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Tumor Heterogeneity in Lymphomas: A Different Breed

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Abstract
The facts that cancer represents tissues consisting of heterogeneous neoplastic, as well as reactive, cell populations and that cancers of the same histotype may show profound differences in clinical behavior have long been recognized. With the advent of new technologies and the demands of precision medicine, the investigation of tumor heterogeneity has gained much interest. An understanding of intertumoral heterogeneity in patients with the same disease entity is necessary to optimally guide personalized treatment. In addition, increasing evidence indicates that different tumor areas or primary tumors and metastases in an individual patient can show significant intratumoral heterogeneity on different levels. This phenomenon can be driven by genomic instability, epigenetic events, the tumor microenvironment, and stochastic variations in cellular function and antitumoral therapies. These mechanisms may lead to branched subclonal evolution from a common progenitor clone, resulting in spatial variation between different tumor sites, disease progression, and treatment resistance. This review addresses tumor heterogeneity in lymphomas from a pathologist's viewpoint. The relationship between morphologic, immunophenotypic, and genetic heterogeneity is exemplified in different lymphoma entities and reviewed in the context of high-grade transformation and transdifferentiation. In addition, factors driving heterogeneity, as well as clinical and therapeutic implications of lymphoma heterogeneity, will be discussed.

Introduction

Tumor heterogeneity is a phenomenon that has long been recognized by pathologists, cancer researchers, and medical oncologists. Tumor heterogeneity can conceptually be divided into intertumoral and intratumoral heterogeneity. Intertumoral heterogeneity describes the variability in morphology, immunophenotypes, genetic aberrations, epigenetic events, therapy responses, and clinical outcomes of distinct tumor entities in different

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patients. In contrast, intratumoral heterogeneity designates the variability of individual tumor cells and tumor subclones within the complex and dynamic ecosystem of a given neoplasm in a single patient [1–6]. Intratumoral heterogeneity can be influenced by the interactions of cancer cells with other cancer cells (clonal cooperativity/competition) [7] and of cancer cells with cells and structures of the tumor microenvironment (i.e., immune cells, vasculature, cancer-associated fibroblasts, and extracellular matrix), by tissue oxygenation, pH, and nutrient availability, and by stochastic variation in cellular function. Intratumoral heterogeneity also describes the divergence between primary tumor and metastatic sites as well as temporal heterogeneity depending on the point of analysis of primary versus recurrent tumors [1–3, 6].

The concepts on the origins of intratumoral heterogeneity were extensively discussed already more than 30 years ago [8]. At that time, evidence for intratumoral heterogeneity was mostly obtained in cell lines or animal experiments and was only indirectly observed in human cancers. In recent years, however, the field of tumor heterogeneity has witnessed unprecedented advances due to new genetic and computational technologies that enable massive parallel DNA sequencing to study cancer genomes at a large scale. These efforts have revealed an intriguing inter- and intratumoral genetic heterogeneity in a wide variety of malignancies including lymphomas and they have had a considerable impact on cancer diagnostics and treatment [1–3, 9]. In addition, genetic heterogeneity has been shown to influence disease progression and outcomes as well as the response to therapy [10–12]. Besides genetic heterogeneity, processes that are not readily analyzable by genome or exome sequencing, such as DNA methylation, histone modification, micro-RNA and noncoding RNA, and tumor cell phenotype, as well as the interactions between tumor cells and the microenvironment, may play important roles in functional heterogeneity [3]. Further layers of complexity are introduced by the hierarchical organization of some tumors into a bulk of malignant cells and so-called cancer stem cells that have the ability to self-renew and thereby pose a reservoir for long-term maintenance of malignant growth [13].

In this review, we will focus on tumor heterogeneity in lymphomas, emphasizing morphologic, immunophenotypic, and genetic heterogeneity; intratumoral heterogeneity and subclonal evolution; and transformation and transdifferentiation, as well as clinical and therapeutic aspects. Further investigation into lymphoma heterogeneity will allow a more precise diagnosis and treatment of individual patients' diseases and it will pave the way towards highly personalized lymphoma management.

Malignant Lymphomas Mirror the Complexity of the Immune System

In the 2016 updated 4th edition of the World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues, more than 90 different categories of B- and T-cell lymphomas are distinguished [14, 15]. This complex classification, which tries to group lymphomas according to their putative cell of origin, as well as their clinical and pathological features, reflects our deepening understanding of the immune system, with different lymphocyte subsets undergoing complex maturation steps and each step potentially having malignant counterparts. The precise classification of a patient's lymphoma is crucial to predict the clinical course (from indolent to aggressive) and to guide the choice of treatment regimen, from "watch and wait" to multimodal (radio-, immuno-, chemo-) therapy [16–19]. Histomorphologic and cytologic analyses of the growth pattern, tissue architecture, cell size, nuclear features, and reactive microenvironment of a given tumor by microscopy of stained tissue slides are still the most important tools for establishing a diagnosis of lymphoma. Ancillary studies, such as immunohistochemistry and sometimes molecular testing, are required to confirm the diagnosis and to further classify the entity for prognostic and predictive purposes.

Intratumoral Heterogeneity in Lymphoma

Lymphomas in individual patients can exhibit different types of intratumoral heterogeneity (Table 1), and this phenomenon is often of prognostic and predictive importance. In a proportion of patients, 2 distinct lymphoma entities as defined by the WHO criteria can be diagnosed either at different time points of the disease or simultaneously at the first diagnosis in the same organ or in different organs, such as lymph nodes (LN) and bone marrow (BM). Irrespectively of the setting, it is of major importance to investigate – usually by studying clonal immunoglobulin or T-cell receptor rearrangements – whether intratumoral heterogeneity is the result of evolution of the neoplastic clone or indicates the presence of a second, clonally unrelated neoplasm [20].

