Plasmablastic lymphoma (PBL) is a rare, particularly aggressive B-cell malignancy with a median overall survival of less than 2 years (1). It was first described as a distinct entity in 1997 (2). Because of its link with acquired immune deficiency syndrome (AIDS), PBL was included in the group of AIDS-defining malignancies. Later, it was recognized that PBL can also occur in patients with other forms of immune deficiency, and occasionally even in apparently immunocompetent individuals (1). The name PBL was chosen, because the lymphoma cells resemble in their morphology, phenotype, and gene expression plasmablasts, which are B cells at an intermediate differentiation stage between activated mature B cells and plasma cells. Typical B-cell markers, including CD20 and PAX5, are downregulated, whereas markers of plasmablasts and plasma cells are consistently expressed. These latter markers include CD38, CD138, IRF4, XBP1, BLIMP1, and cytoplasmic immunoglobulin (1). A global gene expression study confirmed a plasmablast-like global gene expression pattern of PBL cells (3). PBL is considered to derive from germinal center reaction experienced plasmablasts (1).

First studies regarding the pathogenesis of PBL identified a latent infection of the lymphoma cells by Epstein-Barr virus (EBV) in more than half of the cases. EBV is well known to play a role in the pathogenesis of several types of B-cell lymphomas, and to have a B-cell–immortalizing capacity (4). PBL typically show a latency type I EBV program, with expression of only a few EBV-encoded genes, so that the transforming role of EBV in PBL is perhaps less extensive than in other EBV-associated B-cell lymphomas. A second pathogenic hallmark of PBL is translocations of the MYC proto-oncogene, mostly involving the immunoglobulin loci as translocation partner. These translocations are present in about 50% to 60% of cases (1). A further study described mutations in the PRDM1 tumor suppressor gene in 8 of 16 cases studied (5). Other than this, few data on genetic lesions in PBL exist.

In this issue of Blood Cancer Discovery, a first large-scale analysis of the landscape of somatic mutations in human immunodeficiency virus (HIV)–associated PBL is presented by Liu and colleagues (6). Fifteen cases of such lymphomas were studied by whole-exome sequencing and a further 95 lymphomas by targeted deep sequencing for 34 candidate genes, partly selected on the basis of the results of the initial exome sequencing. The most frequently mutated gene was STAT3, with nonsynonymous mutations in 42% of the 110 PBL. These mutations were mostly missense mutations, clustering in four codons, with strong indication that these are gain-of-function mutations. A predominant role of constitutive JAK–STAT signaling in the pathogenesis of PBL is further supported by the frequent detection of mutations in four further members of this pathway, that is, JAK1, JAK2, SOCS1, and PIM1. Overall 62% of the PBL cases studied showed nonsynonymous mutations in at least one of the five genes. Constitutive JAK–STAT signaling in the majority of PBL cases was validated by the detection of JAK–STAT target gene signatures enriched in gene expression profiles of PBL, and of frequent phosphorylated nuclear STAT3, which is the active form of this factor. There is likely a link between the STAT3 mutations and the consistent high expression of MYC in PBL, as MYC is a STAT3 target gene in B cells. Hence, the frequent STAT3 mutations may be an alternative or cooperating event besides the frequent MYC translocations and occasional MYC gains to mediate high MYC expression in PBL.

With frequent somatic mutations in four members of the RAS kinase family, the MAPK–ERK signaling pathway turned out to be the second most commonly mutated program in PBL. Mutations were found in NRAS, KRAS, BRAF, and MAP2K1, affecting 28% of PBL. The pattern of mutations indicates a gain of function for these mutated genes. A third pathway with mutations in several of its members in PBL is the NOTCH pathway. Here, mutations were found in NOTCH1, SPEN, and NCOA2, overall in 24% of cases. Although the functional consequences for most of the mutations remain presently unclear, some mutations indicate a pathway-activating effect. Additional recurrently mutated genes involve the NOTCH signaling pathway.
genes in the cohort of 110 PBL include TET2 (14% of cases), TP53 (9%), and MYC (9%).

