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Lymphomas and Their Microenvironment: A Multifaceted Relationship

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Abstract
It has become evident that the microenvironment – lymphocytes, macrophages, fibroblasts as well as the extracellular matrix, cytokines, chemokines, and a plethora of other cells, structures and substances residing in the vicinity of tumor cells – plays an important part in the maintenance of cancer growth and survival. This is also relevant in lymphomas. In this review, we give an outline on the importance of the microenvironment for tumors in general and lymphomas in particular, by highlighting certain basic principles of tumor-microenvironment interaction. The relationship of lymphomas and their microenvironment is multifaceted: lymphoma cells need growth factors and cytokines derived from microenvironmental cells for their sustenance and growth. On the contrary, many lymphomas silence or at least deregulate the immune system to escape recognition and subsequent elimination by immune cells, while giving advantage to suppressive microenvironmental compounds such as M2 polarized macrophages, regulatory T-cells, mast cells, and immunosuppressive fibroblasts. We also give a detailed insight across different lymphoma types to show the variety of tumor-microenvironment interactions. Due to its tremendous importance, the microenvironment has also become a new target for oncologic therapy. The most important finding concerning lymphomas with a focus on immunomodulatory substances is also, therefore, highlighted.

Introduction: The Role of Microenvironment in Cancer

A perception of the importance of tumor microenvironment (TME) in cancer dates back to the 19th century in contributions by Rudolph Virchow and James Paget, who described the presence of leukocytes in tumors and suggested that metastases of certain tumors depend on the properties of the involved organs [1]. Since the 1970s, due to newly emerging research techniques and investigations, the TME has come back into the focus of attention in cancer research. Many current therapeutic strategies not only aim at eliminating the tumor cells themselves but also influence the TME, the latter being vital for support of tumor growth and survival. It has also been shown that the composition of the TME is a predictive marker for the patients' outcome [2].

A few examples of how the TME protects the tumor and impedes therapy efficacy include expanding vasculature in the tumor areas to increase oxygen and nutrient supply [3], desmoplastic fibrosis, and altered extracellular matrix to hinder the influx of chemotherapeutic drugs and

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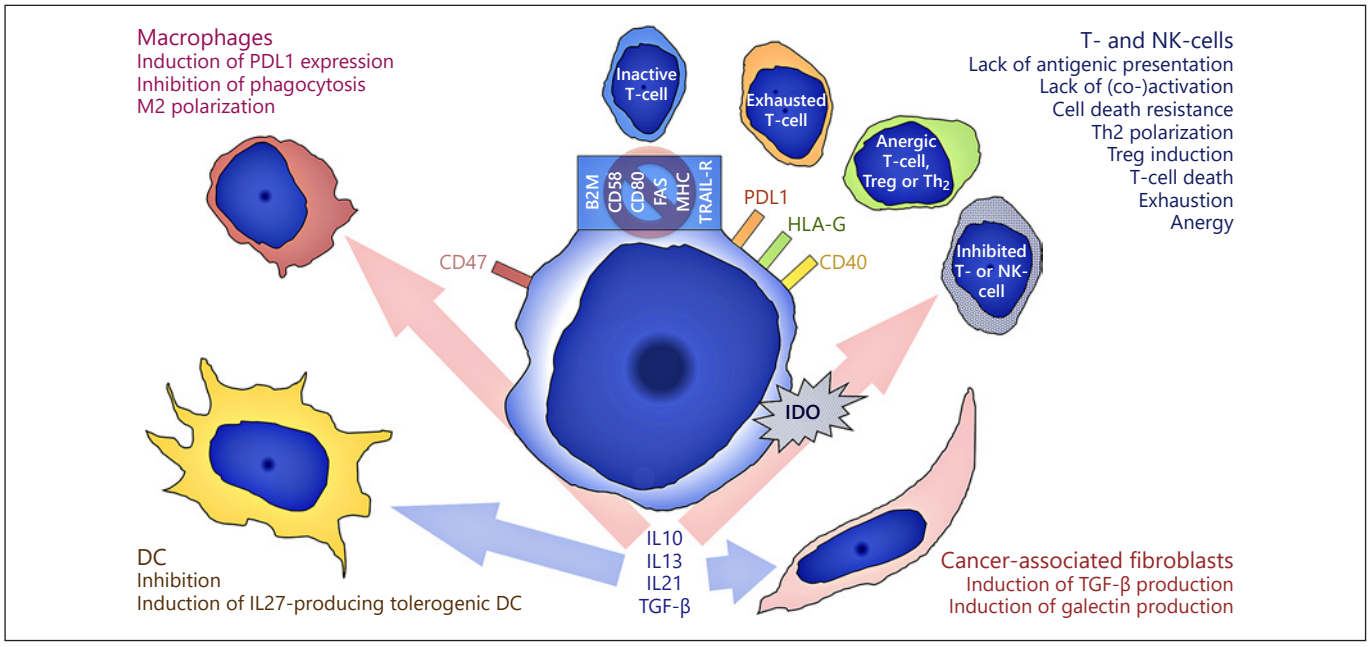

Fig. 1. Schematic overview of interactions between lymphoma cells and the TME. Lymphoma cells deploy different mechanisms in regard to the TME to foster their survival: while silencing effector immune cells and trying to avoid recognition by the immune system on the one hand (upper right), they activate and manipulate other cell types such as regulatory T-cells, CAFs, dendritic cells and macrophages via secretion of various cytokines and receptor-ligand interactions (upper left and lower left and right). DC, dendritic cells; PDL1, programmed cell death ligand 1; IL, interleukin; NK, natural killer; TGF-β, transforming growth factor beta.

immune cells [4] as well as the presence of local hypoxia and acidity to reduce the efficacy of drugs [5]. Furthermore, it has become evident that tumor cells deploy certain mechanisms to alter the cellular composition of the TME to evade recognition and subsequent elimination by the immune system [6] (see Fig. 1 for a schematic overview). Probably the most prominent and best-investigated pathway of this strategy is the programmed cell death 1 (PD1)/programmed cell death ligand 1 (PDL1) axis [7, 8].

Interaction of Lymphomas and Surrounding Reactive Cells

Lymphomas, as cancers of cells of the immune system, also display a TME, with huge differences regarding the various entities [9]. Hodgkin lymphomas (HL), both classic HL (cHL) and nodular lymphocyte predominant HL as well as several T-cell lymphoma entities such as angioimmunoblastic T-cell lymphomas (AITL) predominantly (>80% of the tumor mass) consist of TME cells, the latter even defining the morphological components. In indolent B-cell lymphomas such as follicular lymphoma (FL) or marginal zone lymphomas, the TME constitutes about 50% of the cellular mass. In aggressive lymphomas such as diffuse large B-cell lymphomas (DLBCL), the proportion of the TME varies and is generally lower, while in Burkitt lymphoma, plasmablastic lymphoma and lymphoblastic T-cell and B-cell lymphomas, the TME is barely non-existent.

In the following sections of this review, we will highlight the importance of the TME in various lymphoma entities, starting with HL, followed by the so-called "non-Hodgkin" B-cell lymphomas (B-NHL) and T-cell lymphomas.

Hodgkin Lymphomas

cHL is defined by the presence of Hodgkin and Reed-Sternberg (HRS) cells within a background of reactive cells primarily composed of B- and T-lymphocytes, plasma cells, macrophages, and eosinophils in various degrees (Fig. 2a). Before the introduction of radiotherapy and chemotherapy as treatment strategies, most patients died of the disease – not due to tumor progression but rather due to infections caused by the immunosuppressive abilities of the cHL [10].

