Review Article

Advances in Pathobiology of Primary Central Nervous System Lymphoma

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Abstract

Objective: Primary central nervous system lymphoma (PCNSL) is a specific type of non-Hodgkin lymphoma with poor prognosis. The rare incidence of this disease and difficulty to obtain sufficient tissue material impede deep research into PCNSL. However, application of modern molecular techniques makes it possible to find biological characteristics exclusive to PCNSL. Therefore, we systematically reviewed the latest research progress on biological characteristics and pathogenesis of PCNSL.

Data Sources: The data analyzed in this review were from the articles listed in PubMed database.

Study Selection: Articles focusing on the biology of PCNSL at the cytogenetic or molecular level were reviewed, including clinical, basic research, and review articles.

Results: With respect to histopathology, perivascular growth pattern and reactive perivascular T-cell infiltration are regarded as typical histopathological manifestations of tumor cells in PCNSL. Moreover, tumor cells of PCNSL predominantly express an activated B-cell-like phenotype, including $CD10^-$ $BCL\text{-}6^+$ $MUM1^+$, $CD10^-$ $BCL\text{-}6^-$ $MUM1^+$, and $CD10^-$ $BCL\text{-}6^-$ $MUM1^-$. On the molecular level, some molecular and genetic alterations may contribute to malignant transformation, including mutations of proto-oncogenes and tumor suppressor genes, gains and losses of genetic material, as well as aberrant activation of some important signaling pathways, such as nuclear factor-κB and JAK/STAT pathway.

Conclusions: The integrated molecular mechanisms involved in pathogenesis of PCNSL are not well understood. The important biomarkers indicating prognosis are not identified. Multicenter studies should be carried out to elucidate pathogenesis of PCNSL to find novel and effective therapeutic strategies.

Key words: Biology; Biomarkers; Histopathology; Pathogenesis; Primary Central Nervous System Lymphoma

Introduction

Primary central nervous system lymphoma (PCNSL) is a rare and specific form of malignant lymphoma confined to brain, leptomeninges, eyes, or spinal cord, without the presence of systemic lymphoma.[1] The majority of PCNSLs (>95%) are diffuse large B-cell lymphoma (DLBCL), with only a small proportion comprising Burkitt, lymphoblastic, marginal zone, or T-cell lymphoma.[2,3] Primary DLBCL of central nervous system (CNS-DLBCL) has been considered as an independent subtype in the WHO classification of hematolymphoid tumors in 2008 mainly due to its distinct biological and prognostic features compared with systemic DLBCL.[4] Moreover, the pathogenesis of PCNSL in immunocompetent patients is distinguishable from that in immunocompromised patients. Hence, the term of PCNSL in present review only refers to CNS-DLBCL in immunocompetent patients.

Since the introduction of high-dose methotrexate-based chemotherapy, there has been significant progress in the outcome of patients with PCNSL. But the overall survival (OS) and long-term survival of this disease still remain challenging, with a 5-year survival rate of 30%.[5] This inferior prognosis can be attributed to the following reasons: (1) the blood-brain barrier limits the access of

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drugs to CNS; (2) a large proportion of patients, especially the elderly, are not tolerable for the intensive therapeutic regimens; and (3) tumor cells of PCNSL may possess inherent resistance to chemotherapy, which has not been elucidated clearly so far. Moreover, the incidence of PCNSL has increased significantly in the immunocompetent patients over the past thirty years, particularly among patients aged 65 years and older.[6] Therefore, it is very necessary to better understand the biological characteristics exclusively belong to PCNSL, which can apply opportunities to identify prognostic factors as well as novel and safe therapeutic strategies.

