



Genetic alterations of 9p24 in lymphomas and their impact for cancer (immuno-)therapy

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Abstract

Chromosome 9 harbors several relevant oncogenes related to hematolymphoid malignancies and one specific region, 9p24, has come into the focus of attention in the last years as it contains recurrently mutant genes of therapeutic interest. The most prominent genes of this locus are *programmed death ligands 1 and 2 (PDL1/PDL2)*, with the amplification of *PDL1* being a hallmark of both classical Hodgkin and primary mediastinal B cell lymphoma, and *Janus kinase 2 (JAK2)*, which is point-mutated in myeloproliferative neoplasms and other myeloid malignancies, and rearranged in *PCMI-JAK2*-positive myeloid/lymphoid neoplasms with eosinophilia. Finally, this locus contains the *lysine (K)-specific demethylase 4C (KDM4C/JMJD2C)*, which is also relevant for oncogenesis. Activation of these genes is effectuated, as exemplified, by multiple mechanisms, which is rather unique to oncogenes, since they are usually affected by just one type of mutation, and points towards the central role of these genes in tumor initiation and growth. Amplifications and, less frequently, translocations are the most common findings for *PDL1/PDL2* and *JAK2* in lymphomas. In this review, we describe the role of genes located on chromosome 9p24 and their derived proteins in diverse subtypes of lymphomas, with a special focus on *PDL1* and *PDL2*, which are becoming a central target of immunotherapy, not only in classical Hodgkin lymphoma but also in various types of solid cancers. We also elucidate the role of the surgical pathologists in this setting — concerning what they can contribute — both diagnostically and predictively.

Keywords Chromosome 9p24 · PDL1 · PDL2 · JAK2 · Lymphoma

Introduction

Chromosome 9 has a length of 138,394,717 million base pairs, and is the basis for 774 coding genes [1, 2], representing 4.5% of the total amount of human nuclear DNA. It contains several genes related to hematopoietic functions, ranging from *ABO* histo-blood group glycosyltransferases, *Abelson murine leukemia viral oncogene homolog 1 (ABL1)*, to genes at the 9p24 locus (Fig. 1). The latter has recently gained a lot of interest, as several genes implicated in hematolymphoid malignancies are located in this region.

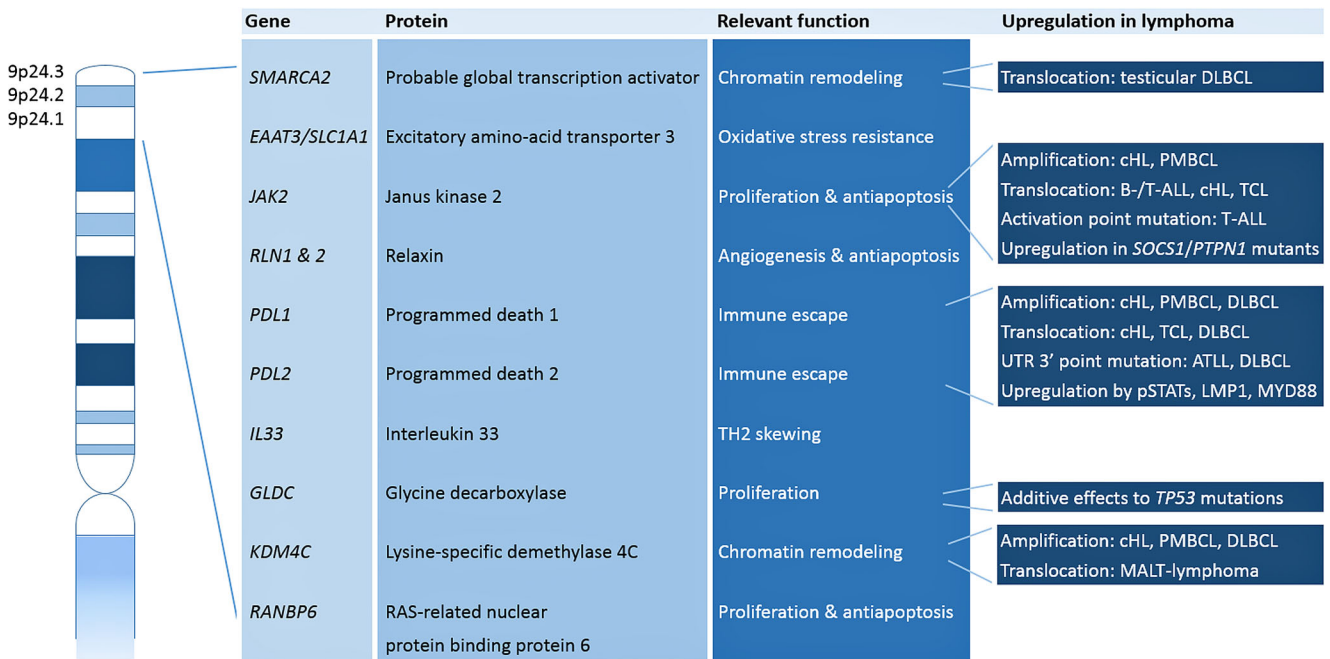
Programmed death ligands 1 and 2 (PDL1/PDL2) are the genes of this locus most attention has been paid to at, as they are key targets of immune checkpoint inhibition. They exert their function by inducing T cell anergy and exhaustion [3].