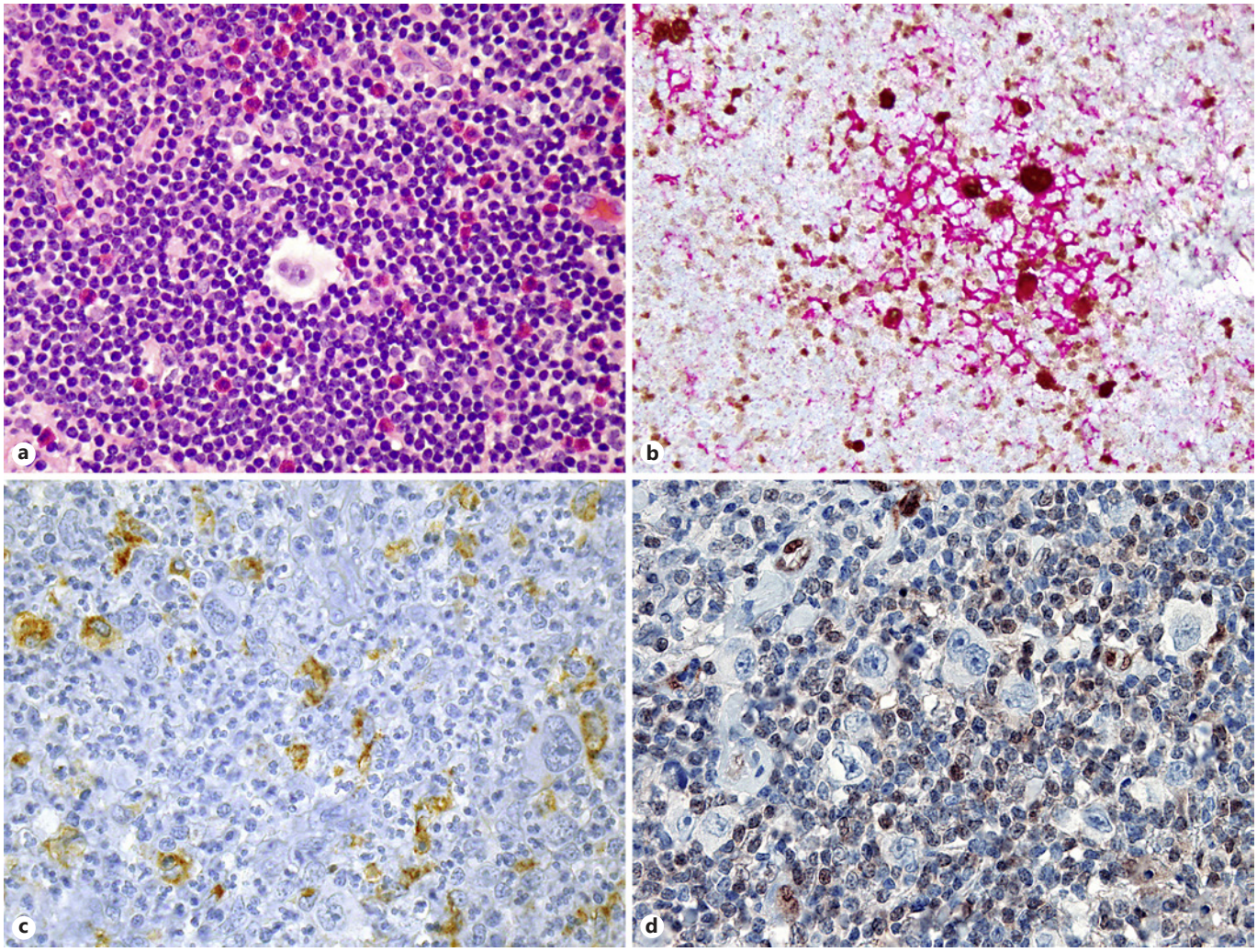

Fig. 2. cHL. **a** Composition of cHL showing one binuclear tumor giant cell and a mixed TME composed of small lymphocytes, eosinophils, and macrophages. **b** Double staining for MUM1 (brown), marking HRS cells, and PDL1 (red membranous stain), showing PDL1 expression both by HRS cells and TME-associated smaller (MUM1-negative) macrophages. **c** Abundance of macrophages marked by CD68 (PGM1) next to fewer, but larger HRS cells and smaller polymorphonuclear (neutrophilic) granulocytes. **d** Positivity for SMAD1, a signal transducer and transcriptional modulator that mediates multiple signaling pathways but particularly TGF-β-related signaling, in a cHL case; note that while almost all tumor-infiltrating reactive lymphocytes are SMAD1 positive, the HRS cells remain negative, thus being resistant to the tumor suppressive effects of TGF-β, while the latter's immunosuppressive activity on the microenvironmental T-cells is likely unaffected.

The question of how HRS cells interact with the TME has been investigated for several decades [11], with the main focus on T-cells. HRS are surrounded by T-cells, which are not capable of eliminating them. It has been shown more than 40 years ago in vitro that these T-cells are attenuated and are less responsive to mitogenic stimuli [12]. This effect is achieved by skewing the differentiation of T-cells towards Th2 cells and regulatory T-cells (Tregs) as well as driving effector T-cells in a state of exhaustion; here the expression of PDL1 is a main instrument used by HRS cells (Fig. 1, 2b) [13]. HRS cells also induce PDL1 expression in macrophages to boost the immunosuppressive environment (Fig. 2b) [14]. We have shown that FOXP3-positive Tregs are associated with improved survival in cHL and other lymphoma entities [15] in contrast to larger amounts of PD1-positive T-cells [16] and CD68-positive macrophages [17] (Fig. 2c). Interestingly, higher expression levels of PDL1 were associated with lower levels of FOXP3 Tregs and larger amounts of macrophages (see later) and PD1- and GATA3-positive

Tregs, which have all been linked to poorer prognosis, in further studies of the TME in cHL [18].

The role of B-cells in cHL – in contrast to nodular lymphocyte predominant HL – is less investigated so far. B-cells are described to be competing with HRS cells for survival signals such as CD40 ligand (CD40L) derived from T-cells, which may explain why high amounts of B-cells have been correlated with a better overall outcome of cHL [19]. Recently, Gholiha et al. [20] explored the role of plasma cells in cHL showing an association of their increased numbers with inferior prognosis and presence of B-symptoms, which might be the final "net readout" of interleukin (IL) 6 overproduction. Another bystander cell type involved in the pathogenesis of cHL is the mast cells [21]. They are attracted to the microenvironment by IL9 and/or chemokine ligand 5 produced by the HRS cells or tumor-infiltrating T-cells [22, 23], and increase angiogenesis [24], and – more importantly – directly stimulate HRS cells via CD30 [25].

Macrophages can be further subdivided into M1 macrophages, which represent the proinflammatory subtype promoting Th1 T-cells, in contrast to M2 macrophages (Fig. 1), which have tumor- and Th2 T-cell promoting activity by inducing angiogenesis, tumor cell proliferation, and immunosuppression [26]. HRS cells are known to be able to induce the M2 phenotype of macrophages in vitro [27]. Some studies reported an association of increased amounts of M2 macrophages with inferior outcome [17, 27]; however, results are conflicting [28].

Epstein-Barr virus (EBV), which is present in 30% of cHL in the Western world and in a much higher proportion in pediatric cases and HIV-related cases [29], is associated with certain distinct features of the TME of cHL. This is appreciable by mere H&E morphology as EBV-association is mainly found in the subtypes of mixed cellularity and lymphocyte-depleted cHL containing more histiocytes and macrophages than EBV-negative cases. Indeed, EBV nuclear antigen 1 (EBNA1) is able to recruit regulatory and Th2 T-cells [30]. In total, the numbers of regulatory and cytotoxic T-cells as well as natural killer (NK) cells are higher in EBV-related cHL than in non-EBV-related cHL [31]. The biggest differences are seen in the number of macrophages [32]. Interestingly, in the respective instances they consist mainly of the proinflammatory and immunostimulating M1 macrophages. This rather counterintuitive effects of EBV are balanced by several mechanisms to impair immune defense and destruction of EBV-infected cells such as latent membrane protein 1 (LMP1) [33] and the induction of Fas ligand, which result in the destruction of attacking T-cells [34]. In addition, PDL1-expression in respective cHL (while in EBV-negative cHL this expression is mainly due to the amplification of the *PDL1* locus; out of the scope of the present review [35]) can be induced by LMP1 via activation of signal transducer and activator of transcription (STAT) proteins (particularly, STAT3)- and activated protein 1-mediated pathways [36].

The TME is also manipulated by HRS cells to provide "paracrine" proliferation and survival-promoting factors [11]. The genuine lack of functioning B-cell receptors in HRS cells is compensated by the activation of the NF-κB pathway via CD30 – a pathognomonic feature of HRS cells – stimulated by the expression of CD30L by eosinophils in the TME, which on their turn are stimulated by eotaxins, IL5 and 13 secreted by the HRS cells [37]. Furthermore, the production of CD40L by T-cells is increased by IL-10 released from the HRS cells [38]. Transforming growth factor beta (TGF-β) secreted by the HRS cells and cancer-associated fibroblasts (CAFs) also stimulate tumor-infiltrating T-cells to differentiate into immunosuppressive Tregs (Fig. 1) [39], while the HRS cells themselves remain resistant to the tumor suppressive attributes of TGF-β as they do not express its intracellular second messenger SMAD1 (Fig. 2d). In EBV-associated cHL, several viral proteins such as LMP1 and LMP2A take over a part of these tumor-TME-interaction functions.

So-Called "B-NHLs"

As mentioned before, there are substantial differences between various B-cell lymphoma entities concerning their composition and their dependence on the TME. The TME only plays a minor role or barely any role in very aggressive and rapidly evolving lymphomas such as Burkitt lymphoma and lymphoblastic lymphomas, while within the group of so-called "indolent" B-NHL, TME seems to play a crucial role, which is best investigated in FL.

