBCL.

Chapuy B. et al. Nat. Med. 2018	Schmitz R. et al. NEJM. 2018	COO Classification	Prognosis	Genetic Characteristics
Cluster 1	**BN2**	ABC or ABC + UC	F	BCL6 rearrangement; Notch pathway: Notch 2, SPEN, DTX1; NF-κB: A20, TNIP1, BCL10, PKCB; immune escape CD70, FAS, PDLI/L2
Cluster 2	**N/C**	Mixed	UF	TP53 biallelic abnormalities; CDKN2A/RB loss; miR17-92 gain; MCL1 gain
Cluster 3	**EZB**	GCB	UF	BCL2 translocation, EZH2 mutation, cRel amplification, TNFRSF14 alteration, MEF2B, and common chromatin modifier mutation: MLL2, CREBBP, EP300; SIPR2 pathway; STAT6; mTOR; MiR17-92; PTEN
Cluster 4	**N/C**	GCB	F	Histone core and linkers; immune evasion; GNA13, RHOA, SGK1; NF-κB; BRAF/STAT3
Cluster 5	**MCD**	ABC	UF	MYD88L265P, CD79B; 18p gain, PRDMI, CDKN2A, ETV6, BTG1/2, TBL1XR1; PIM1; immune editing, high cAID
N/C	**N1**	ABC	UF	NOTCH1 mutation; IRF4, 1D3, BCOR, A20; plasmacytic phenotype

F: favorable; UF: unfavorable.

3.3. Mutation and gCNA Analyses: Peripheral T-Cell Lymphoma

As with GEP studies, the genetic analysis of PTCL also lagged behind its B-cell counterpart, but a number of recent studies have provided important insights into the pathogenesis of several PTCLs [165–167]. One of the earliest mutations detected was *IDH2* mutation found in AITL [168]. Different from AML and glioblastoma, *IDH1* mutations were not found, and IDH2 R172 mutation was the only IDH2 mutation detected. Subsequently, *TET2* mutations were found to be very frequent in AITL, but surprisingly, *IDH2* mutation in AITL [100] almost always occurs together with TET2 mutation, distinct from their mutual exclusivity in AML. DNMT3A was also found to be frequently mutated, and again, it frequently co-occurs with TET2 mutations. This co-occurrence seems paradoxical as these genes have opposite functions in DNA methylation. Both TET2 and DNMT3A mutations are found in other PTCLs, being more frequent in the TBX21 than GATA3 subtype. There is a hotspot *DNMT3A* mutation affecting R882 that seems to be more frequently associated with tumors with the cytotoxic phenotype [169]. *IDH2R172* mutants acquire a neomorphic enzyme activity with the production of 2-hydroxyglutarate (HG) instead of alpha-ketoglutarate (aKG), resulting in the inhibition of all TET enzymes. However, 2HG inhibits a large group of dioxygenases, so there are functional alterations in addition to impaired DNA-demethylation. An interesting finding is that in some PTCL patients with *TET2* mutations, the same mutation was also found in a co-existing myeloid disorder, suggesting that the *TET2* mutation may be present in a hematopoietic stem cell (HSC) which gives rise to both the myeloid and T-cell disorders. There is evidence that AITL cases may also be associated with clonal hematopoiesis of undetermined potential (CHIP) [170] instead of an overt myeloid disorder and share the same *TET2* mutations. Thus, the mutational landscape in AITL is dominated by mutations that aberrantly modify the epigenome.