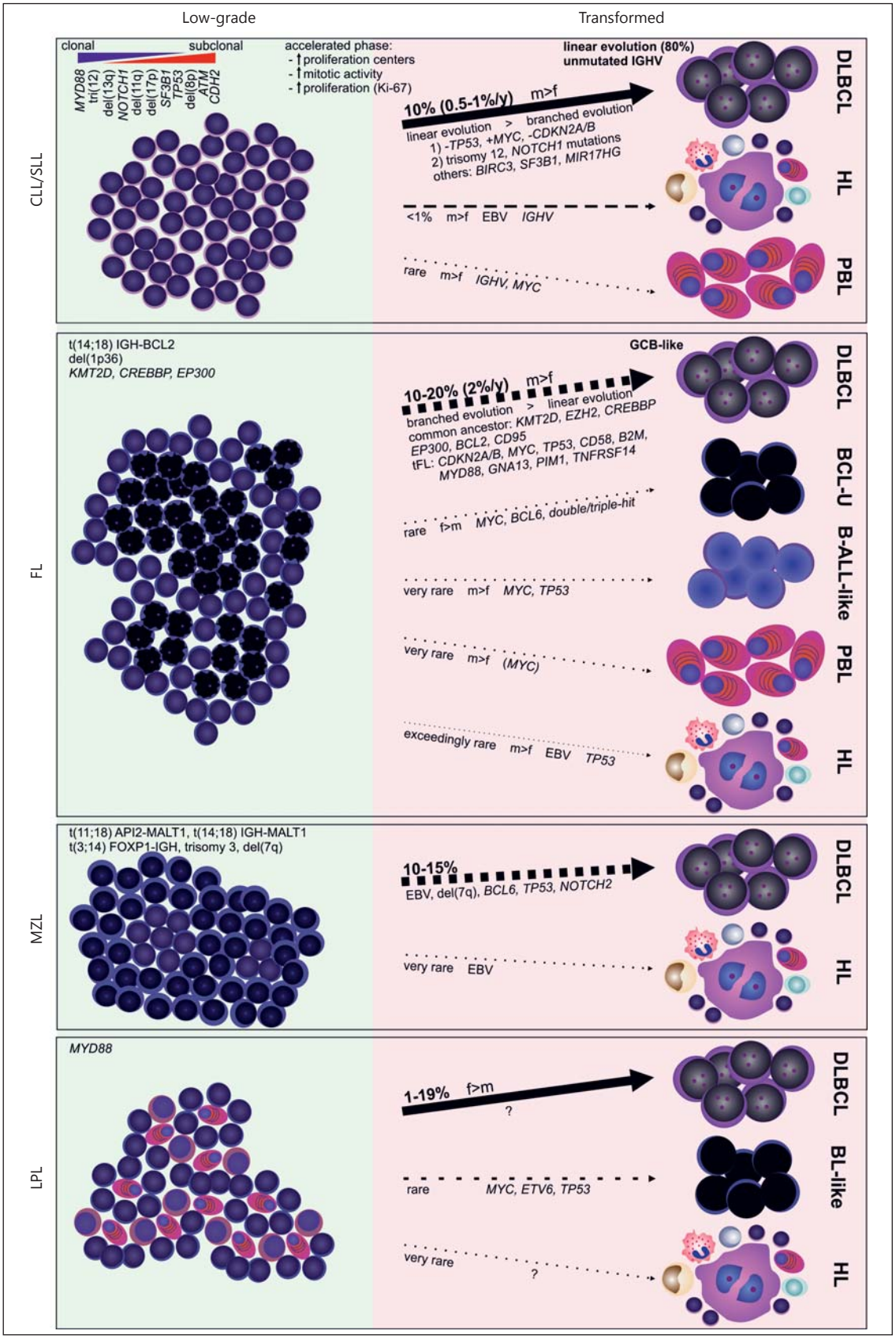
Table 1. Definitions

Composite lymphoma	Example of intratumoral heterogeneity; a lymphoma that consists of at least 2 different entities that occur simultaneously in the same organ ("collision tumor")
Concordant involvement	BM (or other organ) infiltration by the same lymphoma entity
Discordant lymphoma	Example of spatial heterogeneity; occurrence of 2 histologically distinct lymphoma types in 2 different anatomical locations; most often observed as high-grade lymphoma in a lymph node with discordant BM involvement by a low-grade lymphoma
Gray zone lymphomas	High-grade lymphomas that display overlapping or borderline morphologic, immunophenotypic, and biological features between different lymphoma entities and therefore cannot be unequivocally categorized [36, 37]
Relapse	Recurrence of a morphologically identical lymphoma after therapy; most often clonally related, sometimes clonally unrelated [61]; thought to arise from a common lymphoma progenitor through linear or branched evolution in clonally related cases
Transdifferentiation	Example of intratumoral heterogeneity; presence of a myeloid neoplasm (most often histiocytic/dendritic cell sarcoma) in a lymphoma patient, hypothesized to derive from the lymphoma clone or a CPC based on the demonstration of identical gene rearrangements, mutations, or chromosomal translocations in both tumor components
Transformation	Example of temporal heterogeneity; progression of a low-grade lymphoma into a high-grade lymphoma (usually DLBCL; less commonly lymphoblastic lymphoma, Burkitt lymphoma, PBL, BCL-U, or CHL) during the disease course; known as Richter's syndrome in CLL; transformation is associated with treatment resistance, clinical disease progression, and increased disease-specific mortality; cooccurrence of transformed lymphoma is not considered composite lymphoma

BM, bone marrow; CPC, common progenitor cell/clone; DLBCL, diffuse large B-cell lymphoma; PBL, plasmablastic lymphoma; BCL-U, B-cell lymphoma, unclassified; CHL, classical Hodgkin lymphoma; CLL, chronic lymphocytic leukemia.

The most common example of intratumoral heterogeneity is the evolution of a low-grade lymphoma into a high-grade lymphoma during the disease course, known as lymphoma transformation (Fig. 1). Transformation, considered to represent clonal evolution, is usually associated with clinical disease progression and an adverse outcome [21]. In chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), high-grade transformation into diffuse large B-cell lymphoma (DLBCL) is known as Richter's syndrome (RS) and occurs in up to 10% of patients, with an estimated transformation rate of 0.5–1% per year [22]. Of note, 10–20% of DLBCL in patients with CLL/SLL are clonally unrelated to the CLL/SLL. These patients show a superior prognosis compared to true, clonally related RS [23–25]. Rarely, CLL/SLL, as well as other B-cell non-Hodgkin lymphomas (B-NHL), may transform into classical Hodgkin lymphoma (HL). For the cases of classical HL, which are frequently Epstein-Barr virus positive, determination of clonal relationship is very difficult for technical reasons, but several studies using single-cell analysis have demonstrated that classical HL in the setting of CLL/SLL and other indolent B-NHL may be both clonally related and clonally unrelated (Fig. 2) [26, 27]. The 10-year risk of transformation in follicular lymphoma (FL), the most frequent low-grade B-NHL, ranges between 15 and 20%, with an annual transformation rate of about 2–3% [28]. Marginal zone lymphoma transforms into high-grade lymphoma in 10–14% of patients over time, although the true incidence rates of transformation are poorly documented [21].

Secondly and less frequently, patients are simultaneously diagnosed with a low-grade and a high-grade lymphoma at different anatomical sites. This spatial form of intratumoral heterogeneity, known as discordant involvement, occurs in 5–7% of patients according to recent studies [29–31] and most often presents as DLBCL in an LN with discordant low-grade lymphoma infiltration in the BM [20]. In patients with a low-grade and a high-grade component at different sites, it is of major importance to investigate the clonal relationship between the 2 components. Kremer et al. [32] demonstrated that in DLBCL patients a significant fraction of cases with discordant BM involvement harbors clonally unrelated secondary low-grade B-cell neoplasms such as monoclonal



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B-cell lymphocytosis or CLL/SLL. Furthermore, a third corresponded to reactive lymphoid infiltrates. These facts may contribute to the superior survival of patients with discordant as compared to concordant BM involvement in DLBCL.