Another gene located here is *Janus kinase 2 (JAK2)*, mostly known in relation to myeloproliferative neoplasms such as polycythemia vera, primary myelofibrosis, and essential thrombocythemia, in which point mutations (the best-known being *JAK2 V617F*) are even part of the disease definition [4]. Furthermore, fusions of *JAK2* and the *pericentriolar material 1 (PCMI)* gene, mostly leading to myelodysplastic/myeloproliferative neoplasms with eosinophilia and fibrosis, have been described by us and other groups [5, 6] and were considered by the current WHO classification of tumors of hematopoietic and lymphoid tissues as a separate entity in the chapter of myeloid/lymphoid neoplasms with eosinophilia and recurrent gene rearrangements [7]. Moreover, *JAK2* aberrations have also been recognized in subsets of lymphomas [8–10]. Another gene at 9p24, seeming to play a role in lymphomas, along with other much commonly mutant epigenetic modifiers such as the *histone-lysine N-methyltransferase 2D (KMT2D)* [11], is the *lysine (K)-specific demethylase 4C (KDM4C/JMJD2C)* [12].

Immunotherapy of cancer has a long history dating back to early anti-cancer vaccination attempts [13]. It has recently

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Gene	Protein	Relevant function	Upregulation in lymphoma
<i>SMARCA2</i>	Probable global transcription activator	Chromatin remodeling	Translocation: testicular DLBCL
<i>EAAT3/SLC1A1</i>	Excitatory amino-acid transporter 3	Oxidative stress resistance	
<i>JAK2</i>	Janus kinase 2	Proliferation & antiapoptosis	Amplification: cHL, PMBCL Translocation: B-/T-ALL, cHL, TCL Activation point mutation: T-ALL
<i>RLN1 & 2</i>	Relaxin	Angiogenesis & antiapoptosis	Upregulation in <i>SOCS1/PTPN1</i> mutants
<i>PDL1</i>	Programmed death 1	Immune escape	Amplification: cHL, PMBCL, DLBCL Translocation: cHL, TCL, DLBCL
<i>PDL2</i>	Programmed death 2	Immune escape	UTR 3' point mutation: ATLL, DLBCL Upregulation by pSTATs, LMP1, MYD88
<i>IL33</i>	Interleukin 33	TH2 skewing	
<i>GLDC</i>	Glycine decarboxylase	Proliferation	Additive effects to <i>TP53</i> mutations
<i>KDM4C</i>	Lysine-specific demethylase 4C	Chromatin remodeling	Amplification: cHL, PMBCL, DLBCL Translocation: MALT-lymphoma
<i>RANBP6</i>	RAS-related nuclear protein binding protein 6	Proliferation & antiapoptosis	

Fig. 1 Schematic representation of the short arm of chromosome 9 with its 9p24 region and respective oncogenically relevant genes, their coded proteins, functions, and mechanisms of deregulation relevant to lymphomas

gained a tremendous amount of interest in the wake of the discovery of the PD1/PDL1 checkpoint axis as a new therapeutic option in oncology [14]. By overcoming the suppression of the immune system induced by tumor cells, both locally and systemically, the therapeutic approach of PD1/PDL1 immune checkpoint inhibition improves the possibility of patients' organisms to fight cancer. However, this goes in hand with prototypic side effects resembling graft versus host like changes or autoimmune disorders due to immune system (hyper) activation [15].

In this review, we will summarize, from a surgical pathologist's perspective, the different types of genetic alterations of the 9p24 locus and discuss their implications in lymphomas.

Genetic alterations of the 9p24 region

Alterations of 9p24 and the genes situated here can occur in different ways and mainly consist of amplifications and translocations, while single nucleotide (point) mutations as well as insertions and deletions are not of substantial relevance.

Amplifications

Concerning *PDL1* and *JAK2*, amplifications (Fig. 2) are known to occur in classical Hodgkin lymphomas (cHL), mainly the nodular sclerosis subtype, and primary mediastinal B cell lymphomas (PMBCL) [10, 16]. It also has to be kept in mind that especially in PMBCL and cHL, both harboring 9p24 amplifications in approximately a third of instances,

usually several genes are affected as the amplicon encompasses about 3.5 Mb of DNA. Indeed, Rui et al. were the first to describe that more than 10 genes involved in lymphomagenesis are amplified by 9p24 gains [17]. They also suggested a considerable additive “cooperative effect” of *KMD4C* and *JAK2* that leads to increased proliferation and survival advantage of neoplastic cells due to the cumulative effect of epigenetic changes and increased JAK2 downstream signaling.

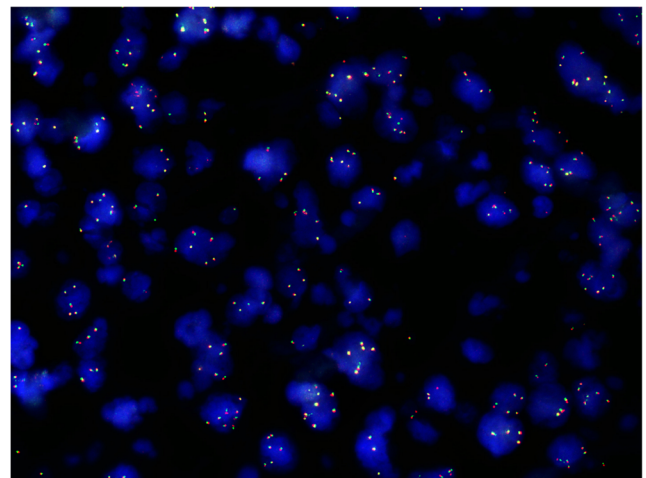


Fig. 2 Multiple *JAK2-PDL1* locus FISH signals indicating a 9p24 gain in a primary mediastinal B cell lymphoma case, $\times 1000$. Note 3 to 6 fused red and green FISH signals/case with the RP11-3H3 and RP11-2302 (red) and RP11-28A9 and RP11-60G18 (green) bacterial artificial chromosome probes for the 5' and 3' regions of *JAK2*. Analogous results can be achieved by, e.g., commercially available *JAK2* break-apart FISH probes

Translocations

Recently, van Roosbroeck et al. have described several translocations of *PDL1* and *PDL2* [9]. Such translocations occur both in cHL and in T cell lymphomas (Fig. 3) showing a plethora of translocation partners. In cHL, a frequency of 2% for *PDL1* translocations was reported, in contrast to 25% of cases showing 9p24 amplifications [16]. *PDL1* rearrangements with *IGH*, *PIM1*, and *TP63* have also been described in diffuse large B cell lymphomas (DLBCL) [18], where they mainly occur in the non-germinal center B cell (non-GCB) subtype.