Histopathology

Historically, this disease was first described in 1929 by Bailey, who used "perithelial sarcoma" for its name.[7] Subsequently, the name changed several times, including "adventitial sarcoma" and "reticulum cell sarcoma." These diverse terms reflected the complexity of this disease, and people were uncertain about the definite derived tissue source of the tumor cells. It was not until the latter half of the 20th century, when morphological, immunological, and molecular cytogenetic techniques had developing rapidly that people gradually realized that tumor cells originated from lymphocyte lineage.[8] Notably, PCNSL is a tumor entity included both in the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues and the WHO Classification of Tumors of the Central Nervous System.[9]

Microscopically, tumor cells of PCNSL, most often composed of centroblasts and less frequently of immunoblasts, infiltrate the neural parenchyma with diffuse, invasive, or perivascular growth patterns. The perivascular growth pattern is a histopathological feature which displays several rims of tumor cells accumulate around small cerebral blood vessels. He *et al*. conducted 62 PCNSLs to determine the prognostic value of histopathological variables, and they found that perivascular growth pattern was observed in 87% of all cases and associated with worse outcome (3-year OS: 31% vs. 64%).[10] Another study conducted by Gill *et al*. also reported the perivascular pattern of infiltration exhibited a higher risk of disease progression and a trend toward shorter progression-free survival (PFS), whereas this growth pattern was only positive for 20% of all cases.[11] Very rarely, tumor cells may present as diffuse, nonenhancing infiltrative lesions without mass effect, which is a variant of PCNSL and termed "lymphomatosis cerebri."[12] In addition, microscopy usually demonstrates a robust inflammatory response with infiltration of reactive T-cells and activated macrophages, as well as reactive astrocytes. Reactive perivascular T-cell infiltration (RPVI) is regarded as another histopathological feature and defined as a rim of small reactive T-lymphocytes occurring alone or located between the vascular wall and large neoplastic cells.[13] Ponzoni *et al*. observed that RPVI was present in 36% (26/73) of all assessable cases, and RPVI-positive cases exhibited a better outcome than RPVI-negative cases (3-year OS: 59% vs. 42%).[13] Chang *et al*. compared 32 PCNSLs with 30 non-CNS DLBCLs and found fewer S100-positive cells and T-cells infiltration, as well as less HLA-DR expression in PCNSLs, so they drew the conclusion that the baseline antitumor immune response in PCNSL is less as compared with non-CNS DLBCL, which may play a role in the poorer prognosis.[14] However, the study about relationship between prognosis and histopathological manifestation, such as perivascular growth pattern or RPVI, should be implemented on the intact tumor specimens excised in the operation, not the small size tissues obtained from the stereotactic biopsy.

Origin of Tumor Cells

According to gene expression profile, DLBCL can be classified into two distinct subgroups: germinal center B-cell-like (GCB) group and activated B-cell-like (ABC) group.[15] Moreover, compared with ABC subgroup, GCB subgroup of DLBCL has a much better clinical outcome when treated with the standard chemotherapy regimen.[16] Although classification of GCB group and ABC group is very important for predicting prognosis of DLBCL, it is impractical to perform gene expression analysis on every patient in daily work. Immunohistochemical analysis of B-cell differentiation markers, which exhibits reliable prognostic value and relatively simple operation, gradually substitutes for gene expression profile to divide DLBCL into two subgroups. Of note, the most widely used immunohistochemistry method is the Hans algorithm, which is based on a few markers, that is, 2 GCB markers, CD10 and BCL-6, and 1 activation marker, MUM1.[17]

Phenotypically, the majority of PCNSLs exhibit pan-B-cell markers, such as CD19, CD20, CD22, and CD79a. Plasma cell markers (CD38, CD138) are always absent. Approximately 10% of PCNSL patient are positive for CD10 whereas the frequency of BCL-6 and MUM1 expression is high, with 60–80% and 80–90%, respectively.[18] Many studies have found that PCNSLs predominantly express an ABC-like phenotype, including $CD10^{-}BCL\text{-}6^{+}MUM1^{+}$, $CD10^{-}BCL\text{-}6^{-}MUM1^{+}$, and $CD10^{-}BCL\text{-}6^{-}MUM1^{-}$.[19] BCL-6 is considered as an essential requirement for GC reaction.[20] MUM1 expresses most strongly in late stages of B-cell differentiation; thus, tumor cells with exclusive expression of MUM1 can be thought as early post-GC origin. The coexpression of MUM1 and BCL-6 does not exist in normal germinal center, because they are mutually exclusive.[19] However, these two markers can be exhibited simultaneously in about half of PCNSLs, indicating that the tumor cells of PCNSL are on their way to leave the GC.[9] Furthermore, Montesinos-Rongen *et al*. compared gene expression profile of 21 PCNSLs with purified normal GC and non-GC B-cells and showed that tumor cells had not reached the post-GC B-cell stage, but they were more closely related to memory B-cell than to GC B-cell, which suggested PCNSL derived from a late GC B-cell.[21] These findings, combined with the presence of ongoing immunoglobulin gene somatic hypermutation and absence of immunoglobulin class switch recombination, manifest that tumor cells of