Thirdly and least frequently, 2 different, usually clonally unrelated lymphoma entities coincide within the same organ, presenting as a "collision tumor" known as a composite lymphoma. Composite lymphomas, intriguing examples of intratumoral heterogeneity, consist of either 2 separate B-NHL (Fig. 3) or a combination of B-NHL and HL and occur in only 1–4% of lymphoma patients [33, 34]. Rarely, classical HL collides with nodular lymphocyte-predominant HL [35]. In composite lymphomas, tumor borders can be clearly defined, or tumor cells can be partly intermixed. Composite lymphomas should not be confounded with the so-called gray zone lymphomas, which are high-grade lymphomas that display overlapping or borderline morphologic, immunophenotypic, and biological features between different lymphoma entities and therefore cannot be unequivocally categorized [36, 37].

In addition, some low-grade lymphoma subtypes show a topographically defined morphologic and immunophenotypic intratumoral heterogeneity. For example, tumor cells in the proliferation centers of CLL/SLL are of a larger size, exhibit an increased proliferation rate as analyzed by Ki-67 immunohistochemistry, and upregulate several antigens. In FL, tumor cells outside of the neoplastic follicles often downregulate CD10 and BCL6. Phenotypic and sometimes morphologic heterogeneity is also observed in different tumor compartments, e.g., between BM and LN or LN and peripheral blood [38–42]. Further aspects of morphologic heterogeneity can be found in lymphomas that display maturation towards plasma cells, such as lymphoplasmacytic lymphoma. Lymphoplasmacytic lymphoma can demonstrate a high intertumoral and intratumoral heterogeneity in terms of plasma cell maturation, with some patients showing nearly no maturation (only small lymphocytic cells) and other patients showing a high degree of maturation towards plasma cells [43]. Importantly, after treatment with the anti-CD20 monoclonal antibody rituximab, the loss of the lymphoid tumor component can be so dramatic that a misdiagnosis of plasma cell neoplasm might occur [44, 45].

Fig. 1. Types and genetic mechanisms of transformation. Common low-grade lymphomas and their transformed counterparts are depicted. Percentages indicate the frequency of the type of transformation, according to Agbay et al. [21], Parikh et al. [22], and Montoto and Fitzgibbon [28]. CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; FL, follicular lymphoma; MZL, marginal zone lymphoma; LPL, lymphoplasmacytic lymphoma; DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin lymphoma; PBL, plasmablastic lymphoma; BCL-U, B-cell lymphoma, unclassified; B-ALL, B-cell acute lymphoblastic leukemia; BL, Burkitt lymphoma.

Genetic Intratumoral Heterogeneity, Clonal Evolution, and Transformation

Recent seminal studies addressing intratumoral genetic heterogeneity and mechanisms of transformation in low-grade lymphomas have revealed highly interesting and important results that may change the clinical practice in the near future.

CLL/SLL is an incurable neoplasm consisting of mature, small B cells that grow diffusely and express surface CD20, CD23, and CD5 and nuclear LEF1. Despite its apparently homogeneous appearance and phenotype, which is stable among patients, CLL/SLL is clinically a highly heterogeneous disease that rapidly progresses in some patients while being indolent without indication for therapy for decades in others [46]. This heterogeneity of CLL is based on a variety of clinical, phenotypic, and genetic parameters, which have led to the development of advanced biological prognostic scores [47]. However, intratumoral heterogeneity in CLL adds another layer of complexity, and recent seminal work by Landau et al. [12] has shed light on the underlying mechanisms. Studying 149 CLL/SLL patients by whole-exome sequencing, they found that driver mutations in CLL/SLL can be divided into predominantly clonal (e.g., *MYD88*, trisomy 12, and del[13q]), clonal and subclonal (e.g., del[11q], del[17p], and *SF3B1*), or predominantly subclonal (e.g., *TP53*, *ATM*, and *CDH2*) (Fig. 1) [12]. When analyzing patients at different time points, they found that 10 of 12 patients receiving chemotherapy underwent clonal evolution originating from subclones with driver mutations that expanded over time. In contrast, this phenomenon was only observed in 1 of 6 patients without treatment. They hypothesized that chemotherapy leads to 2 different scenarios in CLL/SLL depending on the presence or absence of subclonal driver mutations. If subclonal driver mutations are absent, chemotherapy leads to a balanced reduction of all malignant clones (clonal equilibrium). In contrast, the presence of aggressive subclones harboring driver mutations (which may be "controlled" by clonal competition in untreated patients) may be unmasked and selected