Less is known about specific alterations of *JAK2* and *KDM4C* in lymphomas. *JAK2-SEC31 homolog A (SEC31A)* fusions have been described in cHL [8]; *JAK2-ataxin 2 like (ATXN2L)* fusions, in CD4-positive cutaneous T cell lymphoma [19]; *JAK2-PCMI* fusions, in exceptionally rare cases of T cell acute lymphoblastic leukemia/lymphoma and B cell acute lymphoblastic leukemia [20]; and *KMD4C-IGH* fusions, in mucosa-associated lymphoid tissue (MALT) lymphomas [21]. In addition, *E twenty-six variant 6 (ETV6)-JAK2* fusions are observable in B- and T cell acute lymphoblastic leukemia/lymphoma [5, 22–24].

Other genetic alterations of genes at 9p24

Alterations of *PDL1* or *PDL2* by single nucleotide mutations or insertions/deletions seem not to play a major role in lymphomas. However, Kataoka et al. reported a disruption of *PDL1*'s 3'-untranslated region (UTR) leading to a marked increase of PDL1 expression, being stabilized by truncation of the 3'-UTR, in cases of adult T cell leukemia/lymphoma as well as DLBCL [25]. An inversion between *SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a, member 2 (SMARCA2)*, which is also located at

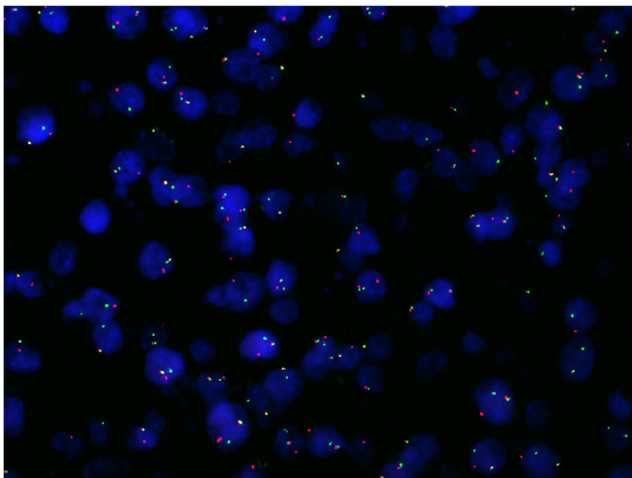


Fig. 3 Rearrangement of the *JAK2-PDL1* locus with split red and green FISH signals with the probes mentioned in Fig. 2 in a peripheral T cell lymphoma case, $\times 1000$

9p24, and *PDL1* has been described in testicular DLBCL, in which this alteration removes a part of the 3'-untranslated region of *PDL1* and, most likely, increases the respective protein expression [26].

Role of the surgical pathologist

By means of diagnostic surgical pathology techniques, both structural and numeric genetic changes of the 9p24 locus, i.e., rearrangements and amplifications, as well as overexpression of the key players PDL1 or JAK2 and their downstream targets such as phosphorylated (p)-STATs (Fig. 4) can be examined. Although PDL1 expression (Fig. 5) is not as mandatory for clinical trials in lymphomas as in solid tumors such as lung carcinomas [29], knowledge on its status can additionally help in some challenging differential diagnostic instances [28], be prognostically informative [30] or possibly predict sensitivity to PD1/PDL1 immune checkpoint inhibition [31], as illustrated later on.

The key players on 9p24

In the second part of this review, we summarize the role of the different genes located on 9p24 and their derived proteins in lymphomagenesis. Furthermore, we discuss how these genes' status can contribute to diagnosis, therapy decision making, and prognosis.

PDL1/PDL2—control of the immune system

PDL1/PDL2 are the best-known genes on 9p24, and their altered expression is a hallmark of immunomodulation used by tumor cells to manipulate host's immune system to improve chances of the tumor to prevail. PDL1/PDL2's mechanistic role in

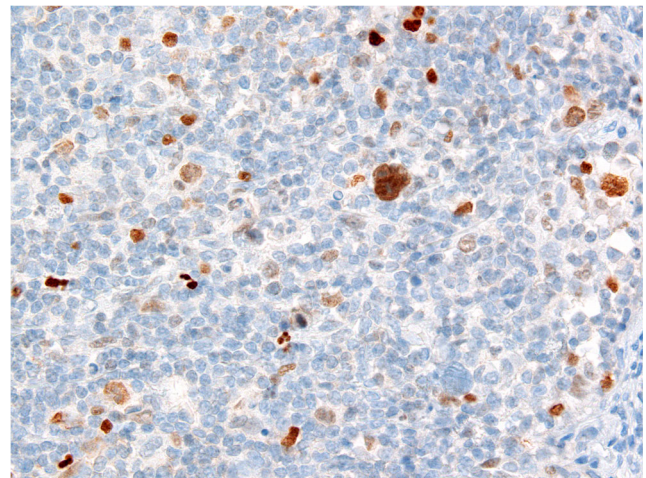


Fig. 4 Overexpression of phosphorylated STAT5 (clone 8-5-2 from Merck; antibody-handling conditions exactly as described in [27]) in a classical Hodgkin lymphoma case, $\times 360$, chromogen diaminobenzidine