PCNSL derive from a late GC or early-post-GC origin.[22-24] However, a number of studies have discovered that the prognostic value of dividing PCNSL into GCB and ABC subgroup is not as significant as that in systemic DLBCL. Raoux *et al.* tested 39 PCNSLs and showed no statistic difference on 2-year OS rate between GCB and non-GCB subgroups (35.9% vs. 33.9%).[25] One prospective trial investigated 119 PCNSLs, of which 29 tumors (26.6%) classified as GCB and 80 (73.4%) as non-GCB, and there was no significant difference of survival outcome between them.[26] Kawaguchi *et al.* used a gene expression-based method to category 32 PCNSLs into GCB (10 cases) and ABC subgroup (9 cases), and no significant differences on PFS were observed between these groups.[27]

Prognostic Value of Important Biomarkers

Prognostic significance of many B-cell differentiation markers in systemic DLBCL has been clarified, whereas they are ambiguous in PCNSL. For example, BCL-6 expression is associated with favorable prognosis in systemic DLBCL, but its prognostic value in PCNSL remains unclear.[28] Levy *et al.* analyzed immunohistochemical staining profile of 66 PCNSLs and found that BCL-6 staining had a significant effect on PFS (20.5 vs. 10.1 months).[29] A cohort study of 33 PCNSLs also revealed that expression of BCL-6 was associated with longer OS (101.0 vs. 14.7 months).[30] Similarly, Lossos *et al.* evaluated 69 PCNSLs and reported that BCL-6 expression was related to longer PFS and OS.[31] All of these studies are retrospective in nature and contain variable therapeutic regimens. In contrast, CALGB 50202 trial, the first prospective study to determine the prognostic value of molecular markers in PCNSL, investigated 44 patients with uniform chemotherapy and demonstrated that high BCL-6 expression correlated with shorter survival.[32] Another prospective trial, G-PCNSL-SG1, analyzed 119 patients with PCNSL homogeneously receiving high-dose methotrexate-based chemotherapy and also revealed that expression of BCL-6 was associated with shorter PFS and OS.[26] No correlation of MUM1 expression and clinical outcome in PCNSL has been observed. However, MUM1 may become a therapeutic target of PCNSL on the evidence that a novel class of immunomodulatory drugs, such as lenalidomide and pomalidomide, can treat patients with multiple myeloma and DLBCL via downregulation of MUM1 expression in CRBN-mediated signaling.[33-35] Indeed, there is a report about lenalidomide monotherapy for refractory intraocular large B-cell lymphoma.[36]