Forty-six PBL cases were studied for copy-number alterations (6). One of the main findings was the detection of focal copy-number gains involving the CD44 gene. Indeed, CD44 was highly expressed in PBL, but also in cases without chromosomal gains, suggesting that various mechanisms can cause high-level protein expression of CD44. CD44 has multiple functions in B cells, can modify migration, homing, and microenvironmental interactions, and often has prosurvival effects. Other regions recurrently affected by chromosomal gains involve numerous histone genes. Supporting a functional relevance of these gains, PBL showed a strong enrichment of a histone expression signature in comparison with various other lymphomas. However, the pathophysiologic role of this finding remains currently unclear.

The study by Liu and colleagues (6) allows us to compare the genetic lesion landscape of PBL to that of related malignancies and thereby to distinguish pathways underlying its pathogenesis. PBL share with multiple myelomas, the most closely related B-cell lineage malignancy, frequent mutations in members of the RAS family and, based on earlier work (1), frequent rearrangements of the MYC gene. However, they differ from multiple myeloma by substantially higher fractions of cases with mutations in members of the JAK–STAT and NOTCH pathways. Particularly STAT3 mutations seem to be specific for PBL, as these occur rarely in multiple myeloma or diffuse large B-cell lymphomas (DLBCL), but in more than 40% of PBL. In another recent targeted sequencing study of PBL, STAT3 mutations were seen in 5 of 15 HIV+ PBL, but in 0 of 9 HIV− cases (7). This, on the one hand, validates the findings made by Liu and coworkers, and on the other hand indicates that STAT3 mutations may be particularly relevant for HIV-associated PBL.

Considering that among DLBCL the activated B-cell–like type (ABC-DLBCL) is most closely related to PBL in terms of cell of origin, it is remarkable how different the mutation profiles of these lymphomas are. Mutations in the JAK–STAT and NOTCH pathways and RAS family members are considerably more frequent in PBL, whereas mutations in NF-κB family members and epigenetic regulators (e.g., CREBBP, KMT2D) are much more prevalent in ABC-DLBCL. An earlier study suggested that frequent mutations in the tumor suppressor gene PRDM1, which plays a major role in terminal plasma cell differentiation, are a common genetic feature of PBL and ABC-DLBCL, with half of PBL analyzed carrying PRDM1 mutations (5), as already mentioned. However, in the work by Liu and colleagues, such mutations were seen in only 4% of cases, whereas another study found PRDM1 mutations in 20% (3/15) of HIV− PBL (7). Whether these differences are due to small patient numbers in the other studies, to patient groups from different continents, or other factors, such as different associations of PBL with HIV and/or EBV in the studies, needs to be clarified in future work.

Overall, from the work discussed here a picture emerges that for the pathogenesis of PBL alterations of single genes are not essential (although translocations of MYC and mutations of STAT3 are remarkably frequent), but a particular combination of genetic alterations in signaling pathways or gene families is disease-defining. Whereas in the early days of lymphoma research the detection of events in single genes in nearly all cases of an entity dominated the field, with translocations of MYC in Burkitt lymphoma, BCL2 in follicular lymphoma, and CCND1 (BCL1) in mantle cell lymphoma as the most famous examples, it was later recognized that in many lymphomas the deregulation of particular pathways by diverse events is more relevant for lymphoma pathogenesis than single genes (8). Often, these genetic lesions in a pathway are mutually exclusive, indicating that in these instances deregulation of one or the other pathway component is sufficient to act as oncogenic driver. However, there are also instances where several pathway members are mutated in a given case, suggesting that in these cases a disruption of the normal activity and regulation of the pathway at various stages is advantageous for cancer development. These patterns of genetic signaling pathway deregulation are also seen in the PBL, with, for example, co-occurrence of STAT3 mutations with JAK1 or SOCS1 mutations in several cases, but mutual exclusivity of NRAS and BRAF mutations.