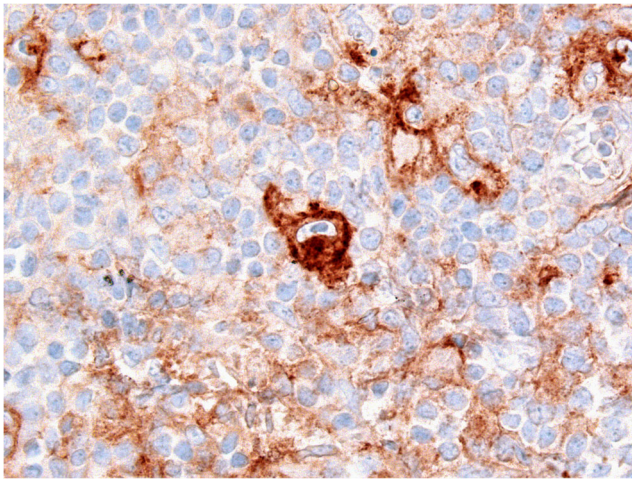


Fig. 5 Strongly PDL1 (clone E1L3N from Cell Signaling; antibody-handling conditions exactly as described in [28]) positive Hodgkin cell of classical Hodgkin lymphoma, $\times 400$, chromogen diaminobenzidine

lymphoma progression is already well established and used in clinical trials. The prognostic and predictive role of PDL1/PDL2 is still a matter of debate.

Background

PD1 and its ligand PDL1 were discovered in the early and late 1990s, respectively [32, 33]; the genes encoding both PDL1 and PD1's second ligand, PDL2, the expression of which is more restricted than that of PDL1 [34], are located on chromosome 9p24. PD1 contains an immunoreceptor tyrosine-based switch motif (ITSM) and an immunoreceptor tyrosine-based inhibitory motif (ITIM); ITSM is essential for the transmission of inhibitory signals [35]. After ligation with PDL1 or PDL2, ITSM and ITIM undergo phosphorylation, which consequently leads, through activation of several downstream signaling cascades, to depression of intracellular ZAP70, AKT, ERK, NF- κ B and AP1 activity, and net T cell inactivation and impedes T cell proliferation [36]. By means of this the PD1/PDL1 axis is an important checkpoint for controlling T cells, and it can both inhibit effector T cells as well as stimulate immunosuppressive regulatory T cells [3, 37]. Unlike cytotoxic T lymphocyte-associated protein 4 (CTLA4), PD1 and its ligands exert their function in the peripheral tissues and, thus, seem to lead to a primarily local and not to a systemic affection of the immune system [38, 39]. CTLA4 impedes both the cell cycle and several intracellular pathways in T cells; it affects T cells in primary lymphatic organs such as the bone marrow and the thymus. In contrast to PDL1, it does not contain ITIMs [40].

Genetic alterations of *PDL1/PDL2* and mechanisms of activation

The genetic mechanisms of PDL1 overexpression have been first discovered in cHL and mainly consist of 9p24 locus

amplifications (Fig. 2). Similar alterations have been found in PMBCL [41] and, to a lower extent, in DLBCL [18] as well as in lymphomas of immune-privileged sites such as the central nervous system and the testis [42]. Other less common genetic mechanisms of PDL1 upregulation and activation comprise translocations [9, 18] (Fig. 3) or disruption of the 3'-UTR of *PDL1*.

PDL1 expression can be regulated by other mechanisms not directly involving aberrations of its gene. It has been shown that PDL1 is inducible by activation of the JAK/STAT pathway [10]. In lymphomas, L265P mutant *myeloid differentiation primary response gene 88* (*MYD88*) can activate JAK2 and PDL1 [43]. In addition, PDL1 expression can be induced by the latent membrane protein 1 (LMP1) of Epstein-Barr virus (EBV) via activation of STAT (particularly STAT3)- and activated protein 1 (AP1)-mediated pathways, which is observable in cHL [44] and extranodal NK/T cell lymphoma of the nasal type [45]. As to be expected, other causes of STAT-activation also enhance PDL1-expression as seen in anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) [46], or in relation to active cytokine signaling [47], which is commonly observable in, e.g., activated B cell (ABC)-like DLBCL and cHL [48, 49]. Finally, at least in DLBCL, translocations of *IGH*, *PIMI1*, and *TP63* with the *PDL1* locus that lead to the latter's overexpression have been described too [18].

Expression of *PDL1/PDL2* and its use in the differential diagnosis of lymphomas

We and other groups have investigated the expression of PDL1 and, to a smaller extent, PDL2 in lymphomas with consistent results regarding most entities [28, 50]. It could be demonstrated that, apart from cHL and nodular lymphocyte predominant Hodgkin lymphoma (NLPHL), up to a third of DLBCL, mainly those of the ABC type [51], and PMBCL express PDL1; in other B cell lymphoma entities, PDL1 is only expressed in a low percentage of cases [28]. PDL1 shows a homogenous staining in lymphomas (Fig. 5), yet in chronic lymphocytic B cell leukemia (CLL), PDL1-expression has been described to be confined to the proliferation centers [52]. PDL1 expression is observed both in the tumor microenvironment (particularly in tumor-infiltrating macrophages; Fig. 6) and in lymphoma cells, which is in contrast to PD1-expression that is primarily seen in T cells of the microenvironment [53, 54]. In T cell- and histiocyte-rich B cell lymphomas (THRBCL), PDL1-expression is seen in both T cells and histiocytes, while the tumor cells themselves are negative for PDL1 as we could demonstrate in double-staining approaches [28]. This is a particularly helpful feature in the difficult differential diagnosis of THRBCL and cHL and NLPHL. The latter two entities show detectable PDL1 expression in the tumor cells in 70 to 50% of cases, respectively, in contrast to THRBCL. Admittedly, result interpretation might be occasionally difficult since all three diseases are characterized by

