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 onco-

logic therapy. The most important finding concerning lymphomas with a focus on immunomodulatory substances is also, therefore, highlighted.

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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

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 instru-

ment 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- κ B 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- κ B, 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 spurs 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 AITL 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-

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 fungoides (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 α 2b- 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 pro-tumoral 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 (R²-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.

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