Similar to cHL, the relationship between B-NHL and the TME is split between the needs of the tumor cells for supportive (cytokine) signaling by the TME and the needs of the tumor cells for immune escape. Like cHL, B-NHL cells are dependent on several cytokines and growth factors derived from TME cells (Fig. 1) such as IL10, which promotes B-cell survival and induces an immunosuppressive TME, as does TGF-β [40]. Another important member of the IL-family is IL6, which also contributes to the proliferation, migration, and invasion of tumor cells [41]; IL6 can also activate and act via matrix metalloproteinases, another subgroup of enzymes shaping the microenvironment [42]. FL also needs the supporting structures of the follicular ar-

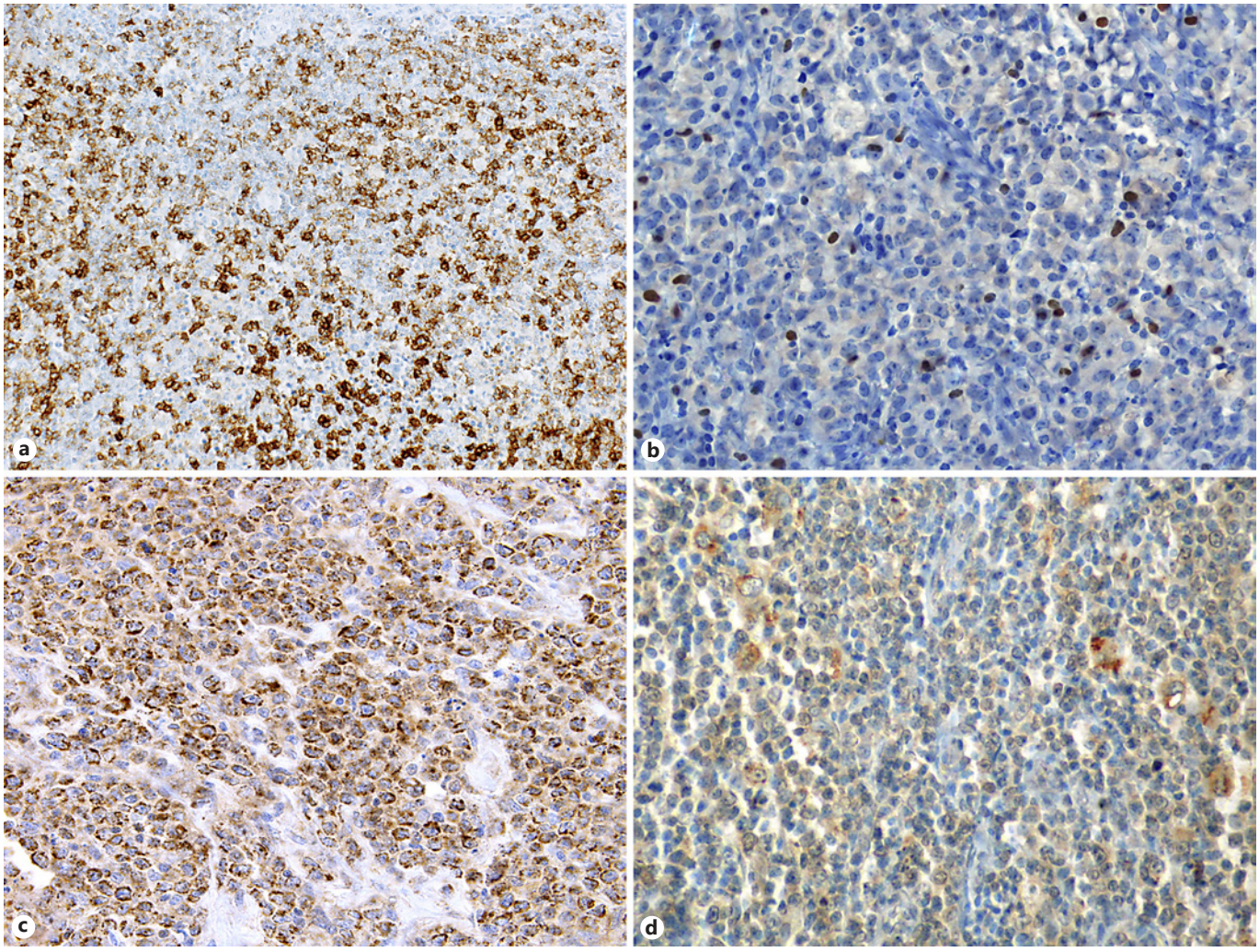

Fig. 3. FL and DLBCL. **a** FL with an abundance of PD1-positive T-cells. **b** DLBCL evolving from FL with FOXP3-positive regulatory T-cells. **c** DLBCL showing expression of the IL10 receptor in almost all tumor cells. **d** VEGF-receptor 2 expression of some DLBCL cells.

chitecture to maintain survival; the need for these structures gets lost in the process of transformation to overt DLBCL shown by a lack of dependence of Gα13-dependent signaling [43, 44]. FL is rich in T-cells, constituting up to 50% of the total cell count. CD4-positive follicular helper (TFH) T-cells provide vital survival signals for FL cells as they do for non-neoplastic germinal center cells by secreting IL2, IL4, interferon-γ, and CD40L [45]. CAF of FL secrete several chemokines such as CXCL12 and CXCL13, which are a prerequisite for lymphocyte homing and retention [46], as well as hedgehog ligands, which help to preclude spontaneous or chemotherapy-induced apoptosis [47]. Macrophages also foster FL growth and survival via the CD40 axis [48] and can activate the B-cell receptor [49]. FL cells can also prime and manipulate the composition of the TME due to *TNFRSF14*/*HVEM* loss-of-function mutations [50]: besides autonomous activation of B-cell receptor signaling in mutant cases, the TME composition is skewed to an abundance of TFH cells and increased CAF activity, which fosters tumor growth and survival. The finding of *HVEM* mutations has led to a new therapeutic approach by administering HVEM-chimeric antigen receptor T-cells, which have shown a therapeutic effect in xenograft models by reactivating B- and T-lymphocyte attenuator receptors.

FL also uses immune escape and immune silencing mechanisms to foster its survival: although not expressing PDL1 themselves, increased numbers of PDL1-expressing macrophages and PD1+ T-cells (Fig. 1, 3a) are

noted in FL [51]. The induction and promotion of TFH-cells also helps to create an immunosuppressive environment besides providing growth stimulation and survival signals for FL cells as mentioned above [45]. Furthermore, TFH-cells induce the migration of Tregs, further promoting silencing and attenuation of the immune system [52]. FOXP3-positive Tregs (Fig. 3b) are known to be of negative prognostic impact and at a higher risk of transformation in FL, which is explained by their immunosuppressive abilities [53]. They do not only act on their own but in cooperation with the M2 macrophages present in the TME.

The complexity of the importance and predictive value of the TME in FL is further complicated by the impact of different therapy approaches. Addition of rituximab seems to have neutralized the negative prognostic role of macrophages [54]. Other groups [55] as well as our own studies (unpublished data) demonstrate that therapy with different agents has an impact on the prognostic value of different TME T-cell subsets.

In DLBCL, less is known about the interaction between tumor cells and the TME. Activation of the B-cell receptor in DLBCL is mainly due to mutations in *MYD88, CD79B*, *BCL10*, *CARD11* or *CD79A* and other mechanisms of tumor promotion are active, such as activation of JAK-STAT signaling due to *SOCS1* and *STAT6* mutations, and immune escape due to *B2M, CIITA, CD58, CREBBP* and *EP300* mutations, such that DLBCL cells seem to be less dependent on the TME (Fig. 1) [56–58]. However, there is also evidence that some DLBCL subgroups are dependent on TME interactions. CD4- and CXCR5-positive T-cells support tumor growth and survival via secretion of IL10, and in some more aggressive instances DLBCL display *IL10RA* or *IL10RB* gene amplifications, being sensitive to IL10R blocking [59, 60] (Fig. 3c). DLBCL cells can also shape their microenvironment by secreting vascular endothelial growth factor (VEGF) and recruiting VEGF-receptor positive macrophages [61, 62]; in addition, isolated DLBCL cases express VEGF-receptors and, thus, some autocrine and paracrine loops related to intratumoral hypoxia might play a role in such instances (Fig. 3d). Interestingly, a so far rather neglected group of cells – neutrophils – has been shown to be very relevant in DLBCL. DLBCL cell line survival is improved by co-culturing with neutrophils [63]. This is thought to be achieved by the secretion of a proliferation-inducing ligand (APRIL), a ligand of tumor necrosis factor family [64]. APRIL activates several vital proteins related to B-cell survival such as B-cell maturation antigen and the transmembrane activator and calcium modulator cyclophilin ligand interactor. APRIL has furthermore been shown to be a negative prognostic marker for DLBCL [65]. DLBCL cells can attract neutrophils by secretion of IL8 and induces the formation of neutrophil extracellular traps [66], which then leads to the activation of Toll-like receptor-induced pathways inducing NF-κB, STAT3 and p38 related signaling [67]. As in cHL, mast cells are associated with increased angiogenesis in DLBCL [68] as well as in other B-cell lymphoma subtypes [69, 70]. Increased angiogenesis has been shown to be linked to poorer outcome in R-CHOP-treated FL [70] and, in historic collectives, with lymphoma progression [71]. In addition, mast cells seem to be a major source of IL17A in germinal center derived lymphomas [72].