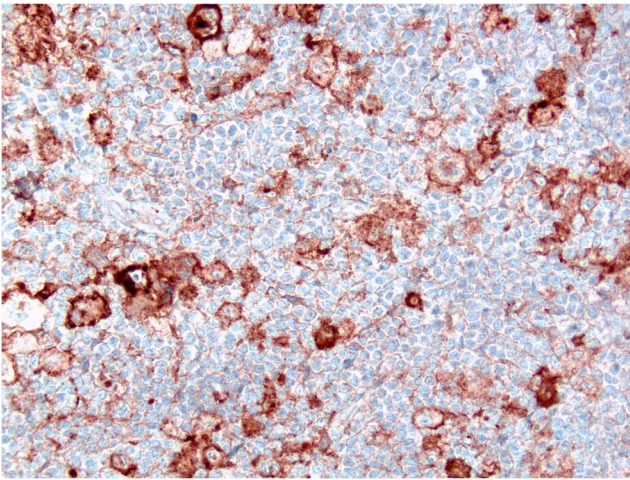


Fig. 6 Multiple PDL1 positive tumor-infiltrating macrophages (TIM) in classical Hodgkin lymphoma intermingled with a few very strongly positive Hodgkin- and Reed-Sternberg cells (HRSC), $\times 200$, chromogen diaminobenzidine. Note that those TIM considerably outnumber the HRSC and, thus, more substantially contribute to the total PDL1-positivity in respective cases

high numbers of PDL1-positive tumor-infiltrating macrophages, an issue that can be elegantly approached by double-stainings for MUM1/PDL1 [35] in case of suspected cHL, for OCT2/PDL1 in NLPHL and BCL6/PDL1 in THRBCL [28] to unequivocally identify respective tumor cells for estimation of PDL1 expression. In T cell lymphomas, PDL1 expression is observable in peripheral T cell lymphoma, ALK-positive ALCL, extranodal NK/T cell lymphoma of the nasal type, cutaneous T cell lymphoma, as well as in adult T cell leukemia/lymphoma [55], which should be taken into differential diagnostic consideration. Expectedly (rev. in [35]), all EBV-associated malignancies with latency types 2 and 3 of virus infection are anticipated to be PDL1 positive.

Shi et al. performed the first larger study investigating the expression of PDL2 in lymphomas in 2014 [56]. Using a cutoff of 20% of tumor cells and not considering the staining intensity, similar results were obtained as in a previously published study on the expression of PDL1 [50]. More than two thirds of PMBCL cases were positive for PDL2, while most DLBCL cases did not show PDL2 expression. This finding led to propose PDL2 as a potential discriminatory marker for PMBCL and DLBCL (specificity 97%, sensitivity 72%), which remains to be validated. PDL2-expression substantially correlated with *PDL2* copy number gains, which was considerably more pronounced than the rather weak link between expression of PDL1 and *PDL1* gene amplifications in lymphomas [28].

PDL1 as a therapeutic target of lymphomas

There are already several finished as well as ongoing, mainly phase 2 trials regarding the PD1/PDL1 immune checkpoint inhibition in B cell lymphomas (reviewed in [57, 58]). Due to

the high expression levels of PDL1, cHL was the first lymphoid malignancy in which this type of therapy was applied. The initial seminal study in a cohort of 18 patients with refractory/relapsing cHL showed complete remissions (CR) in 17% and partial remissions (PR) in 70% [59]. Subsequent studies showed similar encouraging results ($n = 31$, CR 16%, PR 48%/ $n = 210$, CR 22%, PR 47%) [60, 61]. Currently, two antibodies (nivolumab and pembrolizumab) are approved by the American and European agencies for treatment of relapsed and/or refractory cHL [57, 58]. Combinatory/additive approaches of radio- and chemotherapy together with PDL1-centered immunotherapy have been successfully tested in first cohorts too [62]. These approaches base on the hypothesis that the damage induced by radio- and chemotherapy renders tumor cells more “visible” to an immune system (re-)activated by immune checkpoint inhibition [63]. In PMBCL, which shares 9p24 amplifications with cHL, first clinical trials using similar approaches have been reported as well, yet the overall response rates are approximately 40% (heavily pretreated patients, $n = 18$) [64]. In DLBCL, PDL1-targeted therapy has only been tested in small cohorts or cohorts mixed with other entities such as PMBCL and small B cell lymphomas, and data still remains somewhat inconclusive [65], which can be related to, e.g., the less prominent interactions of PMBCL with its microenvironment compared to cHL. In small B cell lymphomas such as follicular lymphoma (FL), mantle cell lymphoma, and CLL, immunotherapy in general has not been investigated at a larger scale; in relapsed FL, a first study combining PDL1-centered immunotherapy and rituximab has shown promising results ($n = 29$, CR 52%, PR 14%) [66]. As in cHL, adding PDL1 blockers to conventional therapy regimens has been reported to imply a benefit in comparison to only very limited treatment response if given as a single agent [58]. PDL1 inhibition in lymphomas of immunoprivileged sites may deserve further evaluation too (5 investigated cases) [67].

So far, no drugs specifically targeting PDL2 have been developed [57].

While clinical trials with PD1/PDL1 immune checkpoint inhibition in T cell lymphomas in general have thus far shown limited response rates [65], in extranodal NK/T cell lymphoma of the nasal type, which is known to have an aggressive and mostly fatal course, the situation is different. A small case series ($n = 3$) has shown that PDL1 is substantially upregulated in this entity due to EBV infection of the tumor cells, and PD1 blockade is very effective in otherwise fatal relapses of this disease [68].