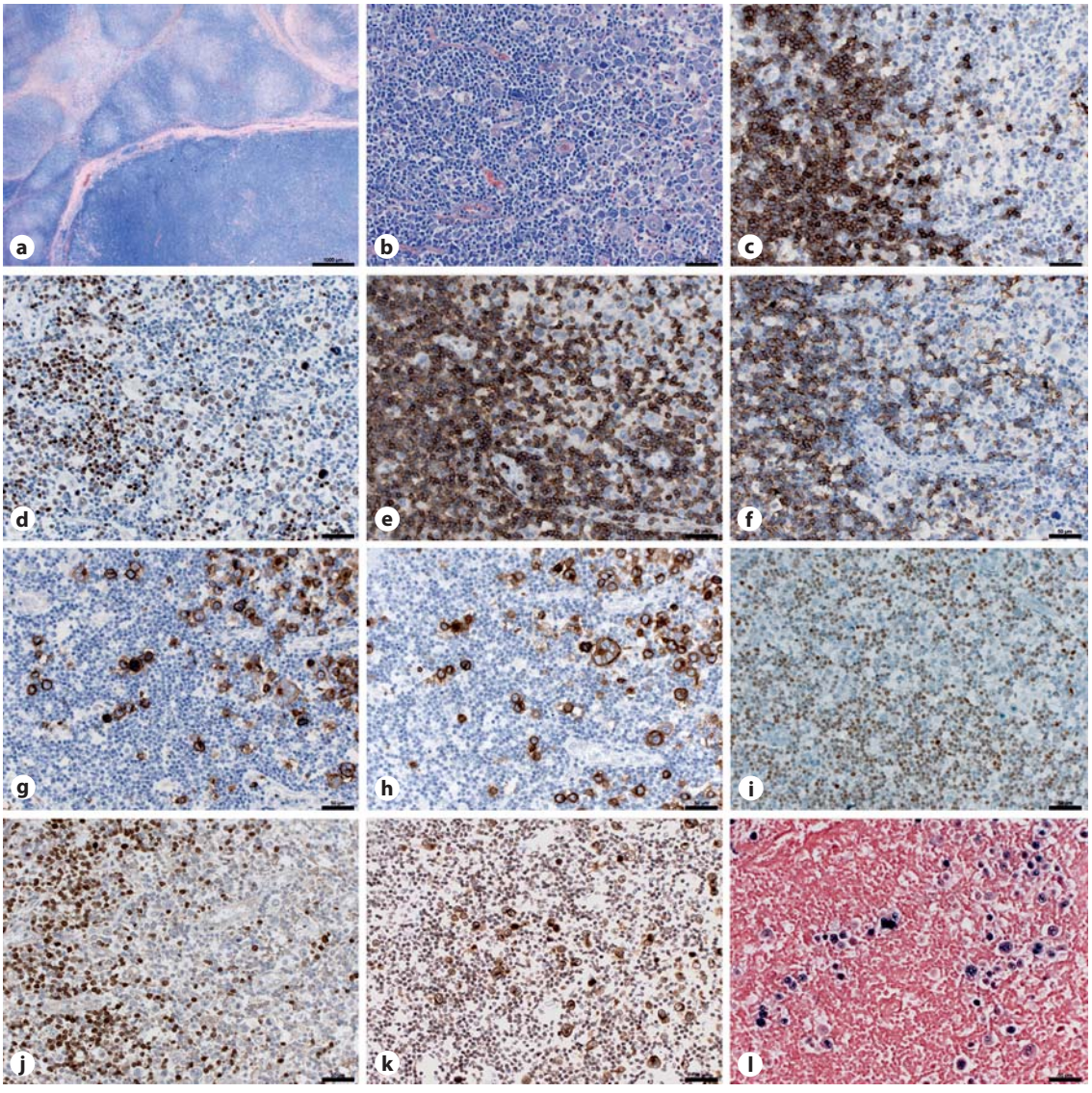

Fig. 2. Nodular sclerosis classical Hodgkin lymphoma transformation of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). The clonal relationship was not tested in this case. **a** Scanning magnification shows an enlarged lymph node subdivided into large nodules by broad fibrous septa. Some darker, diffuse areas and lighter nodules are seen (Giemsa stain). **b** Cytologically, at the border of the darker areas with lighter nodules, there is an admixture of small, round CLL/SLL lymphocytes with large Hodgkin and Reed-Sternberg cells (Giemsa stain). **c** Immunohistochemically, CD20 is positive in the CLL/SLL area (left) and shows the typical negativity in the Hodgkin and Reed-Sternberg cells (right). **d** PAX5 is strongly nuclear positive in the CLL/SLL cells and has less staining intensity in the Hodgkin and Reed-Sternberg cells, consistent with shutdown of the B-cell gene expression programs in these cells. **e** Staining for CD5 shows positivity in the CLL/SLL cells (left) and an abundant infiltrate of reactive T lymphocytes (CD3, not shown) intermixed with the Hodgkin and Reed-Sternberg cells (right). **f** CD23 marks the CLL/SLL cells. CD15 (**g**) and CD30 (**h**) are strongly positive in the Hodgkin and Reed-Sternberg cells. OCT2 (**i**) and BOB1 (**j**) show nuclear positivity in the CLL/SLL cells and are negative in the Hodgkin and Reed-Sternberg cells. LMP1 (**k**) and Epstein-Barr virus (**l**) mRNA in situ hybridization (EBER) are positive in the Hodgkin and Reed-Sternberg cells, consistent with Epstein-Barr virus infection. Magnifications: ×12.5 (scale bar, 1,000 μm) (**a**) and ×200 (**b–l**) (scale bars, 50 μm).

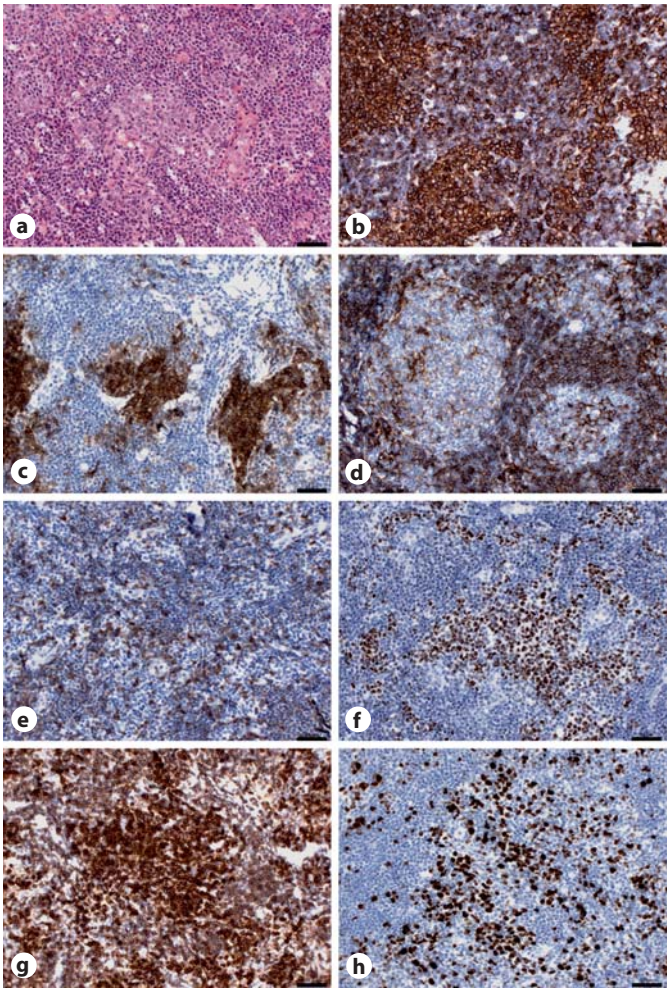

Fig. 3. Example of a composite lymphoma consisting of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) admixed with follicular lymphoma (FL). **a** The H&E stain shows a lymphatic infiltrate that has a partly diffuse and partly nodular growth pattern with germinal center-like structures. Cytologically, the cells in the diffuse areas are small, round lymphocytes with little cytoplasm and dense nuclear chromatin, corresponding to CLL/SLL. In contrast, the cells in the nodules are medium sized centrocytes with angular nuclei, rather open chromatin, and ample cytoplasm with some larger, interspersed centroblasts, corresponding to FL. **b** CD20 staining shows diffuse positivity in all cells with strong staining intensity in the FL nodules and a weaker intensity in the diffuse CLL/SLL areas. **c** CD10 is positive in the nodular areas. **d** CD23 stains the diffuse areas and marks some follicular dendritic cells within the nodules. **e** CD5 is weakly positive in the diffuse areas and strongly stains the T lymphocytes (CD3, not shown). **f** BCL6 is positive in the nodules. **g** BCL2 shows a pattern similar to CD20 with 2 staining intensities. **h** The proliferation rate (Ki-67) is low in the diffuse areas (~5%) and higher in the nodules (~30%). All magnifications: ×200 (scale bars, 50 μm).