The other highly frequent mutation, present in about 70% of AITL, affects *RHOA*, which is a small GTPase important in a number of T-cell functions in addition to cytoskeleton organization and cellular motility/migration [171–173]. In AITL and PTCL with T_{FH} phenotype, the *RHOA* mutation is a unique G17V mutation resulting in an inability of the protein to associate with GTP or GDP and believed to be a dominant negative mutation. Other *RHOA* mutations have been described in other PTCLs, including some that are gain-of-function mutations such as *RHOA C16R and K118*. How these RHOA mutants contribute to T-cell transformation needs further investigation. As RHOA G17V mutation almost always occurs with TET2 mutation, their functional interaction is also intriguing. Another group of mutations in PTCL affects the proximal TCR signaling pathway [174–176]. They are much less common than the mutations just mentioned and affect signaling molecules including CD28, PI3K components, FYN, PCLG1 and VAV1. A number of fusion proteins have been described including CTLA4-CD28 [177], ICOS-CD28 [175], ITK-SYK [178], FYN-TRAF3IP2 [179,180] and VAV1 fusions [181], with a number of partners with deletion of the C-terminal autoregulatory SH3 domain of VAV1. These are generally activating mutations, but exactly how TCR signaling is altered to favor T-cell transformation is unclear. Another group of mutations affect the JAK/STAT pathway. JAK1 and JAK3 are the most commonly mutated with the mutation affecting most frequently the pseudo kinase domain. JAK fusions have also been described in ALK neg ALCL, which also contain a group of cases with DUSP22 rearrangement and rarely TP63 rearrangement with the former associated with good prognosis, while the latter with a very poor outcome [182,183]. Activated JAK may not only promote phosphorylation of the associated STATs, but may also phosphorylate other targets unrelated to STAT functions [184,185]. Of the STAT genes, STAT3 and STAT5B are the ones involved. Mutations occur mostly in the SH2 domain and affect the affinity and stability of the phosphorylated dimers, which persist much longer than the WT with increased target occupancy and changes in transcription [186] (Figure 2). STAT5B and STAT3 mutations have a different distribution profile, with STAT5B the dominant mutation in T-PLL [187], γδ -TCL and HSTCL [186] while STAT3 mutated is more frequent in ALCL and NK-cell lymphoma [188].