The impact of PDL1 expression on prognosis and therapy response

The prognostic and predictive role of PDL1 expression in lymphomas is still a matter of debate. Due to the lack of large

randomized trials as available in solid tumors such as lung carcinomas, most experience is gathered from retrospective studies, which might be difficult to compare, especially when dealing with rarer entities such as PMBCL. This might be not only due to limited case numbers but also due to different antibodies or different evaluation strategies being used. A large study on 1253 DLBCL patients showed negative correlation between PDL1 expression and overall survival [51]. However, Xing et al. could show that PDL1 expression in DLBCL treated with standard R-CHOP treatment is associated with a better overall survival rate, yet not with other important variables such as remission after first therapy, relapse- or progression-free survival [69]. Bledsoe et al. demonstrated that high PDL1 expression and low MUM1 expression is correlated with better outcome than vice versa expression of these two proteins in PMBCL [30]. In our opinion, the “conflicting” results on the prognostic impact of PDL1 expression in lymphomas are on the one hand linked to technical issues related to diagnostic antibodies and to difficulties in distinguishing expression on tumor cells and tumor-microenvironment cells; on the other, probably due to the subentity-specific and patient’s immunologic/immunogenetic-specific context, PDL1’s rather moderate prognostic effect might be highly modified by the specific type of therapy applied (e.g., whether steroids, cereblon-targeted therapy, or other immunomodulatory compounds are given or not).

In a landmark study of cHL, 9p24 alterations were associated with inferior outcome (in conventionally treated patients); on the other hand, 9p24 alterations in general seemed to be an indicator for response to PD1/PDL1 immune checkpoint inhibition [31]. Several smaller cohort studies suggested that best responses with immune checkpoint inhibition (targeting PD1/PDL1) are seen in lymphomas harboring specific 9p24 alterations such as cHL-, PMBCL-, and EBV-associated lymphomas and lymphomas of immunoprivileged sites [67]. In therapy-refractory lymphomas, there seems to be a discrepancy between PDL1 expression and amplification of the *PDL1* locus, supporting the hypothesis that other mechanisms, next to gene amplifications, are involved in upregulation of PDL1 expression [70].

Hands-on PDL1 immunohistochemistry

Several antibodies for PDL1 immunohistochemistry are available for routine and research purposes. In lung carcinomas, immunohistochemical evaluation of PDL1-expression both in tumor cells and in the microenvironment is an essential part for treatment decision, and depending on the drug used, several antibody clones and detailed guidelines for their respective evaluation are available [29, 71]. For lymphomas, no such guidelines exist, and results of the PDL1 immunohistochemistry are not part of a treatment decision. However, apart from being useful in some difficult differential diagnoses as detailed

above, information on the PDL1 expression quality is regularly asked for by our clinical colleagues particularly in relapsed/refractory instances. In our study on PDL1 expression in lymphomas, we directly compared the performance of two different clones, E1L3N and SP142 [28]. In our hands, both antibodies showed good practicability, with SP142 being less sensitive and considerably more expensive than E1L3N, so the latter clone was used in our lymphoma cohorts. Other clones, which are currently mainly used in PDL1 evaluation of lung carcinomas, such as SP263 und 22C3 [72], show in our hands result very similar to E1L3N when evaluated in lymphomas, so that all these clones might be considered equivalent for the particular circumstances of lymphoma diagnostics. Indeed, the main differences between the assays are rather linked to the antigenic retrieval conditions, to which the tissue sections are exposed as per protocol, than to genuine biological issues.

JAK2—functions beyond mere signal transduction

JAK2 is an important signal transducer and is also involved in activation of histones and is thus directly influencing gene expression. It plays a role in both B cell and T cell lymphomas, and its therapeutic role has not yet been thoroughly explored in lymphomas.

Background

JAK2 is a member of a family of cytoplasmic tyrosine kinases, comprising JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). JAKs are associated with cytokine receptors, which themselves lack intrinsic tyrosine kinase activity. JAKs activate target genes by phosphorylation of signal transducer and activator of transcription (STAT) factors. JAKs can also activate other signaling cascades such as the mitogen-activated protein (MAP) kinase and the phosphatidylinositol 3 (PI3)-kinase/protein kinase B (also called AKT) pathway. Besides phosphorylating proteins of signal transduction cascades, JAK2 can also be found in the nucleus directly phosphorylating histone H3, which leads to chromatin remodeling (non-canonical JAK signaling) [73].

Genetic alterations of JAK2 and mechanisms of activation

JAK2 point mutations are common in myeloid neoplasms such as the *JAK2* V617F mutation in myeloproliferative neoplasms [74] or mutation in exon 12 in polycythemia vera [75]. However, mutations in lymphoid neoplasms have only been found in subsets of acute lymphoblastic leukemia but not in lymphomas [76, 77]. With respect to lymphomas, *JAK3*, the gene of which is located on chromosome 19, is the primarily mutant JAK family member [78]. The very rare translocations *JAK2-SEC31A* in cHL [8] and *JAK2-PCMI* in B/T cell acute lymphoblastic leukemias [20] have been mentioned before. In

the latter, the fusion partner PCMI supports oligomerization and, thus, activation of JAK2 and increases STAT-, particularly STAT5-mediated signaling [79]. Nevertheless, JAK2 has an important function in lymphomas as being confirmed in JAK2 inhibition experiments in in vitro models [17]. *JAK2* is part of the 9p24 amplicon in cHL and PMBCL, which causes its enhanced activity in these entities (Fig. 7) even in the absence of activating mutations [17]. It has been shown that V617F mutant JAK2 can stimulate PDL1 expression in myeloproliferative neoplasms [80], so — provided these findings can be translated to lymphoma cells as well — another direct link between JAK2 and PDL1 has been found.