for by chemotherapy, resulting in clonal outgrowth and disease progression [12]. These findings were confirmed and extended in a more recent study by the same group that included a total of 538 CLL/SLL patients of whom 278 were prospectively recruited [48]. Importantly, some of the subclonal driver mutations described by Landau et al. [48] (*TP53* loss or del[17p], mutations in *NOTCH1* or *SF3B1*) are implicated in the pathogenesis of RS, along with additional genetic events (*MYC* amplification, *CDKN2A/B* loss, and tri[12]) [49, 50]. Based on their findings that TP53 and/or CDKN2A/B inactivation were mutually exclusive with tri(12), Chigrinova et al. [49] proposed that RS may evolve via 2 main genetic pathways, i.e., (1) *TP53* inactivation, *MYC* activation, and *CDKN2A/B* loss and (2) tri(12) followed by *NOTCH1* mutation (Fig. 1) These findings were independently confirmed by Fabbri et al. [50], who proposed a linear evolution model for CLL/SLL transformation into RS and demonstrated that the genetic landscape in RS-DLBCL is substantially different from that of de novo DLBCL. This provides an explanation for the different disease biology, the higher aggressiveness, and the much poorer outcome of RS-DLBCL compared to de novo DLBCL [23–25].

Like CLL/SLL, FL is an incurable malignancy that most often presents as a low-grade tumor (grade 1–2) consisting of small neoplastic B cells with a follicular growth pattern. FL harbors an inherent risk of high-grade transformation with an annual incidence of 2–3%. In contrast to CLL/SLL, which is believed to evolve linearly, the current hypothesis for transformed FL (tFL) is derivation from a long-lived common progenitor cell/clone (CPC). Okosun et al. [51] sequenced 10 FL-tFL sample pairs and identified 2 distinct patterns of evolution, which they coined "rich" and "sparse" CPC. In 8 patients undergoing evolution along the "rich" CPC pathway, FL and tFL samples showed a high clonal semblance, and CPC harbored many mutations previously reported in DLBCL, such as in histone modifiers (*KMT2D*, *CREBBP*, *EP300*, *EZH2*, and *MEF2B*), immune genes (*B2M*, *CD58*, and *TNFRSF14*), JAK-STAT signaling (*SOCS1* and *STAT6*), and B-cell receptor-signaling genes (*BCL10*, *CARD11*, and *CD79B*). Conversely, in 2 patients, only 4 nonsynonymous mutations were shared by the FL and tFL samples ("sparse" CPC). Importantly, the FL and tFL clones in these 2 cases independently acquired different mutations in *KMT2D*, *TNFRSF14*, and *CREBBP*, indicating that these genes play a very important role in FL lymphomagenesis and transformation. Furthermore, by performing deep sequencing of 28 selected genes in an extension cohort, those authors could demonstrate

intratumoral heterogeneity in FL in analogy to CLL/SLL. Clonal mutations were mostly observed in early event genes such as *KMT2D*, *CREBBP*, *EZH2*, *STAT6*, and *TNFRSF14*, whereas subclonal mutations were observed in genes that were associated with transformation, like *MYD88*, *EBF1*, and *TNFAIP3* [51]. In line with these findings, a divergent pattern of evolution from an ancestor CPC was observed in 10 of 12 FL-tFL sample pairs studied by Pasqualucci et al. [52]. Linear evolution from a minor subclone that harbored tFL-specific mutations and was already present in the diagnostic FL sample was demonstrated in 2 patients. Importantly, this study confirmed and extended the findings of Okosun et al. [51] regarding important genes involved in FL pathogenesis and transformation (*KMT2D*, *CREBBP*, *EZH2*, *FAS*, *BCL2*, *TP53*, *MYC*, *CDKN2A/B*, *B2M*, and *PIM1*). Furthermore, these analyses revealed a marked genomic instability in tFL compared to FL and other lymphoid neoplasms [52]. In analogy to the subclonal heterogeneity of CLL/SLL [12], Green et al. [53] found that the majority of mutations in their 8 FL samples corresponded to minor subclonal mutations that were heterozygous, with the exception of homozygous *CREBBP* and *KMT2D* mutations that were most likely clonal. Studying 2 samples with matched relapsed FL, those authors proposed an elegant genetic evolution model for (nontransformed) FL that is based on founder mutations (e.g., *BCL2*), leading to a premalignant tumor cell population ("CPC") stable enough to acquire further genetic events. This is followed by driver mutations in the progenitor clone (e.g., *CREBBP*) that lead to an early malignant clone that may acquire further accelerator mutations (e.g., *KMT2D* and *TNFRSF14*) during the pathway of disease progression [53].

Intertumoral and Intratumoral Heterogeneity beyond Histopathological Classification: the Example of DLBCL

DLBCL, the most frequent B-NHL in adults, is clinically heterogeneous in terms of treatment response and long-term outcome. The molecular basis of this heterogeneity was first characterized by Alizadeh et al. [54], who studied the cell-of-origin phenotype by DNA microarrays and identified distinct gene expression profiles related to germinal center B-cell (GCB) or activated B-cell types. A further layer of complexity was introduced by Lenz et al. [55], who identified signatures of the tumor microenvironment that are associated with survival. However, because these technologies are very costly and time consuming, they have not been implemented in the daily routine pathological diagnostics of DLBCL. Since the many DLBCL subtypes cannot readily be identified based on morphology alone, each case of suspected DLBCL requires a more or less extensive immunohistochemical workup to be correctly classified for prognostic and predictive purposes. Hence, we use antibodies against CD20 and CD3 to establish the cell lineage (with CD20 also being predictive for rituximab treatment); CD10, BCL6, MUM1, CD30, and CD5 to assess prognostic immunohistochemical cell-of-origin subgroups (GCB vs. non-GCB type; $CD5^+$ type; and CD30 expression); and the expression of MYC and BCL2 proteins (double-expressers with ≥40% MYC- and ≥50% BCL2-positive cells, respectively, that are associated with a worse prognosis) and Ki-67 to address cell proliferation [56]. The Hans classifier using CD10, BCL6, and MUM1 is the most widely used immunohistochemical surrogate marker for the molecular cell-of-origin subgroups of GCB versus activated B-cell DLBCL types that was recently validated using NanoString® technology [54, 57, 58]. Other, less commonly used, classifiers include Visco-Young, Choi, Muris, Nyman, and Tally, some of which implement additional antibodies such as FOXP1, GCET1, BCL2, and LMO2 [56]. All classifiers have their advantages and disadvantages and can complement each other in the classification of difficult cases. Intertumoral heterogeneity in DLBCL can thus readily be examined by pathologists and exemplifies a clinically important basis for prognosis and probably in the future also for treatment decisions. Although subtyping of DLBCL according to the GCB versus non-GCB is recommended in the 2016 updated version of the WHO classification [15], it is not yet clear which method or algorithm is the best to address this distinction for clinical purposes. Similarly, there is currently no accepted selection strategy to identify cases of high-grade B-cell lymphoma carrying translocations of *MYC* with *BCL-2* and/or *BCL-6*, so-called double- or triple-hit lymphomas, which need to be recognized according to the 2016 updated WHO classification [15, 59]. Nevertheless, double- or triple-hit lymphomas are concentrated in the GCB type, whereas double-expressers are concentrated in the non-GCB group.