The PD1/PDL1 axis is also of importance in DLBCL and, thus, a potential point of action for new therapy approaches [18, 35, 73]. Particularly applying to DLBCL, but most likely valid in general, it is becoming increasingly clear that expression patterns of various markers of immunologic interactions including PDL1 must be evaluated very carefully in regard to the question, which cells are expressing them: while PDL1-expression on DLBCL cells is associated with better survival, PDL1-expression on tumor-associated macrophages seems to be related to adverse outcome.

T-Cell Lymphomas

Compared to cHL and B-NHL, knowledge of the TME in general and its importance for tumor growth and survival in T-cell lymphomas is lacking. This is mainly due to the less common incidence and heterogeneity of this disease group.

The TME of AITL is comparably well investigated. Due to their descent of TFH-cells, AITL have a prominent TME, which is also part of the disease definition: it consists of an increased number of high endothelial venules, increased networks of follicular dendritic cells (FDCs), and a mixed inflammatory infiltrate consisting of reactive, both CD4- and CD8-positive T-cells, plasma cells, EBV-infected B-immunoblasts, eosinophils, and macrophages (Fig. 4a, b). The set-up of the TME resembles that of the surroundings of non-neoplastic TFH cells and is mainly due to the secretion of CXCL13 (Fig. 4c) and IL21 by the lymphoma [74]. B-cells are stimulated by CXCL13 secreted by the tumor cells, which also spurns their differentiation into abnormal plasma cells. This relationship can explain the paraneoplastic phenomena of

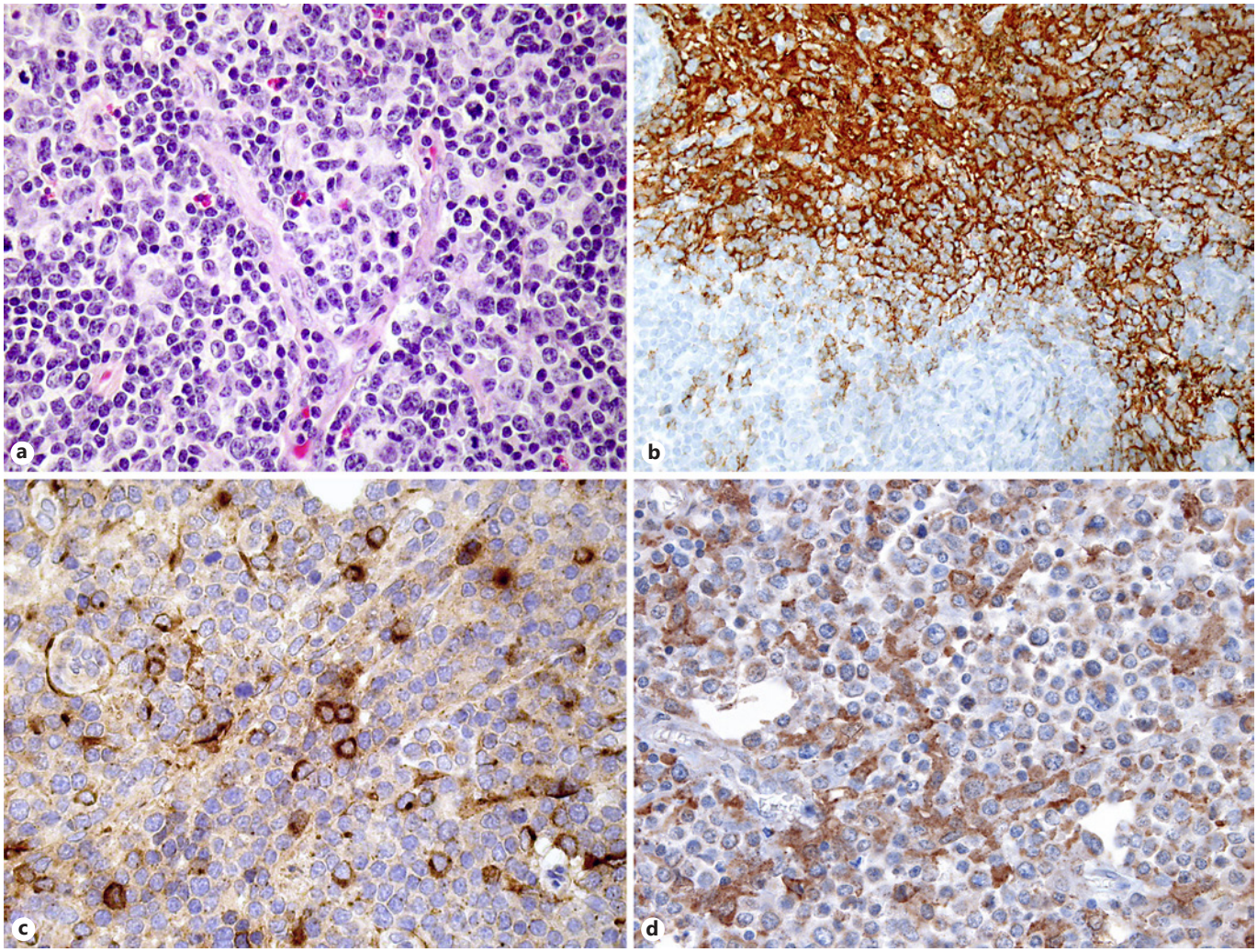

Fig. 4. AITL. **a** AITL showing medium-sized tumor cells in close interaction with high endothelial venules and TME cells composed of small lymphocytes, non-tumoral T-cells, eosinophils, and plasma cells. **b** CD21 staining shows the dense network of FDCs as a part of the TME of AITL. **c** Expression of CXCL13 by lymphoma and endothelial cells. **d** High expression of VEGF in endothelial and dendritic cells vessels as well as histiocytes, and low expression by lymphoma cells.

AITL such as hypergammaglobulinemia, presence of various autoantibodies, and Coombs-positive hemolytic anemia. Hypereosinophilia in the bone marrow and peripheral blood is also a common finding in AITL, and it is still unclear whether the neoplastic cells or reactive Th2 T-cells are responsible for the activation and growth stimulation of eosinophils. The expanded FDC networks are also due to the secretion of lymphotoxin β by B-cells stimulated by CXCL13 (Fig. 4b, c) [75]. VEGF secretion by both neoplastic cells, endothelial cells themselves, and FDC cells is responsible for the enriched vasculature of high endothelial venules (Fig. 4d) [76, 77]. Similar to transformed FL, the importance of the TME as well as its spatial extent gets reduced in the course of progressive disease indicating that with time the neoplastic cells of AITL become less dependent on the microenvironment [78]. Mast cells also play a role in AILT as they are preferentially accumulated at lymphoma sites through CXCL13 interactions with CXCR3 and CXCR5 expressed on them and, reciprocally, synthesize IL6 within the tumor [79], molding the immunological microenvironment of AITL towards the maintenance of pro-inflammatory conditions prone to Th17 generation and autoimmunity.

Other T-cell lymphomas with TFH-like phenotypes such as peripheral T-cell lymphomas (PTCL), not other-

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wise specified, PTCL follicular variant, some of the so-called "T-zone lymphomas", and primary cutaneous CD4+ small/medium-sized T-cell lymphoproliferative disease show similarities of their TME to AITL.

The most common group of cutaneous T-cell lymphomas are Mycosis fungoïdes (MF) and Sézary syndrome; the latter is characterized by the presence of blood, skin and lymph node spread as well as systemic B-symptoms [80]. In both MF and Sézary syndrome, the neoplastic T-cells are mature CD4-positive memory T-cells. It has been shown in vitro that these neoplastic cells can manipulate – along with disease progression – reactive T-cells and change their profile from Th1 to Th2 [81]. In progressive disease, gaining additional mutations, the tumor cells start expressing different immunosuppressive molecules such as IL10, Fas ligand, PD1 and CTLA4, overcoming immunosurveillance and promoting dissemination [82]. Th2-related cytokines and eotaxins might be the cause of eosinophilia, erythroderma and immunosuppression observed in advanced instances, which is, however, also the point of counteraction by interferon α2b- and extracorporeal photopheresis-therapy, both known to reduce Th2 activity [81]. MF-cells also need the TME for their survival: they are in close contact with Langerhans cells, which provide survival signals mainly through CD40-CD40L interaction, and MF's reliance on these cells has also been shown in vitro [83]. Mast cells seem to be important for cutaneous T-cell lymphomas as well as cutaneous B-cell lymphomas, and their increased number is correlated with disease progression and angiogenesis, the effects being most probably linked to multiple inflammatory cytokines and chemokines produced by these cells [84].

Several different T-cell lymphoma entities express PDL1, thus, promoting an immunosuppressive TME [85], yet its therapeutic utility is unclear with one exception. Similar to cHL, EBV can induce upregulation of PDL1 in extranodal NK- and T-cell lymphoma of the nasal type, a lymphoma with a very aggressive and often fatal outcome. PD1 blockade as "salvage therapy" has been reported to be very effective in a small series of otherwise hopeless relapsed cases [86].