The 110 PBL cases studied by Liu and colleagues were explicitly selected to be HIV-associated, and all informative cases from the whole-exome sequencing panel were EBV-positive, with no information on the EBV status of the cases in the screening panel. This prevents an evaluation of whether the pattern of mutated genes in PBL is linked to the HIV status of the patients and/or EBV infection of the lymphoma cells. On the background of a report that some genes are more frequently mutated in EBV+ PBL than in negative ones (7), and that in classic Hodgkin lymphoma, EBV-positive cases appear to have an overall much lower mutation load in their exome than virus-negative cases (9), this is an interesting topic for future studies and may inform about the relative contributions of viral infection and genetic lesions to the pathogenesis of this lymphoma.

It is also remarkable that even in the era of viral control by antiretroviral therapy, the risk of developing a B-cell lymphoma is still about eight times higher in HIV+ individuals than in healthy controls (10). This argues for a pathogenic role of HIV in B-cell lymphomagenesis beyond its role in T-cell immunodeficiency and the resulting impaired control of EBV-infected B cells. Indeed, there are some hints that HIV may have a direct mutagenic and oncogenic effect on B cells (10). This can potentially be revealed by comparing the nucleotide exchange patterns of point mutations in HIV-associated versus HIV-independent PBL, but may require a whole-genome sequencing analysis to sample enough mutations for such an analysis.

In conclusion, Liu and colleagues provide the first comprehensive insight into the landscape of gene mutations in PBL (Fig. 1). Their findings point to a major role of the JAK–STAT pathway (in particular STAT3), the RAS family, and the NOTCH pathway in this malignancy. Gains of CD44 and of histone genes seem to be further relatively specific features of PBL. This study thereby reveals that PBL has a distinct molecular pathogenesis, clearly separating it from multiple myeloma and ABC-DLBCL. These findings may on the one hand provide new genetic markers for a sometimes challenging differential diagnosis of this lymphoma, and also provide new ideas for targeted therapy of PBL, considering that attempts are currently being made to target the
Disclosures of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Published first June 22, 2020.

REFERENCES

1. Castillo JJ, Bilas M, Miranda RN. The biology and treatment of plasmablastic lymphoma. Blood 2015;125:2323–30.
2. Delecluse HJ, Anagnostopoulos I, Dallenbach F, Hummel M, Marafioti T, Schneider U, et al. Plasmablastic lymphomas of the oral cavity: a new entity associated with the human immunodeficiency virus infection. Blood 1997;89:1413–20.
3. Chapman J, Gentles AJ, Sujoy V, Vega F, Dumur CI, Blevins TL, et al. Gene expression analysis of plasmablastic lymphoma identifies downregulation of B-cell receptor signaling and additional unique transcriptional programs. Leukemia 2015;29:2270–3.
4. Küppers R. B cells under influence: transformation of B cells by Epstein-Barr virus. Nat Rev Immunol 2003;3:801–12.
5. Montes-Moreno S, Martinez-Magunacelaya N, Zecchini-Barrese T, Villambrosia SG, Linares E, Ranchal T, et al. Plasmablastic lymphoma phenotype is determined by genetic alterations in MYC and PRDM1. Mod Pathol 2017;30:85–94.
6. Liu Z, Filip I, Gomez K, Engelbrecht D, Meer S, Laloo P, et al. Genomic characterization of HIV-associated plasmablastic lymphoma identifies pervasive mutations in the JAK-STAT pathway. Blood Cancer Discov 2020;1:112–25.
7. García-Reyero J, Martinez-Magunacelaya N, Gonzalez de Villambrosia S, Loghavi S, Gomez Mediavilla A, Tonda R, et al. Genetic lesions in MYC and STAT3 drive oncogenic transcription factor overexpression in plasmablastic lymphoma. Haematologica 2020.
8. Küppers R. Mechanisms of B-cell lymphoma pathogenesis. Nat Rev Cancer 2005;5:251–62.
9. Wienand K, Chapuy B, Stewart C, Dunford AJ, Wu D, Kim J, et al. Genomic analyses of flow-sorted Hodgkin Reed-Sternberg cells reveal complementary mechanisms of immune evasion. Blood Adv 2019;3:4065–80.
10. Dolcetti R, Gloghini A, Caruso A, Carbone A. A lymphomagenic role for HIV beyond immune suppression? Blood 2016;127:1403–9.
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Blood Cancer Discov 2020;1:23-25.