In contrast to the long-recognized intertumoral heterogeneity in DLBCL, which is now implemented in daily diagnostics as outlined above, intratumoral heterogeneity in DLBCL is only beginning to be understood. A promising strategy to investigate DLBCL intratumoral heterogeneity is the genetic comparison of paired samples at first diagnosis and relapse. In doing so by deep se-

quencing the variable, diversity, and joining regions of the immunoglobulin heavy chain in tumors from 14 relapsed patients, Jiang et al. [60] discovered 2 distinct evolutionary scenarios of DLBCL. They could show that diagnosis and relapse tumors are clonally related, and characterization of somatic hypermutation patterns allowed the identification of unique subclones. Phylogenetic analysis of these subclones revealed that the major subclone at diagnosis and relapse either had very different somatic hypermutation patterns (early divergence) or clustered together very closely (late divergence). The authors hypothesized that in the early divergence mode of clonal evolution, diagnosis and relapse clones develop in parallel, whereas in the late divergence mode relapse clones develop directly from the diagnosis clone. In addition, by targeted ultradeep resequencing and exome sequencing, they could demonstrate recurrent mutations in epigenetic modifiers such as *EP300*, *KMT2D*, and *SETDB1* in both diagnosis and relapse clones, as well as mutations in immune surveillance genes, such as *CD58* and *IL9R* in relapse clones. This indicates that epigenetic modifiers are real driver mutations in DLBCL and that the failure of immune surveillance contributes to disease relapse [60]. Similar conclusions were drawn by Juskevicius et al. [61], who also identified 3 clonally unrelated relapses in their cohort of 20 paired diagnosis-relapse samples.

Mutations in epigenetic modifiers are frequent in DLBCL [62]; however, the contribution of epigenomic alterations to tumor evolution is poorly understood. In an attempt to characterize the epigenome of DLBCL during disease progression, Pan et al. [63] performed genome-wide DNA methylation profiling in 13 diagnosis-relapse sample pairs at single base pair resolution. They found heterogeneous evolution of DLBCL methylomes and identified a relapse-associated methylation signature enriched in key cellular pathways such as transforming growth factor-β signaling and antiapoptotic pathways. Importantly, the current standard treatment regimen for DLBCL (R-CHOP; rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) does not seem to be linked to direct effects on DNA methylation or epigenetic modifiers, favoring the conclusion that epigenomic alterations are disease-intrinsic mechanisms of relapse [63].

Transdifferentiation

In recent years, accumulating case reports have demonstrated the cooccurrence of lymphoid and myeloid lineage neoplasms with a clonal relationship. An example of transdifferentiation is shown in Figure 4. Reported cases include histiocytic/dendritic cell (H/DC) neoplasms in patients suffering from low-grade B-cell lymphomas, such as FL, Mantle cell lymphoma, hairy cell leukemia, or CLL/SLL [64], as well as Langerhans cell neoplasms in patients with lymphoblastic leukemia/lymphoma of either B-cell (B-LBL) [65] or T-cell (T-LBL) [66] origin (Table 2). Myeloid differentiation in a low-grade lymphoma patient sample may pose diagnostic problems because of a morphologic resemblance to large cell lymphoma, mimicking transformation. In the cases reported in the literature, myeloid cell differentiation was suspected based on morphology (cells with abundant eosinophilic cytoplasm, spindle cells, and whorled growth pattern) but it was often confirmed after extensive an immunohistochemical workup using markers like CD34, CD43, CD33, CD68, CD163, lysozyme, S100, CD1a, and CD207. Therefore, though a very rare event, we suspect that the incidence of myeloid differentiation in lymphomas is likely underestimated because of diagnostic difficulty and the lack of appropriate immunohistochemical and molecular methodologies for its identification. Mechanistically, there are several models that may explain the cooccurrence of a lymphoid and a myeloid neoplasm in the same patient. Firstly, it could be a coincidence of 2 clonally unrelated neoplasms (de novo H/DC neoplasm). Secondly, both lymphoma and H/DC neoplasm could arise from an immature CPC, because normal mature hematopoietic cells originate from multipotent hematopoietic stem cells that differentiate via oligopotent precursor cells along either the myeloid or the lymphoid lineages [67]. Thirdly, plasticity between lymphoid and myeloid cells could be explained by dedifferentiation of lymphoid cells towards more immature cell types, followed by differentiation along the myeloid lineage. And fourthly, lymphoid cells may directly transdifferentiate into myeloid cells. This latter hypothesis is supported by experimental models mainly used by Graf and colleagues, demonstrating that committed T-cell progenitors and B-cell lymphoma/leukemia cells can be effectively transdifferentiated into myeloid cells by overexpression of *SPL1* (*PU.1*) and/or *CEBPA* transcription factors [68–70]. In addition, Wang et al. [71, 72] found hypermutation in *IGVH* loci in the H/DC neoplasm component in 2 patients harboring low-grade lymphomas. This strongly suggests derivation from a mature B cell that underwent somatic hypermutation in the LN germinal center reaction [71, 72]. A seminal study by Feldman et al. [73] investigated 8 patients with FL and syn- or metachronous H/DC neoplasm, a clonal relation which was proven by demonstration of identical t(14;18)