Besides B-cell differentiation markers, expression of tumor associated proteins is also worthy to be discussed. MYC protein is a nuclear transcription factor and plays an important role in cell cycle progression, apoptosis, and transformation. *MYC* is a proto-oncogene, and aberrant alterations of this gene have been associated with lymphoid malignancies. Overexpression of MYC protein and *MYC* gene rearrangements account for approximately 30% and 10% of systemic DLBCL, respectively; both of them have been associated with poor prognosis in systemic DLBCL.[37,38] BCL-2 functions as an anti-apoptotic protein of lymphocytes. Overexpression of BCL-2 protein has been reported in about 60% of systemic DLBCL and predicts an inferior outcome.[39] Translocation of *BCL-2* gene to *IGH* locus is considered as the pathogenesis of follicular lymphoma. Furthermore, "Double-hit" lymphoma, which is mainly related to *MYC* and *Bcl-2* genes translocation, as well as double-expressing lymphoma defined as coexpression of MYC with BCL-2 proteins, has recently demonstrated to carry prognostic significance in systemic DLBCL.[40,41] In PCNSL, overexpression of MYC protein or BCL-2 protein occurs more frequently, while *MYC* gene rearrangement or *BCL-2* gene rearrangement occurs rare. Moreover, the prognostic role of MYC protein, BCL-2 protein, or their double expression remains controversial in PCNSL. The prospective trial, CALGB50202, demonstrated that high MYC protein expression was detected in 54% of all 26 tested cases, but MYC protein expression did not correlate with outcome in this series.[32] A cohort study of 59 PCNSLs by Gill *et al.* revealed that MYC protein, BCL-2 protein, and their double overexpression were detected in 73%, 71%, and 60% of all cases, respectively; none of them were predictive in clinical outcome.[11] Another cohort study of 42 PCNSLs by Tapia *et al.* showed high MYC protein expression occurred in 43% of all cases, which was associated with lower OS, while high BCL-2 protein expression (71%) and their double expression (29%) had no prognostic value.[42] Brunn *et al.* conducted a series of 50 PCNSLs and found that there was a striking discrepancy between the high frequency of prominent MYC protein overexpression (92%) and the rarity of *MYC* breaks (8%).[43] Son *et al.* also found that *MYC* translocation had a lower prevalence (7%), while MYC protein overexpression was more frequent (66%).[44] This phenomenon suggests overexpression of MYC protein not only resulted from translocation or increased copies of *MYC* gene but also many other mechanisms, including (1) increased MYC mRNA expression; (2) high Ki-67 proliferation index; (3) the activation of nuclear factor-κB (NF-κB), which is a transcriptional activator of *MYC* gene; and (4) numerous miRNAs have been shown to regulate MYC expression.[45]

Molecular and Genetic Abnormalities of Primary Central Nervous System Lymphoma

To address the molecular pathogenesis of PCNSL, many studies have been focused on mutations of proto-oncogenes and tumor suppressor genes. Montesinos-Rongen *et al.* demonstrated that PCNSLs were targeted by aberrant somatic hypermutations with involvement of 4 potent proto-oncogenes – *MYC, PAX5, PIM1,* and *Rho/TTF* – all of which play an important role in differentiation, proliferation, and apoptosis of B-cell.[46] Yamada *et al.* reported that somatic mutations in *MYD88* and *CD79B*, the important upstream components of NF-κB signaling, were observed in 94.4% and 61.1% of PCNSLs, respectively.[47] These

findings indicate that aberrant somatic hypermutations may play a pathogenic role in PCNSL development. Besides, several tumor suppressor genes including *DAPK* (84%), *CDKN2A* (75%), *MGMT* (52%), and *RFC* (30%) are targeted by DNA hypermethylation.[9] Thereby, DNA demethylation agent 5-aza-2'-deoxycytidine may be an effective therapeutic approach.

Recurrent chromosomal abnormalities have been identified by a number of studies. A cohort FISH analysis of 37 PCNSLs by Schwindt *et al.* revealed that *BCL-6* translocations were present in a large fraction (38%) of PCNSLs, and translocation partners included *IGH* gene in 14q32.33, *IGL* gene in 22q11.22, *histone 1 H4I* gene in 6p22.1, and *LPP* gene in 3q27.3-3q28.[48] In addition, gains and losses of genetic material also occur frequently in PCNSL. Schwindt *et al.* analyzed 19 PCNSLs using high-density single-nucleotide polymorphism arrays and revealed that the most frequent genetic abnormalities were the loses in 6p21.32 and gains in 18q21.[49] The former region harbors *HLA-DRB*, *HLA-DQA*, and *HLA-DQB* genes, while the latter region includes *BCL-2* and *MALT1* genes. The absence of these *HLA* genes may be involved in the mechanism of tumor-immune escape, but Kurzwelly *et al.* reported no significant differences in frequencies of *HLA-A*, *HLA-B*, and *HLADRB1* alleles between 82 PCNSLs and 327 healthy individuals, which do not support the hypothesis of an involvement of *HLA* alleles in the pathogenesis of PCNSL.[50] Another cohort study of 18 PCNSLs by Braggio *et al.* displayed the most common abnormality was the deletion of 9p21.3 which contained *CDKN2A* and *CDKN2B* genes, and they found that deletion of 6q21 (*PRDM1*) was associated with shorter OS.[51] The deletion involving 6q21-6q23 also happens regularly whereas it contains candidate genes such as *PRDM1* and *TNFAIP3*, the former as a tumor suppressor regulates B-cell differentiation and the latter as a key negative regulator of NF-κB pathway.