It has also become evident that, particularly in lymphomas, alterations of other genes can lead to increased JAK2 activation and, thus, enhanced JAK2-mediated signaling and cell proliferation: inactivating mutations of *suppressor-of-cytokine-signaling 1 (SOCS1)*, a downregulator of JAK2, have been first described in cHL and PMBCL lacking 9p24 amplifications [81]. Later studies of the same group and our own observations show that *SOCS1* mutations and 9p24 amplifications are not as mutually exclusive as previously thought, and can also be found in DLBCL and small B cell lymphomas as well as with a “pervasive” high frequency in cHL [27, 82]. In addition, JAK2 can be dephosphorylated and, thus, inactivated by tyrosine-protein phosphatase non-receptor type 1 (PTPN1), which is also mutated in a subset of cHL and PMBCL [83]. Mutations of *STAT*-genes themselves have been described in small subsets of DLBCL [84], and similar to *SOCS1*, concurrent mutations including *JAK2*, *SOCS1*, and *STAT6* have been described in PMBCL [85]. Finally, *MYD88*, which is rather linked to activation of the NF- κ B pathway, also interferes with JAK/STAT signaling, as Ngo et al. demonstrated in cell culture experiments of ABC DLBCL cell lines that *MYD88* L265P mutant clones rely on JAK-

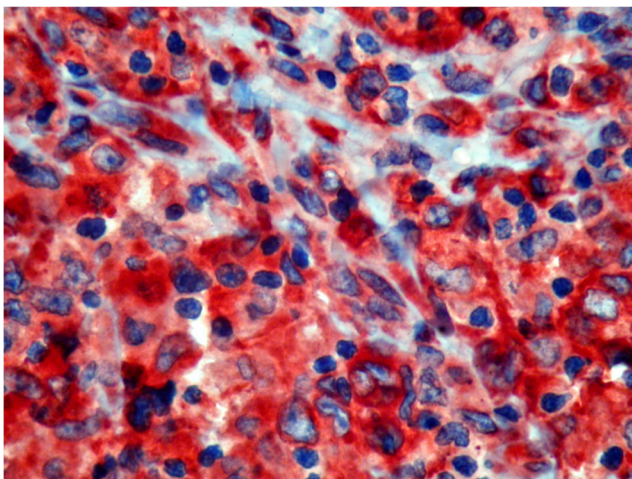


Fig. 7 Overexpression of phosphorylated JAK2 (clone C80C3 from Cell Signaling; 1, antibody-handling conditions exactly as described in [16]) in a primary mediastinal B cell lymphoma case, $\times 400$, chromogen aminoethyl carbazole

related activation of STAT3 for NF- κ B mediated cell proliferation and survival [86].

In T cell lymphomas, JAK2 may also play a role. In angioimmunoblastic T cell lymphoma, gain of function mutations of *JAK2* have been observed in 2/85 cases [87]. *JAK2-PCMI* fusions are known to occur in a small subset of T cell acute lymphoblastic leukemia/lymphoma [20]. In addition, Roncero et al. [88] recently described some new *JAK2* mutations and fusions in this entity leading to JAK2 upregulation associated with activation of LIM domain only 2 (LMO2), a key molecule in this entity.

Expression of JAK2

A previous large scale study of our group could confirm the high prevalence rate of *JAK2* gains in cHL and PMBCL [16]. An analysis of phosphorylated, and, thus, functional p-JAK2, p-STAT3, and p-STAT5 protein expressions showed, as to be expected, that their phosphorylation correlated with *JAK2* gains; furthermore, p-STAT3 expression defined a group of non-GCB DLBCL with inferior outcome.

Importantly, with respect to 9p24 gains, besides canonical and non-canonical JAK signaling, JAK2 synergistically enhances PDL1 expression, which has been shown by Green et al. in cell culture experiments [10], and JAK2 inhibition had a direct effect on PDL1 expression in these cells.

The interactions between JAK2 and KDM4C are discussed in the next section of this review.

There are no practical published guidelines on how to qualitatively and quantitatively analyze JAK2 and p-JAK2 expressions; moreover, the p-JAK2 staining is prone to fixation artifacts, and as so far these markers are mainly applied in research settings and not in the diagnostic routine. Yet, in the context of myeloproliferative malignancies, application of p-STAT5 stainings can serve as a diagnostic substitute for pathologic activation of JAK2 signaling and has some routine applications [89, 90]; the relevance of which remains to be determined in lymphomas.

JAK2 as a therapeutic target of lymphomas

One of the first clinical trials using JAK2 inhibition with ruxolitinib in cHL has recently been published (NCT01877005) [91]. The overall response rate was only 9.4% with partial responses only; transient stable disease was achieved in 34% of the 32 enrolled patients. The authors suggest that despite this limited success, ruxolitinib might still be included in combination therapy approaches with other drugs due to its minor toxicity profile.

KMD4C—A key to the epigenome

The 9p24 locus plays a role in epigenetic regulation hosting the *KMD4C* gene. *KMD4C* synergistically interacts with other proteins such as *JAK2*. However, its therapeutic potential still needs further evaluation.