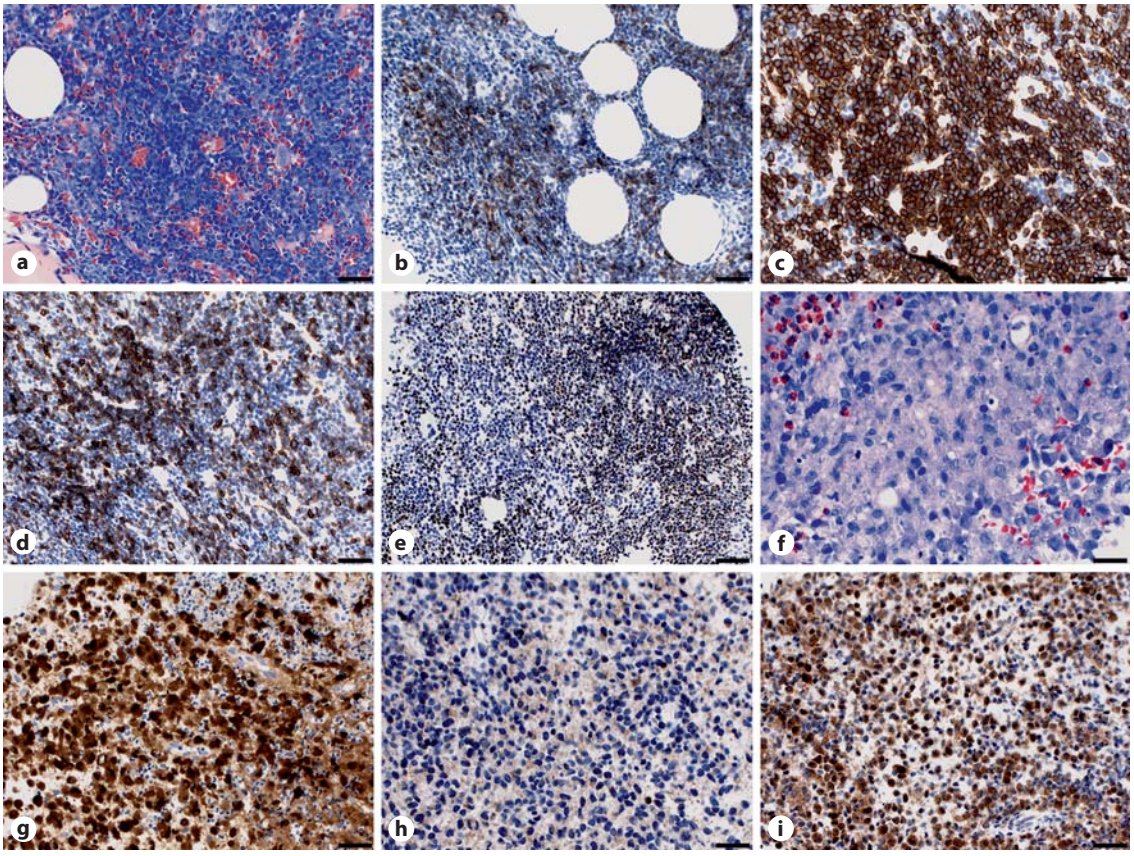

Fig. 4. Example of transdifferentiation of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) to Langerhans cell histiocytosis (LCH). **a** Bone marrow (BM) infiltration by small, round lymphocytes with little cytoplasm and dense nuclear chromatin, corresponding to CLL/SLL (Giemsa stain). Immunohistochemically, the CLL/SLL cells are weakly positive for CD20 (**b**) and strongly positive for CD5 (**c**), and they show intermediate positivity for CD23 (**d**) and positivity for PAX5 (**e**). In the femur of the same patient, radiological imaging revealed a mass that was suspicious for high-grade transformation. **f** An excisional biopsy was performed, which showed large polygonal cells with histiocytic morphology, abundant eosinophilic cytoplasm, and bean-shaped nuclei. These cells were positive for S-100 (**g**) as well as CD1a (not depicted) and negative for PAX5 (**h**). **i** Staining with an antibody specific for the *BRAF* V600E mutation was positive. Molecular analyses revealed identical *IGH* rearrangements and *TP53* mutations in both the CLL/SLL and the LCH tumors. The LCH component exhibited an additional *BRAF* V600E mutation, which was absent in the CLL/SLL component.

translocations and *IGH* rearrangements in both FL and H/DC clones. They postulated that the H/DC tumor arises from either a differentiated FL cell or a CPC at least at the pre-B-cell stage of differentiation. In contrast, Buser et al. [74], who analyzed a compound pro-T LBL and indeterminate dendritic cell tumor simultaneously occurring at 3 different anatomical sites in a 59-year-old woman, found a tri(21) in both tumor components, whereas only the pro-T LBL additionally contained a monosomy(18) and *NRAS*^{G13D} mutation. Therefore, they concluded that this composite tumor must have arisen by divergent cell differentiation from a CPC [74]. Zhang et al. [75] reported on a very unusual case of biphasic FL progression presenting as a collision tumor consisting of an H/DC sarcoma along with DLBCL in the hip of a 50-year-old male who harbored an FL in the axillary LN. In this intriguing example of spatial and intratumoral heterogeneity, the authors could show that all 3 different tumors were clonally related by analysis for *BCL2* rearrangement, and they concluded that both DLBCL and H/DC sarcoma had arisen from the FL clone [75]. On the other hand, Brunner et al. [76] provided elegant evidence for a CPC giving rise to FL and histiocytic sarcoma using fluorescence in situ hybridization (FISH) and array comparative genomic hybridization studies. In their case report, the histiocytic sarcoma clone contained a t(14;18) transloca-

Table 2. Examples of transdifferentiation

Cases, *n*	Postulated cell of origin	Lymphoid neoplasm	Myeloid neoplasm	Clonal relationship	Reference
1	CPC	B-LBL	Langerhans cell sarcoma	Identical *IGH* and *TCRG* rearrangement	65
2	CPC	T-LBL	Langerhans cell sarcoma	Identical *TCRG* rearrangement	66
8	Mature tumor cell or CPC	FL	Histiocytic sarcoma (*n* = 7), interdigitating DC sarcoma (*n* = 1)	Identical *BCL2* and *IGH* rearrangement	73
1	CPC	T-LBL	Indeterminate DC tumor	tri(21)	74
1	Mature tumor cell or CPC	FL (axilla) DLBCL (hip)	H/DC sarcoma (hip)	Identical *BCL2* rearrangement	75
2	Mature tumor cell	FL (*n* = 1) DLBCL (*n* = 1)	H/DC sarcoma	Identical *IGH* rearrangement	102
1	Mature tumor cell	FL	H/DC sarcoma	Identical *BCL2* and *IGH* rearrangement	103
2	Mature tumor cell	Splenic MZL (*n* = 1) FL (*n* = 1)	Histiocytic sarcoma	Identical *IGH* rearrangement	71
1	Mature tumor cell	CLL/SLL	Interdigitating DC sarcoma	Identical *IGH* rearrangement tri(12)	104
7	Mature tumor cell	CLL/SLL	Interdigitating DC sarcoma (*n* = 4) Langerhans cell sarcoma (*n* = 1) Histiocytic sarcoma (*n* = 2)	Identical *IGH* rearrangement	105
2	Mature tumor cell	FL	Langerhans cell neoplasm	Identical *BCL2* and *IGH* rearrangement	106
1	Mature tumor cell or CPC	Nodal MZL	Langerhans cell sarcoma	Identical *IGH* rearrangement del(11q), tri(12)	107
1	Mature tumor cell	CLL/SLL	Langerhans cell sarcoma	del(6q23)	108
2	NA	FL (*n* = 1) FL, DLBCL (*n* = 1)	Histiocytic sarcoma	Identical *BCL2* rearrangement	109
1	CPC	FL	Histiocytic sarcoma	Identical *BCL2* and *IGH* rearrangement	76
1	Mature tumor cell	MCL	Histiocytic sarcoma	Identical *IGH* rearrangement and *CCND1-IGH* fusion	110
1	CPC	HCL	Histiocytic sarcoma	*BRAF* V600E Multiple cytogenetic aberrations (aCGH)	111