Similar to FL of the pre-rituximab era, high numbers of macrophages are associated with worse outcome in several T-cell lymphomas, in ALK-positive anaplastic large cell lymphoma, a specific subtype, namely the lymphohistiocytic variant, which bears a description of its TME in the name, is generally known to be associated with a worse prognosis [87].

Use of Immunomodulatory Therapy in Lymphomas

For a deeper insight into this clinical topic, we refer to other reviews [88–92]. In this review, we would like to focus on the PD1/PDL1 axis of checkpoint inhibition and the use of immunomodulatory drugs such as lenalidomide.

The discovery of the PD1/PDL1 axis as a new point of action for targeted therapy is a major achievement in oncology in the last years [93]. This concept – immune checkpoint blockade inhibiting antibodies – has been transferred from solid tumors to lymphomas (reviewed in [94, 95]), the paradigm in the field of lymphomas being cHL. The igniting study comprised a cohort of 18 patients with refractory/relapsing cHL, who had been received nivolumab and demonstrated complete remissions (CR) in 17% and partial remissions (PR) in 70% [96]. Further studies showed similar promising results ($n = 31$, CR 16%, PR 48%/$n = 210$, CR 22%, PR 47%) [97, 98]. Two different anti-PD1-antibodies (nivolumab and pembrolizumab) are now approved for treatment of relapsed and/or refractory cHL [94, 95]. Combinatory/additive approaches of radio- and chemotherapy together with PDL1-centered immunotherapy have also been successfully tested [99]. These therapy regimens are based on the hypothesis that damage induced by radio- and chemotherapy renders tumor cells more "visible" to immune cells (re)activated by immune checkpoint inhibition [100]. In primary mediastinal B-cell lymphoma, which shares *PDL1* amplifications with cHL, first clinical trials using similar approaches have also been published, yet the overall response rates are approximately 40% (heavily pretreated patients, $n = 18$) [101]. In DLBCL, immune checkpoint inhibition focusing on the PD1/PDL1 axis is still evolving with several trials being planned currently [88]. Such treatment strategies will mainly be applied in second relapse settings, which affect 10–15% of DLBCL patients. After the initial phase I studies, there is currently one running phase II study (CheckMate 139, NCT02038933) showing an overall response rate of 10% in the patient cohort with relapse after autologous stem cell transplantation and 2.3% in patients ineligible for autologous stem cell transplantation [88]. In FL, mantle cell lymphoma, and CLL, immunotherapy in general has not been investigated at a larger scale. Yet, in relapsed FL, a first study combining PDL1-centered immunotherapy and rituximab has shown promising results ($n = 29$, CR 52%, PR 14%) [102]; further studies showed overall response rates of up to 40% [103]. In T-cell lymphomas, the use of brentuximab vedotin showed a significant effect in different

series. Besides directly targeting CD30, the additional monomethyl auristatin E payload helps to attenuate protumoral macrophages, thus, facilitating the effect of brentuximab vedotin [104]. With the impressive exception of EBV-related T-cell lymphomas, the use of PD1-blockade might prove difficult. It might lead to the removal of inhibitory signals for tumor cells and promote tumor growth [105]. Taken together, the most important conclusion derived from various studies so far is that immune checkpoint inhibition in lymphomas has to be seen as an additive therapy in combination with other treatment modalities as there is mostly only limited treatment response if given as a single agent [95]. PDL1 inhibition in lymphomas of immunoprivileged also needs further evaluation (5 investigated cases) [106].

Another option to influence the immune system to tackle tumor cells is the use of immunomodulatory drugs such as lenalidomide. Lenalidomide acts by promoting the degradation of 2 transcription factors, Aiolos and Ikaros, which are part of the cereblon-mediated signaling [107, 108]. Lenalidomide facilitates apoptosis of lymphoma cells and activates T-cells of the TME by enhanced secretion of IL2. Lenalidomide has been tested in several trials of FL so far and the combination of lenalidomide and rituximab showed similar results as rituximab and conventional chemotherapy [109, 110]. The effect on the restoration of immune synapses has also been shown by in vitro analysis of patients' immune cells of the RELEVANCE trial [111]. In DLBCL, several studies have been undertaken for analyzing the benefit of lenalidomide [112]. It has been shown to support the efficacy of other drugs activating the immune system such as MOR208, a humanized monoclonal anti-CD19 antibody [113], which primarily renders lymphoma cell "visible" for NK-cells and macrophages. Very promising results have been obtained from several studies testing the use of lenalidomide in maintenance therapy of DLBCL, its addition to classical R-CHOP therapy (R^2-CHOP), and even as monotherapy [114–116].

Conclusion

The TME has left its niche of being merely regarded as the background for neoplastic cells to become a focus of our understanding of cancer development, cancer progression and point of action for new therapeutic concepts.

We have demonstrated the role of TME in the pathogenesis of various lymphoma subtypes, however many questions still need to be answered. The plasticity of the microenvironment makes it difficult to be studied in static circumstances and, for obvious reasons, in animal models as the constitution of the TME and its interactions might differ from that in humans. Nevertheless, many breakthroughs have already been achieved regarding the contribution of TME to lymphoma development and progression, and this knowledge has been transferred into therapeutic strategies. Future work will help to get better insights with regard to inter- and intracellular signaling, metabolomics of the TME, the impact of therapy on the TME and its predictive implications.

Disclosure Statement

The authors have no disclosures to make. No funding was received for this study.

Author Contributions

Both T.M. and A.T.: conceived and wrote the paper. A.T.: designed the figures.

References

1 Maman S, Witz IP. A history of exploring cancer in context. Nat Rev Cancer. 2018 Jun;18(6):359–76.
2 Galon J, Costes A, Sanchez-Cabo F, Kirilovsky A, Mlecnik B, Lagorce-Pagès C, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science. 2006 Sep;313(5795):1960–4.
3 Folkman J. The role of angiogenesis in tumor growth. Semin Cancer Biol. 1992 Apr;3(2):65–71.
4 Malik R, Lelkes PI, Cukierman E. Biomechanical and biochemical remodeling of stromal extracellular matrix in cancer. Trends Biotechnol. 2015 Apr;33(4):230–6.
5 Parks SK, Chiche J, Pouysségur J. Disrupting proton dynamics and energy metabolism for cancer therapy. Nat Rev Cancer. 2013 Sep;13(9):611–23.
6 Wang K, Karin M. Tumor-Elicited Inflammation and Colorectal Cancer. Adv Cancer Res. 2015;128:173–96.
7 Francisco LM, Salinas VH, Brown KE, Vanguri VK, Freeman GJ, Kuchroo VK, et al. PD-L1 regulates the development, maintenance, and function of induced regulatory T cells. J Exp Med. 2009 Dec;206(13):3015–29.
8 Zhang X, Schwartz JC, Guo X, Bhatia S, Cao E, Lorenz M, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity. 2004 Mar;20(3):337–47.
9 Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th Edition. Lyon, France: IARC; 2017.
10 Diehl V. Hodgkin's disease—from pathology specimen to cure. N Engl J Med. 2007 Nov;357(19):1968–71.
11 Aldinucci D, Celegato M, Casagrande N. Microenvironmental interactions in classical Hodgkin lymphoma and their role in promoting tumor growth, immune escape and drug resistance. Cancer Lett. 2016 Sep;380(1):243–52.