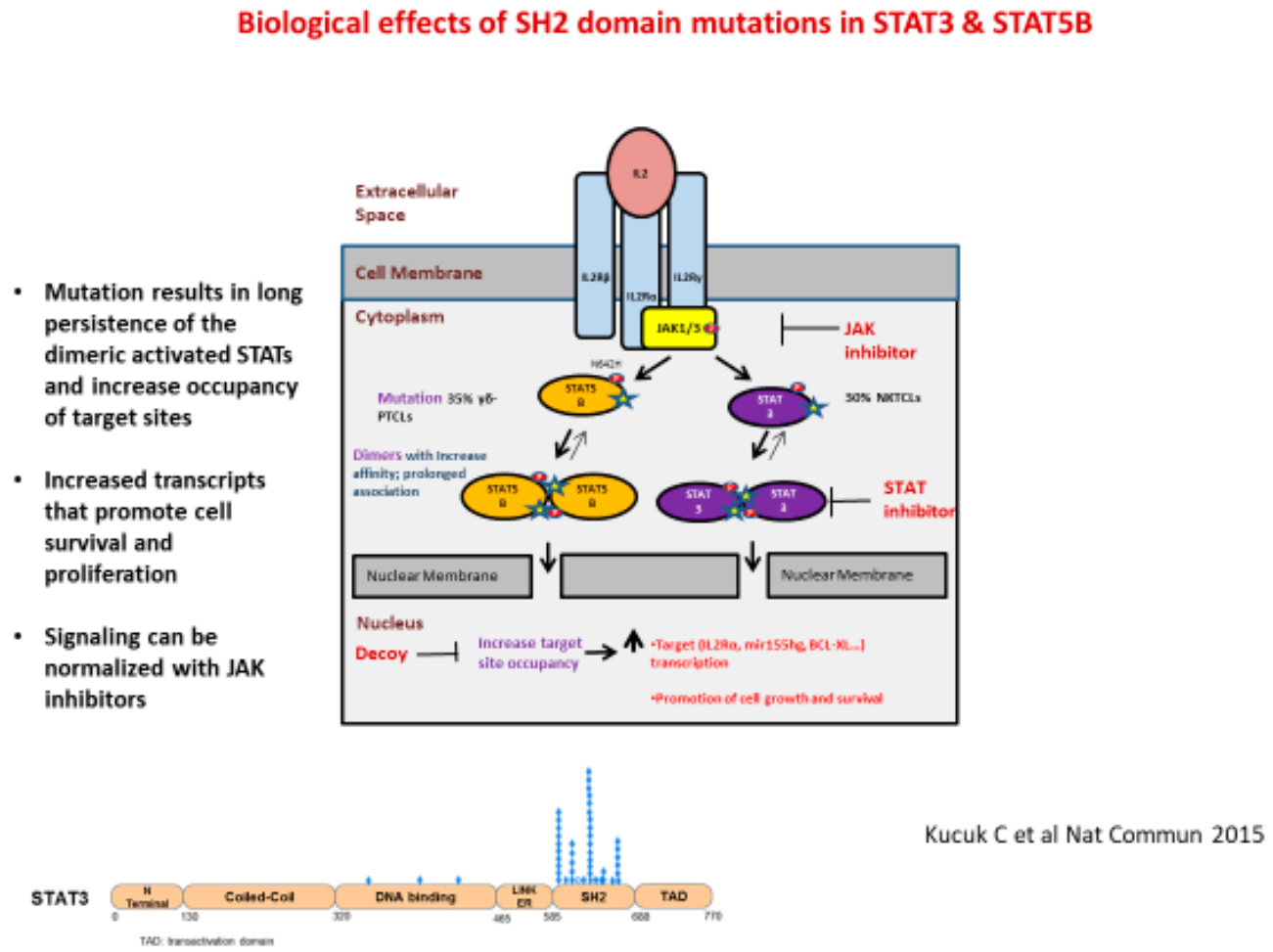

Figure 2. Biological effects of SH2 domain mutations in STAT3 and STAT5B (modified from Kucuk C et al. Nat Commun 2015 [186]).

gCNAs have been studied in AITL and several other PTCL, including the GATA3 and TBX21 subtypes, and they have distinctive profiles [101]. PTCL-GATA3 has the highest gCNAs, and there are highly frequent deletions of tumor suppressor genes (TSG) such as TP53, p16/19, RB, PRDM1 and PTEN, while there are gains including *STAT3* and *MYC* [101]. An unusual feature is the co-occurrence of TP53 mutation/deletion and heterozygous loss of *PTEN*, rarely observed in lymphomas. These cases have similar genetic features to a cluster of cases identified in the study by Watatani Y et al. [189] that probably also represented mostly GATA3 cases. All these observations support the GEP classification of PTCL-GATA3 and TBX21 as unique entities.

The concept of T_{FH} cell-derived lymphoma has been expanded from AITL to tumors with T cells having similar immunophenotype but a follicular growth pattern (follicular T-cell lymphoma), and PTCL that would have been classified as PTCL-NOS except that the tumor T cells express two or more T_{FH} cell-associated markers, such as PD1, ICOS1, BCL6, CXCL13 and CD10 (PTCL-T_{FH}) [74,190]. PTCL-T_{FH}, as currently defined, is likely to be heterogeneous. Most of these cases appeared to have a stronger T_{FH} signature and AITL-like signature by GEP as well as mutations associated with AITL and thus likely to be part of the spectrum of T_{FH}-associated lymphoma [104,191]. However, there are also cases that appear to be unrelated to T_{FH} cells, and a more comprehensive study with more cases may be needed to further characterize this group of cases.

3.4. Cooperativity of Genetic Alterations

A mutation does not occur in isolation in a lymphoma; it co-operates with other alterations that could be genetic or epigenetic to mediate neoplastic transformation. *STAT3* is the most frequently mutated gene in ENKTCL and is often associated with PRDM1 deficiency, which is also a very common event in this lymphoma. A recent study examined the possible co-operation between these two abnormalities in normal NK-cells and found that STAT3 mutants can only mediate enhanced cell growth for a limited period of time. However, if *PRDM1* is knockout, the double mutant cells can undergo persistent proliferation which can be sustained using IL15 alone without other cytokines or the presence of feeder cells [188]. If the *STAT3* mutant was replaced with a common *STAT5B* mutant, *STAT5B N642H*, a co-operative effect with PRDM1 was not observed (unpublished observation). This co-operative event may partly explain the difference in *STAT* mutations observed in ENKTCL and γδ PTCL. Similar investigations in the future may unravel additional important co-operative events.