Background

Epigenetic regulation of genes is mainly effectuated by histone methylation or acetylation or by direct methylation of DNA [92]. *KMD4C*, also known as *JMJDC2* and *gene amplified in squamous cell carcinoma 1 (GASC1)*, is a member of the Jumonji family of demethylases and exerts its function by removing methyl groups from the repressive histone mark, trimethylated lysine 9, of histone H3 (H3K9me3), thus, leading to gene activation [93]. It acts contrarily to *histone-lysine N-methyltransferase 2D (KMT2D/MLL2)*, a histone methyltransferase. Importantly, *KMT2D* is the gene with the highest mutational frequency in DLBCL (20–35% of cases) and FL (up to 80% of cases), with mutations leading to a loss of its function [94].

Genetic alterations of *KMD4C* and mechanisms of activation

A role for *KMD4C* in lymphoid malignancies has first been suggested in MALT lymphomas in 2008 [21]. Two years later, a seminal study of Rui et al. revealed the co-amplification of *JAK2* and *KMD4C*, supposed to be a new way to modify the epigenome of lymphomas [17], and *JAK2* and *KMD4C* were titled “partners in crime” by the accompanying editorial [95]. This study revealed a new role for *JAK2* to activate histones, as described in the section above, as well as showed the importance of epigenetic regulation in lymphomas. The synergistic functional importance of these two oncogenes has been corroborated by experimental evidence showing that inhibition of *JAK2* and *KMD4C* knockdown lead to cell death, and that *JAK2* and *KMD4C* synergistically upregulate *MYC* expression in lymphoma cells. Direct interactions between *KMD4C* and *PDL1* have not been described yet.

Epigenetic modifiers as a therapeutic target of lymphomas

Therapeutic epigenetic modification has been already applied to DLBCL and FL [96]. Here, besides the already mentioned *KMT2D* mutants, key molecularly selected instances might be *enhancer of zeste homolog 2 (EZH2)* and *cAMP-response element-binding binding protein/E1A-associated protein p300 (CREBBP/EP300)* mutant cases. First clinical phase 1 and phase 2 studies have been or are currently undertaken utilizing histone deacetylase inhibitors. In vitro studies have produced conflicting equivocal results so far [96]. In cHL and PMBCL, epigenetic-targeted therapy has yet not been studied in clinical trials.

Is there still something else? Less well-studied genes on 9p24 with potential oncogenic importance

What is known about the other genes encoded by the region 9p24? Besides *PDL1*, *PDL2*, *KMD4C*, and *JAK2*, 6 genes have been shown to be upregulated in lymphomas with 9p24 amplifications [17]:

Glycine decarboxylase (GLDC) is involved in the folate mediated one-carbon metabolism, and its upregulation is associated with tumorigenesis, tumor cell growth, and poorer outcome in lung cancer patients [97]. A higher expression of *GLDC* has been found in lymphoma cell lines harboring *TP53* mutations [98], and this was accompanied by changes in glycolysis and glycine/serine metabolism fostering tumor cell growth.

RAS-related nuclear protein binding protein 6 (RANBP6) has been initially identified to be a potential oncogene as it was included in the minimal amplification region of 9p24 in PMBCL [17]. In cell culture experiments, knockdown of *RANBP6*, along with *KMD4C* and *JAK2*, had an effect on cell survival by induction of apoptosis in PMBCL and cHL, yet not in DLBCL cell lines [17]. *RANBP6* is an 80% homolog of *RANBP1* (the latter located at 22q11.21). *RANBP1* stimulates the GTPase activity of RAN and is important in the complex process of mitosis [99]. So far, its function and relevance in lymphomas has not been elucidated further.

The remaining identified four genes, *C9orf46*, *KIAA1432*, *KIAA2026*, and *UHRF2*, have not been yet linked to lymphomagenesis.

Other genes located on 9p24 such as *relaxin 1* and *2 (RLN1/RLN2)*, *interleukin 33 (IL33)*, and *excitatory amino-acid transporter 3 (EAAT3)* have not been related to lymphomas, yet may play a general role in tumorigenesis (Fig. 1). *SMARCA2* (also located at 9p24) as a fusion partner of *PDL1* has been mentioned above.

Conclusions

Coming back to the question raised initially regarding the role of the surgical pathologist in this setting, many pathologists including our research group have been involved in and significantly contributed to studies deciphering alterations of the 9p24 locus and their importance for lymphomagenesis. By tools already implemented in routine diagnostic procedures such as FISH and sequencing techniques, amplifications, translocations, and mutations of genes at 9p24 can be actively sought for. Furthermore, protein expression of *PDL1*, *PDL2*, and *JAK2* as well as downstream targets of *JAK2* such as p-STATs can be quantified or at least visualized.

Diagnostically, PDL1 and potentially PDL2 can be used in equivocal cases with the differential diagnosis of cHL, PMBCL, and THRBCL. So far and in contrast to solid cancers, PDL1 scoring is not required for current therapeutic trials, and no guidelines exist regarding how to qualitatively and quantitatively analyze PDL1 in lymphomas. This, according to our experience, is a substantial lack and potentially also a restraint which has to be addressed accordingly.

Indeed, although 9p24 locus alterations in lymphomas do not (yet?) contribute significantly to the routine diagnostic work of surgical pathologists, investigation in this field by pathologists has certainly improved our knowledge on lymphomas and empowered clinical studies, as this chromosomal region 9p24 harbors several genes of interest concerning the emerging therapeutic approach of immune checkpoint inhibition therapy, targeted signaling inhibition, and epigenetic modulation. It has become evident that not only *PDL1* and *PDL2* are of significance in this regard, since other genes of the amplicon, particularly *JAK2* and *KDM4C* also play a distinctive additive role. All these genes and their derived proteins have a broad impact on the manipulation of the immune system as well as on tumor cell growth and survival. Their effects may provide a potential new starting point of chemotherapy-saving treatment approaches aiming at blocking several factors and pathways of this complex.

Contributions Both authors conceived and wrote the manuscript. Both authors gave final approval for publication. AT takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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