12 Payne SV, Jones DB, Wright DH. Reed-Sternberg-cell/lymphocyte interaction. Lancet. 1977 Oct;2(8041):768–9.
13 Menter T, Tzankov A. Mechanisms of Immune Evasion and Immune Modulation by Lymphoma Cells. Front Oncol. 2018 Mar;8:54.
14 Carey CD, Gusenleitner D, Lipschitz M, Roemer MG, Stack EC, Gjini E, et al. Topological analysis reveals a PD-L1-associated microenvironmental niche for Reed-Sternberg cells in Hodgkin lymphoma. Blood. 2017 Nov;130(22):2420–30.
15 Tzankov A, Meier C, Hirschmann P, Went P, Pileri SA, Dirnhofer S. Correlation of high numbers of intratumoral FOXP3+ regulatory T cells with improved survival in germinal center-like diffuse large B-cell lymphoma, follicular lymphoma and classical Hodgkin's lymphoma. Haematologica. 2008 Feb;93(2):193–200.
16 Muenst S, Hoeller S, Dirnhofer S, Tzankov A. Increased programmed death-1+ tumor-infiltrating lymphocytes in classical Hodgkin lymphoma substantiate reduced overall survival. Hum Pathol. 2009 Dec;40(12):1715–22.
17 Tzankov A, Matter MS, Dirnhofer S. Refined prognostic role of CD68-positive tumor macrophages in the context of the cellular micromilieu of classical Hodgkin lymphoma. Pathobiology. 2010;77(6):301–8.
18 Menter T, Bodmer-Haecki A, Dirnhofer S, Tzankov A. Evaluation of the diagnostic and prognostic value of PDL1 expression in Hodgkin and B-cell lymphomas. Hum Pathol. 2016 Aug;54:17–24.
19 Greaves P, Clear A, Coutinho R, Wilson A, Matthews J, Owen A, et al. Expression of FOXP3, CD68, and CD20 at diagnosis in the microenvironment of classical Hodgkin lymphoma is predictive of outcome. J Clin Oncol. 2013 Jan;31(2):256–62.
20 Gholiha AR, Hollander P, Hedstrom G, Sundstrom C, Molin D, Smedby KE, et al. High tumour plasma cell infiltration reflects an important microenvironmental component in classic Hodgkin lymphoma linked to presence of B-symptoms. Br J Haematol. 2019 Jan;184(2):192–201.
21 Molin D, Edström A, Glimelius I, Glimelius B, Nilsson G, Sundström C, et al. Mast cell infiltration correlates with poor prognosis in Hodgkin's lymphoma. Br J Haematol. 2002 Oct;119(1):122–4.
22 Glimelius I, Edström A, Amini RM, Fischer M, Nilsson G, Sundström C, et al. IL-9 expression contributes to the cellular composition in Hodgkin lymphoma. Eur J Haematol. 2006 Apr;76(4):278–83.
23 Aldinucci D, Gloghini A, Pinto A, De Filippi R, Carbone A. The classical Hodgkin's lymphoma microenvironment and its role in promoting tumour growth and immune escape. J Pathol. 2010 Jul;221(3):248–63.
24 Mizuno H, Nakayama T, Miyata Y, Saito S, Nishiwaki S, Nakao N, et al. Mast cells promote the growth of Hodgkin's lymphoma cell tumor by modifying the tumor microenvironment that can be perturbed by bortezomib. Leukemia. 2012 Oct;26(10):2269–76.
25 Molin D, Fischer M, Xiang Z, Larsson U, Harvima I, Venge P, et al. Mast cells express functional CD30 ligand and are the predominant CD30L-positive cells in Hodgkin's disease. Br J Haematol. 2001 Sep;114(3):616–23.
26 Mills CD. Anatomy of a discovery: m1 and m2 macrophages. Front Immunol. 2015 May;6:212.
27 Tudor CS, Bruns H, Daniel C, Distel LV, Hartmann A, Gerbitz A, et al. Macrophages and dendritic cells as actors in the immune reaction of classical Hodgkin lymphoma. PLoS One. 2014 Dec;9(12):e114345.
28 Hollander P, Rostgaard K, Smedby KE, Molin D, Loskog A, de Nully Brown P, et al. An anergic immune signature in the tumor microenvironment of classical Hodgkin lymphoma is associated with inferior outcome. Eur J Haematol. 2018 Jan;100(1):88–97.
29 Johnson PC, McAulay KA, Montgomery D, Lake A, Shield L, Gallagher A, et al. Modeling HLA associations with EBV-positive and -negative Hodgkin lymphoma suggests distinct mechanisms in disease pathogenesis. Int J Cancer. 2015 Sep;137(5):1066–75.
30 Baumforth KR, Birgersdotter A, Reynolds GM, Wei W, Kapatai G, Flavell JR, et al. Expression of the Epstein-Barr virus-encoded Epstein-Barr virus nuclear antigen 1 in Hodgkin's lymphoma cells mediates Up-regulation of CCL20 and the migration of regulatory T cells. Am J Pathol. 2008 Jul;173(1):195–204.
31 Wu R, Sattarzadeh A, Rutgers B, Diepstra A, van den Berg A, Visser L. The microenvironment of classical Hodgkin lymphoma: heterogeneity by Epstein-Barr virus presence and location within the tumor. Blood Cancer J. 2016 May;6(5):e417.
32 Chetaille B, Bertucci F, Finetti P, Esterni B, Stamatoullas A, Picquenot JM, et al. Molecular profiling of classical Hodgkin lymphoma tissues uncovers variations in the tumor microenvironment and correlations with EBV infection and outcome. Blood. 2009 Mar;113(12):2765–3775.
33 Dukers DF, Meij P, Vervoort MB, Vos W, Scheper RJ, Meijer CJ, et al. Direct immunosuppressive effects of EBV-encoded latent membrane protein 1. J Immunol. 2000 Jul;165(2):663–70.
34 Ahmed W, Philip PS, Attoub S, Khan G. Epstein-Barr virus-infected cells release Fas ligand in exosomal fractions and induce apoptosis in recipient cells via the extrinsic pathway. J Gen Virol. 2015 Dec;96(12):3646–59.
35 Menter T, Tzankov A. Genetic alterations of 9p24 in lymphomas and their impact for cancer (immuno-)therapy. Virchows Arch. 2019 Apr;474(4):497–509.
36 Green MR, Rodig S, Juszczynski P, Ouyang J, Sinha P, O'Donnell E, et al. Constitutive AP-1 activity and EBV infection induce PD-L1 in Hodgkin lymphomas and posttransplant lymphoproliferative disorders: implications for targeted therapy. Clin Cancer Res. 2012 Mar;18(6):1611–8.
37 Pinto A, Aldinucci D, Gloghini A, Zagonel V, Degan M, Improta S, et al. Human eosinophils express functional CD30 ligand and stimulate proliferation of a Hodgkin's disease cell line. Blood. 1996 Nov;88(9):3299–305.
38 Ohshima K, Karube K, Hamasaki M, Suefuji H, Tutiya T, Yamaguchi T, et al. Imbalances of chemokines, chemokine receptors and cytokines in Hodgkin lymphoma: classical Hodgkin lymphoma vs. Hodgkin-like ATLL. Int J Cancer. 2003 Sep;106(5):706–12.
39 Liu Y, Zhang P, Li J, Kulkarni AB, Perruche S, Chen W. A critical function for TGF-beta signaling in the development of natural CD4+CD25+Foxp3+ regulatory T cells. Nat Immunol. 2008 Jun;9(6):632–40.
40 de Charette M, Houot R. Hide or defend, the two strategies of lymphoma immune evasion: potential implications for immunotherapy. Haematologica. 2018 Aug;103(8):1256–68.
41 Voorzanger N, Touitou R, Garcia E, Delecluse HJ, Rousset F, Joab I, et al. Interleukin (IL)-10 and IL-6 are produced in vivo by non-Hodgkin's lymphoma cells and act as cooperative growth factors. Cancer Res. 1996 Dec;56(23):5499–505.
42 Malaponte G, Hafsi S, Polesel J, Castellano G, Spessotto P, Guarneri C, et al. Tumor microenvironment in diffuse large B-cell lymphoma: matrixmetalloproteinases activation is mediated by osteopontin overexpression. Biochim Biophys Acta. 2016 Mar;1863(3):483–9.
43 Muppidi JR, Schmitz R, Green JA, Xiao W, Larsen AB, Braun SE, et al. Loss of signalling via Gα13 in germinal centre B-cell-derived lymphoma. Nature. 2014 Dec;516(7530):254–8.
44 Pasqualucci L, Khiabanian H, Fangazio M, Vasishtha M, Messina M, Holmes AB, et al. Genetics of follicular lymphoma transformation. Cell Rep. 2014 Jan;6(1):130–40.
45 Amé-Thomas P, Le Priol J, Yssel H, Caron G, Pangault C, Jean R, et al. Characterization of intratumoral follicular helper T cells in follicular lymphoma: role in the survival of malignant B cells. Leukemia. 2012 May;26(5):1053–63.
46 Pandey S, Mourcin F, Marchand T, Nayar S, Guirriec M, Pangault C, et al. IL-4/CXCL12 loop is a key regulator of lymphoid stroma function in follicular lymphoma. Blood. 2017 May;129(18):2507–18.
47 Mourcin F, Pangault C, Amin-Ali R, Amé-Thomas P, Tarte K. Stromal cell contribution to human follicular lymphoma pathogenesis. Front Immunol. 2012 Sep;3:280.
48 Epron G, Ame-Thomas P, Le Priol J, Pangault C, Dulong J, Lamy T, et al. Monocytes and T cells cooperate to favor normal and follicular lymphoma B-cell growth: role of IL-15 and CD40L signaling. Leukemia. 2012 Jan;26(1):139–48.
49 Coelho V, Krysov S, Ghaemmaghami AM, Emara M, Potter KN, Johnson P, et al. Glycosylation of surface Ig creates a functional bridge between human follicular lymphoma and microenvironmental lectins. Proc Natl Acad Sci USA. 2010 Oct;107(43):18587–92.