CPC, common progenitor cell/clone; NA, not applicable; B-LBL, B-cell lymphoblastic leukemia; T-LBL, T-cell lymphoblastic leukemia; FL, follicular lymphoma; DLBCL, diffuse large B-cell lymphoma; MZL, marginal zone lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; MCL, Mantle cell lymphoma; HCL, hairy cell leukemia; DC, dendritic cell; H, histocytic.

tion and clonal *IGH* rearrangement identical to the FL clone; however, the FL clone had additional complex genetic changes detected by array comparative genomic hybridization that were not present in the histiocytic sarcoma, ultimately favoring the CPC hypothesis [76].

In summary, experimental and clinical evidence indicates that different mechanisms may lead to H/DC neoplasms in patients suffering from lymphomas, the most frequent one being transdifferentiation from mature tumor lymphocytes (Table 2). For future studies that investigate transdifferentiation, it is essential to properly address this issue using molecular techniques, either by physically separating the 2 tumor types via immune-directed laser capture microdissection or by morphology-directed FISH for chromosomal aberrations [64].

Clinical and Radiological Implications of Tumor Heterogeneity in Lymphomas

The morphologic, immunophenotypic, and molecular heterogeneity of lymphomas has a major influence on clinical practice and therapy decisions at different time points in the course of the disease. At first diagnosis, it is

important to classify the lymphoma correctly because the best therapy for an individual patient can vary from "watch and wait" to multimodal (radio-, immuno-, and chemo-) therapy, depending on variables such as disease subtype, evidence for high-grade transformation, and various molecular risk factors [16–19].

As described above, disease heterogeneity may present as transformation from low- to high-grade lymphoma or as a second, clonally unrelated neoplasm. Clinical suspicion for transformation is based on rising serum lactate dehydrogenase levels, rapidly progressive lymphadenopathy, unexplained deterioration of the general condition, the appearance of B symptoms, or the development of extranodal disease [77]. Due to its prognostic relevance and impact on therapy decisions, high-grade transformation of low-grade B-NHL needs to be confirmed by a biopsy, since it can be mimicked by a variety of unrelated conditions. Because transformation can arise focally, selection of the best location for biopsy based on clinical findings and imaging studies is critical. In this context, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT), which is routinely performed for clinical staging or reevaluation of lymphoma patients, can provide additional help [78, 79]. High standardized uptake values in ^{18}F-FDG-PET/CT correlate with high-grade histology and show a positive predictive value for transformed lymphoma. Therefore, high standardized uptake values in ^{18}F-FDG-PET/CT may guide the best site for biopsy [80–82]. In patients who cannot undergo invasive diagnostic procedures due to impaired coagulation, ^{18}F-FDG-PET/CT may corroborate a suspicion for relapse or high-grade transformation but does clearly not carry the same diagnostic weight as a tissue biopsy.

Another indication for a repeat biopsy is to demonstrate a potential change in the surface marker profile. As discussed above, the administration of rituximab can lead to a loss of CD20 expression on the neoplastic cells and/or to increased plasma cell differentiation, which may require a modification of therapy.

The survival of patients with high-grade transformation of a preexisting low-grade HNL is generally worse as compared to patients with de novo high-grade disease, with a slight improvement in the era of rituximab. This inferior outcome is the result of both patient-specific and tumor-related factors, such as previous therapies, delayed hematopoietic recovery, and lower response rates after therapy on one hand and a more frequent presence of molecular risk factors and preselection of resistant clones on the other [82]. Patients with composite or transformed lymphomas are often excluded from clinical trials, and since standard therapies are lacking, current therapy concepts are highly individualized, with autologous or allogeneic hematopoietic stem cell transplantation as potential options in fit patients [33].

The current rapid advances in molecular diagnostics with the identification of novel genetic and epigenetic alterations, as well as an improved characterization of the tumor microenvironment have led to new insights into the pathogenesis of lymphoma and provide an opportunity for refined, biology-based treatments. However, the validation and integration of novel biomarkers in daily clinical practice and their translation into new treatment algorithms remains a challenge [83]. CLL/SLL is a paradigmatic disease in which molecular heterogeneity directly influences treatment decisions. In CLL/SLL, del(17p) is associated with a worse prognosis and a resistance against fludarabine and alkylating agents. Mutations of the *TP53* gene and an unmutated *IGHV* status are also associated with an adverse outcome, and these molecular alterations favor treatment decision towards high-intensity therapy with the use of novel agents like inhibitors of the B-cell antigen receptor signaling pathway such as ibrutinib or allogeneic hematopoietic stem cell transplantation in fit patients [84, 85].

Concluding Remarks

Personalized therapy for lymphoma patients requires precision diagnostics on all levels from molecular studies to radiological imaging. The current diagnostic gold standard still is histopathology; however, novel molecular developments will likely guide treatment decisions in the near future. The studies discussed in this review have provided important and invaluable insights into the genetic heterogeneity and pathogenesis of lymphomas, but knowledge about the genotypes in tumor cell clones at the single-cell level is still lacking. In addition, besides single-cell genome, epigenome, and transcriptome information, future investigations should include single-cell proteomes and metabolomes [86–94] and address the cells of the tumor microenvironment, like immune cell subsets. In addition, methods to analyze these parameters in situ in intact tissue will become crucial to investigate cellular localization and cell-cell interactions [95–99]. Computational integration of all these data in a so-called "cancer phenomics" approach will possibly guide future personalized medicine [100, 101]. In conclusion, tumor heterogeneity in lymphomas will keep scientists, clinicians, and pathologists busy for time to come.

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Author Contributions

C.M.S. and F.F. conceived the review. C.M.S. drafted and wrote this paper and prepared the figures. B.F. wrote the clinical part and contributed histological photographs. All of the authors discussed and revised this paper and approved the final version.

Disclosure Statement

The authors declare that no conflict of interest exists.

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