4. The Integration of Multiomics Data

With the ability of performing multiomics studies on the same biological samples, it is possible to obtain important complementary information that can lead to greater and more comprehensive understanding of the biological processes under investigation that may also provide novel leads to future investigations. This requires greater planning to obtain the requisite tissues and perform the necessary studies. The analyses and interpretation are more complex and require more expertise. An example of such an approach is the investigation of transcription factor binding and its functional consequences. Traditionally, ChIP analysis is performed and currently combined with NGS to identify binding sites. However, binding may not be associated with functional activities, which are now generally accessed by simultaneously determining chromatin accessibility and RNA expression. Some binding peaks occur in genomic regions without clear association with a particular gene. The availability of Hi-C data would be very helpful in identifying associations with specific genomic sequences with each of these peaks [192], thus allowing the prediction of the target of the TF when bound to specific DNA sequences.

5. The Tumor Microenvironment

It is quite clear from numerous studies that the TME is an integral and important component of the tumor which may be critical for tumor cell survival and in regulating the host/tumor interaction, particularly the immune reaction to the tumor, which could be especially relevant in this era of immunotherapy. It is notoriously difficult to derive cell lines from PTCL, clearly indicating the importance of TME in supporting the growth and survival of the tumor cells. In multiple lymphomas, TME signatures have been shown to be predictive of patient survival as mentioned above. In a bulk population, the GEP signature is a mixture of signals from multiple components, and it is challenging to decipher what components are present and their contributions to the GEP. Recent development in computational analysis such as the CiberSort approach [193,194] may help to deconvolute bulk GEP data to provide an estimate of the immune cell populations present in the TME. An extension of this approach includes the subtyping of tumor cells by GEP and defining their association with stromal elements to form unique tumor ecosystems that may provide further insight into tumor biology and clinical behavior [195]. It would be even more informative if these analyses are combined with immunophenotyping [196] to validate the computational findings and visualize the distribution and spatial relationship of the immune/tumor cells. Flow cytometry may be employed on isolated cells from the tissue, but spatial information is lost. Multiparameter immunophenotyping by multicolor fluorescence such as the Vectra Polaris (PerkinElmer) or CODEX (PhenoCycler, Akoya Biosciences) technology has been developed and has the advantage of maintained spatial relationship of the cells. The recent development of CyTOF technology [197–199] allows the determination of more markers than possible using fluorescence-based assays and

tissue-based CyTOF assay. Imaging mass cytometry (IMC) is being developed to evaluate cellular populations in situ [200,201]. The drawback of IMC is the small area that can be examined and the limited panel of labeled antibodies available, often necessitating the labeling of antibodies by the user. The procedure is also destructive to the labeled tissues. The technical and analytical considerations of these high dimensional imaging approaches have been reviewed recently [202]. These are very promising tools for the study of the TME, but computational approaches [203,204] to fully exploit the data from these systems are challenging but critically needed.

Single-cell (sc) RNA-seq studies are now feasible, and the technology has been recently reviewed [205,206]. It has been employed recently to decipher the biological complexity of the tumor cells as well as the stromal cell populations [207–209]. When scRNA-seq is performed on isolated cells, spatial information is lost, and various artefacts may also be introduced. To overcome these barriers, techniques such as Slide-seq [210] that attempt to preserve the spatial information have been reported. Commercial platforms such as the 10X genomics (Visium) and NanoString platforms are now available for similar purposes and applicable for FFPE tissues. These platforms are not at true single cell resolution yet, and scRNA-seq has limitations such as high costs and low transcriptome coverage, but it is a valuable component of GEP analysis and can provide important insight into the functional states and activities of single cells, the heterogeneity of the tumor cell population, the potential interactions of neighboring cells and the possible trajectories of these interactions.