50 Boice M, Salloum D, Mourcin F, Sanghvi V, Amin R, Oricchio E, et al. Loss of the HVEM Tumor Suppressor in Lymphoma and Restoration by Modified CAR-T Cells. Cell. 2016 Oct;167(2):405–18.e13.
51 Meirav K, Ginette S, Tamar T, Iris B, Arnon N, Abraham A. Extrafollicular PD1 and Intrafollicular CD3 Expression Are Associated With Survival in Follicular Lymphoma. Clin Lymphoma Myeloma Leuk. 2017 Oct;17(10):645–9.
52 Rawal S, Chu F, Zhang M, Park HJ, Nattamai D, Kannan S, et al. Cross talk between follicular Th cells and tumor cells in human follicular lymphoma promotes immune evasion in the tumor microenvironment. J Immunol. 2013 Jun;190(12):6681–93.
53 Farinha P, Al-Tourah A, Gill K, Klasa R, Connors JM, Gascoyne RD. The architectural pattern of FOXP3-positive T cells in follicular lymphoma is an independent predictor of survival and histologic transformation. Blood. 2010 Jan;115(2):289–95.
54 Canioni D, Salles G, Mounier N, Brousse N, Keuppens M, Morchhauser F, et al. High numbers of tumor-associated macrophages have an adverse prognostic value that can be circumvented by rituximab in patients with follicular lymphoma enrolled onto the GELA-GOELAMS FL-2000 trial. J Clin Oncol. 2008 Jan;26(3):440–6.
55 de Jong D, Koster A, Hagenbeek A, Raemaekers J, Veldhuizen D, Heisterkamp S, et al. Impact of the tumor microenvironment on prognosis in follicular lymphoma is dependent on specific treatment protocols. Haematologica. 2009 Jan;94(1):70–7.
56 Young RM, Shaffer AL 3rd, Phelan JD, Staudt LM. B-cell receptor signaling in diffuse large B-cell lymphoma. Semin Hematol. 2015 Apr;52(2):77–85.
57 Juskevicius D, Jucker D, Klingbiel D, Mamot C, Dirnhofer S, Tzankov A. Mutations of CREBBP and SOCS1 are independent prognostic factors in diffuse large B cell lymphoma: mutational analysis of the SAKK 38/07 prospective clinical trial cohort. J Hematol Oncol. 2017 Mar;10(1):70.
58 Dubois S, Viailly PJ, Mareschal S, Bohers E, Bertrand P, Ruminy P, et al. Next-Generation Sequencing in Diffuse Large B-Cell Lymphoma Highlights Molecular Divergence and Therapeutic Opportunities: a LYSA Study. Clin Cancer Res. 2016 Jun;22(12):2919–28.
59 Cha Z, Qian G, Zang Y, Gu H, Huang Y, Zhu L, et al. Circulating CXCR5+CD4+ T cells assist in the survival and growth of primary diffuse large B cell lymphoma cells through interleukin 10 pathway. Exp Cell Res. 2017 Jan;350(1):154–60.
60 Béguelin W, Sawh S, Chambwe N, Chan FC, Jiang Y, Choo JW, et al. IL10 receptor is a novel therapeutic target in DLBCLs. Leukemia. 2015 Aug;29(8):1684–94.
61 Tzankov A, Heiss S, Ebner S, Sterlacci W, Schaefer G, Augustin F, et al. Angiogenesis in nodal B cell lymphomas: a high throughput study. J Clin Pathol. 2007 May;60(5):476–82.
62 Ruan J, Hyjek E, Kermani P, Christos PJ, Hooper AT, Coleman M, et al. Magnitude of stromal hemangiogenesis correlates with histologic subtype of non-Hodgkin's lymphoma. Clin Cancer Res. 2006 Oct;12(19):5622–31.
63 Grégoire M, Guilloton F, Pangault C, Mourcin F, Sok P, Latour M, et al. Neutrophils trigger a NF-κB dependent polarization of tumor-supportive stromal cells in germinal center B-cell lymphomas. Oncotarget. 2015 Jun;6(18):16471–87.
64 Manfroi B, McKee T, Mayol JF, Tabruyn S, Moret S, Villiers C, et al. CXCL-8/IL8 Produced by Diffuse Large B-cell Lymphomas Recruits Neutrophils Expressing a Proliferation-Inducing Ligand APRIL. Cancer Res. 2017 Mar;77(5):1097–107.
65 Schwaller J, Schneider P, Mhawech-Fauceglia P, McKee T, Myit S, Matthes T, et al. Neutrophil-derived APRIL concentrated in tumor lesions by proteoglycans correlates with human B-cell lymphoma aggressiveness. Blood. 2007 Jan;109(1):331–8.
66 Brinkmann V, Reichard U, Goosmann C, Fauler B, Uhlemann Y, Weiss DS, et al. Neutrophil extracellular traps kill bacteria. Science. 2004 Mar;303(5663):1532–5.
67 Nie M, Yang L, Bi X, Wang Y, Sun P, Yang H, et al. Neutrophil Extracellular Traps Induced by IL8 Promote Diffuse Large B-cell Lymphoma Progression via the TLR9 Signaling. Clin Cancer Res. 2019 Mar;25(6):1867–79.
68 Marinaccio C, Ingravallo G, Gaudio F, Perrone T, Nico B, Maoirano E, et al. Microvascular density, CD68 and tryptase expression in human diffuse large B-cell lymphoma. Leuk Res. 2014 Nov;38(11):1374–7.
69 Ribatti D, Molica S, Vacca A, Nico B, Crivellato E, Roccaro AM, et al. Tryptase-positive mast cells correlate positively with bone marrow angiogenesis in B-cell chronic lymphocytic leukemia. Leukemia. 2003 Jul;17(7):1428–30.
70 Taskinen M, Jantunen E, Kosma VM, Bono P, Karjalainen-Lindsberg ML, Leppä S. Prognostic impact of CD31-positive microvessel density in follicular lymphoma patients treated with immunochemotherapy. Eur J Cancer. 2010 Sep;46(13):2506–12.
71 Ribatti D, Vacca A, Marzullo A, Nico B, Ria R, Roncali L, et al. Angiogenesis and mast cell density with tryptase activity increase simultaneously with pathological progression in B-cell non-Hodgkin's lymphomas. Int J Cancer. 2000 Jan;85(2):171–5.
72 Ferretti E, Di Carlo E, Ognio E, Guarnotta C, Bertoni F, Corcione A, et al. Interleukin-17A promotes the growth of human germinal center derived non-Hodgkin B cell lymphoma. OncoImmunology. 2015 Jun;4(10):e1030560.
73 Xu-Monette ZY, Xiao M, Au Q, Padmanabhan R, Xu B, Hoe N, et al. Immune Profiling and Quantitative Analysis Decipher the Clinical Role of Immune-Checkpoint Expression in the Tumor Immune Microenvironment of DLBCL. Cancer Immunol Res. 2019 Apr;7(4):644–57.
74 Gaulard P, de Leval L. The microenvironment in T-cell lymphomas: emerging themes. Semin Cancer Biol. 2014 Feb;24:49–60.
75 Foss HD, Anagnostopoulos I, Herbst H, Grebe M, Ziemann K, Hummel M, et al. Patterns of cytokine gene expression in peripheral T-cell lymphoma of angioimmunoblastic lymphadenopathy type. Blood. 1995 May;85(10):2862–9.
76 Zhao WL, Mourah S, Mounier N, Leboeuf C, Daneshpouy ME, Legrès L, et al. Vascular endothelial growth factor-A is expressed both on lymphoma cells and endothelial cells in angioimmunoblastic T-cell lymphoma and related to lymphoma progression. Lab Invest. 2004 Nov;84(11):1512–9.
77 Fukushima N, Satoh T, Sano M, Tokunaga O. Angiogenesis and mast cells in non-Hodgkin's lymphoma: a strong correlation in angioimmunoblastic T-cell lymphoma. Leuk Lymphoma. 2001 Aug;42(4):709–20.
78 Sato F, Ishida T, Ito A, Mori F, Masaki A, Takino H, et al. Angioimmunoblastic T-cell lymphoma mice model. Leuk Res. 2013 Jan;37(1):21–7.
79 Tripodo C, Gri G, Piccaluga PP, Frossi B, Guarnotta C, Piconese S, et al. Mast cells and Th17 cells contribute to the lymphoma-associated pro-inflammatory microenvironment of angioimmunoblastic T-cell lymphoma. Am J Pathol. 2010 Aug;177(2):792–802.
80 Jawed SI, Myskowski PL, Horwitz S, Moskowitz A, Querfeld C. Primary cutaneous T-cell lymphoma (mycosis fungoides and Sezary syndrome): part I. Diagnosis: clinical and histopathologic features and new molecular and biologic markers. J Am Acad Dermatol. 2014;70(2):205. e1–16; quiz 21–2.
81 Guenova E, Watanabe R, Teague JE, Desimone JA, Jiang Y, Dowlatshahi M, et al. TH2 cytokines from malignant cells suppress TH1 responses and enforce a global TH2 bias in leukemic cutaneous T-cell lymphoma. Clin Cancer Res. 2013 Jul;19(14):3755–63.
82 Wong HK, Mishra A, Hake T, Porcu P. Evolving insights in the pathogenesis and therapy of cutaneous T-cell lymphoma (mycosis fungoides and Sezary syndrome). Br J Haematol. 2011 Oct;155(2):150–66.
83 Berger CL, Hanlon D, Kanada D, Dhodapkar M, Lombillo V, Wang N, et al. The growth of cutaneous T-cell lymphoma is stimulated by immature dendritic cells. Blood. 2002 Apr;99(8):2929–39.
84 Rabenhorst A, Schlaak M, Heukamp LC, Förster A, Theurich S, von Bergwelt-Baildon M, et al. Mast cells play a protumorigenic role in primary cutaneous lymphoma. Blood. 2012 Sep;120(10):2042–54.
85 Wilcox RA, Feldman AL, Wada DA, Yang ZZ, Comfere NI, Dong H, et al. B7-H1 (PD-L1, CD274) suppresses host immunity in T-cell lymphoproliferative disorders. Blood. 2009 Sep;114(10):2149–58.

86 Chan TS, Li J, Loong F, Khong PL, Tse E, Kwong YL. PD1 blockade with low-dose nivolumab in NK/T cell lymphoma failing L-asparaginase: efficacy and safety. Ann Hematol. 2018 Jan;97(1):193–6.
87 Lamant L, McCarthy K, d'Amore E, Klapper W, Nakagawa A, Fraga M, et al. Prognostic impact of morphologic and phenotypic features of childhood ALK-positive anaplastic large-cell lymphoma: results of the ALCL99 study. J Clin Oncol. 2011 Dec;29(35):4669–76.
88 Zhang J, Medeiros LJ, Young KH. Cancer Immunotherapy in Diffuse Large B-Cell Lymphoma. Front Oncol. 2018 Sep;8:351.
89 Renner C, Stenner F. Cancer Immunotherapy and the Immune Response in Hodgkin Lymphoma. Front Oncol. 2018 Jun;8:193.
90 Hu B, Oki Y. Novel Immunotherapy Options for Extranodal NK/T-Cell Lymphoma. Front Oncol. 2018 Apr;8:139.
91 Pierpont TM, Limper CB, Richards KL. Past, Present, and Future of Rituximab-The World's First Oncology Monoclonal Antibody Therapy. Front Oncol. 2018 Jun;8:163.
92 Stenner F, Renner C. Cancer Immunotherapy and the Immune Response in Follicular Lymphoma. Front Oncol. 2018 Jun;8:219.
93 Hughes PE, Caenepeel S, Wu LC. Targeted Therapy and Checkpoint Immunotherapy Combinations for the Treatment of Cancer. Trends Immunol. 2016 Jul;37(7):462–76.
94 Wang Y, Wu L, Tian C, Zhang Y. PD-1-PD-L1 immune-checkpoint blockade in malignant lymphomas. Ann Hematol. 2018 Feb; 97(2):229–37.
95 Merryman RW, Armand P, Wright KT, Rodig SJ. Checkpoint blockade in Hodgkin and non-Hodgkin lymphoma. Blood Adv. 2017 Dec;1(26):2643–54.
96 Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med. 2015 Jan;372(4):311–9.
97 Armand P, Shipp MA, Ribrag V, Michot JM, Zinzani PL, Kuruvilla J, et al. Programmed Death-1 Blockade With Pembrolizumab in Patients With Classical Hodgkin Lymphoma After Brentuximab Vedotin Failure. J Clin Oncol. 2016 Nov;34(31):3733–9.
98 Chen R, Zinzani PL, Fanale MA, Armand P, Johnson NA, Brice P, et al.; KEYNOTE-087. Phase II Study of the Efficacy and Safety of Pembrolizumab for Relapsed/Refractory Classic Hodgkin Lymphoma. J Clin Oncol. 2017 Jul;35(19):2125–32.
99 Herrera AF, Moskowitz AJ, Bartlett NL, Vose JM, Ramchandren R, Feldman TA, et al. Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma. Blood. 2018 Mar;131(11):1183–94.
100 Bracci L, Schiavoni G, Sistigu A, Belardelli F. Immune-based mechanisms of cytotoxic chemotherapy: implications for the design of novel and rationale-based combined treatments against cancer. Cell Death Differ. 2014 Jan;21(1):15–25.
101 Zinzani PL, Ribrag V, Moskowitz CH, Michot JM, Kuruvilla J, Balakumaran A, et al. Safety and tolerability of pembrolizumab in patients with relapsed/refractory primary mediastinal large B-cell lymphoma. Blood. 2017 Jul;130(3):267–70.
102 Westin JR, Chu F, Zhang M, Fayad LE, Kwak LW, Fowler N, et al. Safety and activity of PD1 blockade by pidilizumab in combination with rituximab in patients with relapsed follicular lymphoma: a single group, open-label, phase 2 trial. Lancet Oncol. 2014 Jan; 15(1):69–77.
103 Lesokhin AM, Ansell SM, Armand P, Scott EC, Halwani A, Gutierrez M, et al. Nivolumab in Patients With Relapsed or Refractory Hematologic Malignancy: Preliminary Results of a Phase Ib Study. J Clin Oncol. 2016 Aug;34(23):2698–704.
104 Prince HM, Kim YH, Horwitz SM, Dummer R, Scarisbrick J, Quaglino P, et al.; ALCANZA study group. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. Lancet. 2017 Aug; 390(10094):555–66.
105 Bennani NN, Ansell SM. Tumor Microenvironment in T-Cell Lymphomas. In; Querfeld C, Zain J, Rosen ST, editors. T-Cell and NK-Cell Lymphomas. Cham: Springer Nature; 2019. pp. 69-82.
106 Nayak L, Iwamoto FM, LaCasce A, Mukundan S, Roemer MG, Chapuy B, et al. PD-1 blockade with nivolumab in relapsed/refractory primary central nervous system and testicular lymphoma. Blood. 2017 Jun;129(23):3071–3.
107 Gandhi AK, Kang J, Havens CG, Conklin T, Ning Y, Wu L, et al. Immunomodulatory agents lenalidomide and pomalidomide co-stimulate T cells by inducing degradation of T cell repressors Ikaros and Aiolos via modulation of the E3 ubiquitin ligase complex CRL4(CRBN.). Br J Haematol. 2014 Mar; 164(6):811–21.
108 Lopez-Girona A, Mendy D, Ito T, Miller K, Gandhi AK, Kang J, et al. Cereblon is a direct protein target for immunomodulatory and antiproliferative activities of lenalidomide and pomalidomide. Leukemia. 2012 Nov; 26(11):2326–35.
109 Morschhauser F, Fowler NH, Feugier P, Bouabdallah R, Tilly H, Palomba ML, et al.; RELEVANCE Trial Investigators. Rituximab plus Lenalidomide in Advanced Untreated Follicular Lymphoma. N Engl J Med. 2018 Sep;379(10):934–47.
110 Tilly H, Morschhauser F, Casasnovas O, Molina TJ, Feugier P, Gouill SL, et al.; Lymphoma Study Association. Lenalidomide in combination with R-CHOP (R2-CHOP) as first-line treatment of patients with high tumour burden follicular lymphoma: a single-arm, open-label, phase 2 study. Lancet Haematol. 2018 Sep;5(9):e403–10.
111 Chiu H, Trisal P, Bjorklund C, Carrancio S, Toraño EG, Guarinos C, et al. Combination lenalidomide-rituximab immunotherapy activates anti-tumour immunity and induces tumour cell death by complementary mechanisms of action in follicular lymphoma. Br J Haematol. 2019 Apr;185(2):240–53.
112 Goldfinger M, Xu M, Bertino JR, Cooper DL. Checking in on Lenalidomide in Diffuse Large B Cell Lymphoma. Clin Lymphoma Myeloma Leuk. 2019 Jun;19(6):e307–11.
113 Salles GA, Duell J, González-Barca E, Jurczak W, Liberati AM, Nagy Z, et al. Single-arm phase II study of MOR208 combined with lenalidomide in patients with relapsed or refractory diffuse large B-cell lymphoma: L-Mind. Blood. 2017;(130):4123.
114 Nowakowski GS, LaPlant B, Macon WR, Reeder CB, Foran JM, Nelson GD, et al. Lenalidomide combined with R-CHOP overcomes negative prognostic impact of non-germinal center B-cell phenotype in newly diagnosed diffuse large B-Cell lymphoma: a phase II study. J Clin Oncol. 2015 Jan;33(3): 251–7.
115 Castellino A, Chiappella A, LaPlant BR, Pederson LD, Gaidano G, Macon WR, et al. Lenalidomide plus R-CHOP21 in newly diagnosed diffuse large B-cell lymphoma (DLBCL): long-term follow-up results from a combined analysis from two phase 2 trials. Blood Cancer J. 2018 Nov;8(11):108.
116 Dada R. Lenalidomide Maintenance after R-CHOP Therapy in Diffuse Large B-Cell Lymphoma: Can It Be a Standard of Care. Acta Haematol. 2017;138(4):216–20.