6. A New Diagnostic Platform

Traditionally, diagnosis is based on tissue biopsy and study of the tissue thus obtained, but a biopsy is an invasive procedure; yet, the biopsy obtained for diagnosis may not be the most diagnostic or representative. Lymphoma patients frequently relapse after therapy and usually a very limited needle biopsy or no biopsy is obtained, which is a tremendous impediment in the adequate characterization of relapsed disease even for clinical purposes. Thus, a new approach that addresses these major issues will have a powerful clinical impact. *Technological advances* have allowed the performance of sophisticated analysis on the small amounts of DNA and RNA present in cell-free plasma [211–213], an easily obtainable biospecimen that allows more frequent sampling without an invasive procedure. In addition, the plasma analytes represent the summation of the contribution from all tumor sites and provide a more global picture of the entire tumor content [212]. The successful development of the technology and implementation of it as a clinical assay would represent a major breakthrough in diagnostics, allowing molecular characterization of each patient at diagnosis and at different points of treatment to guide further actions. Circulating tumor DNA (ctDNA) also enables monitoring of tumor evolution and characterization of resistant clones [212,214]. The technology is applicable not only to lymphoma but also to other types of cancer [215]. In lymphoma, many of the studies had been focused on DLBCL using the Cancer Personalized Profiling by Deep Sequencing (CAPP-seq) approach [211], which used a pre-defined panel to capture the DNA from selected loci for deep sequencing. Another approach is to sequence the tumor to determine the mutations present and then design a custom panel for deep sequencing [216]. An exciting report on HL [217] has been published, demonstrating that it is possible to perform CAPP-seq successfully in liquid biopsy, even in a disease where the neoplastic cells may be as low as or lower than 1% of the cells in the tumor. Interestingly, their findings on the predictive value of early reduction in ctDNA on chemotherapy on treatment response and survival are quite similar to findings reported in DLBCL [218]. While ctDNA is the most frequently investigated analyte, other analytes include plasma miRNA and 5mC [219] and possibly 5hmC-modified DNA that may be assayed and may complement ctDNA information or constitute new assays. This is a rapidly evolving area with new technological and analytical developments [220]. Liquid biopsy may provide the platform for sensitive and specific molecular assays for multiple types of cancer and become the next-generation diagnostics for precision medicine [221,222]. However, much still needs to be done to determine

various preanalytical variables, standardize the assay and platforms and validate the clinical characteristics and usefulness of the assays.

7. Perspectives

The last 22 years have seen an explosive growth in genomics data in lymphoid malignancies leading to a marked improvement in the understanding of their pathogenesis and biology. For the more common lymphomas, the genomic landscapes are fairly well defined, but the less common entities are still largely unexplored. A better understanding of the tumor/microenvironment interaction is crucial, and we have better tools to make significant discoveries in this area. Obtaining good, well-annotated tissue samples is particularly challenging in lymphoma, and samples collected often lack corresponding normal controls, making tissue availability a major barrier in future research. As mentioned above, multiomics investigations are important to more fully explore the omics data, but few studies have performed such investigations. In the future, the integration of omics and comprehensive TME findings, particularly with spatial information, would markedly improve our understanding of tumor biology and host/tumor interaction. The incorporation of single cell analysis will further provide essential information on tumor heterogeneity, clonal evolution and the diverse stromal components. While gaining genomic information is critical, painstakingly focused investigations are still necessary to understand the biological implications of specific findings. The information generated so far has suggested many potential drug targets against individual genes and/or pathways, which has led to many clinical trials. Further understanding of tumor biology and host/tumor interaction will no doubt lead to more novel targets, better stratification of patients for clinical studies and the elucidation of mechanisms of therapy resistance. This is true not only for traditional drug-based trials but also for immunotherapy. Plasma-based diagnostic platforms are rapidly advancing and could become the next-generation diagnostics that may vastly improve the monitoring of patients under treatment and on prognostication.

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