The application of array-based genomic analysis has provided many useful insights into molecular features of PCNSL, including some new genetic features that have not been observed by other methods, the prognostic value of some genetic alteration, and the important role of BCR/TLR/NF-κB signaling pathway in the pathogenesis of PCNSL. Kawaguchi *et al.* conducted gene expression profile on 32 PCNSLs and identified that 23 genes were related to patient survival; among these genes, overexpression of BRCA1 mRNA or protein was most strongly associated with poor survival.[27] Milena *et al.* reported that *TP53* and *ATM* genes could be involved in the molecular pathophysiology of PCNSL, whereas mutations of *PTEN* and *SMO* genes could affect survival regardless of treatment approaches.[52] Lim DH *et al.* performed microarray gene expression profiling analysis to compare 10 PCNSLs and non-CNS DLBCLs, and identified that five genes were predominantly expressed in PCNSL (*C16orf59, SLC16A9, HPDL, SPP1*, and *MAG*); alteration of *SPP1* gene expression was involved in many biological activities, such as CNS tropism, B-cell migration, proliferation, and aggressive clinical behavior.[53] A comprehensive genomic study of 19 PCNSLs by Braggio *et al.* demonstrated that biallelic inactivation of *TOX* and *PRKCD* was recurrently found in PCNSL but not in systemic DLBCL; additionally, 90% of all cases harbored mutations leading to activation of the NF-κB signaling pathway such as activating mutations of *MYD88, CARD11*, and *CD79*, and deletions of *TNFAIP3* and *TBL1XR1*, indicating that the activation of NF-κB signaling pathway is a key driver of lymphoma genesis in PCNSL.[51] Bruno *et al.* analyzed 9 PCNSLs and identified recurrent somatic mutations in 37 genes involved in key biological processes, including transcription (*ETV6, IRF2BP2, EBF1, IRF4,* and *TBL1XR1*), cell cycle (*PIM1, BTG1*), nucleosome assembly (*HIST1H1D, HIST1H2AC*), and cell adhesion (*MUC16, ACTG1*), as well as NF-κB and B-cell or T-cell receptor signaling pathways.[54] Whether PCNSL initially arises inside or outside of the CNS has been a mystery for decades and still confuses us today, the latest discovery from Kazutaka *et al.* may expand our horizons. They conducted 41 PCNSLs using whole-exome sequencing and revealed high frequency of *MYD88* mutation (86%), one quarter of which was concomitant presence of *MYD88* mutation in PBMNCs, speculating that *MYD88* mutation-positive "pre-lymphoma" cells first appear outside of the CNS and circulate in peripheral blood, then enter the CNS and accumulate additional genetic or epigenetic alterations that provide a growth advantage in this environment.[55]

JAK/STAT pathway plays an important role in physiological processes such as cell proliferation, survival, and immune response and has been shown to be aberrantly activated in several solid and hematological tumors. This pathway is activated by a wide variety of cytokines via binding with their specific receptors. The negative regulation of JAK/STAT pathway includes: (1) suppressors of cytokine signaling and protein inhibitor of activated STAT proteins acting on the degradation of JAKs and STATs proteins; (2) LNK and phosphatase acting on JAKs or receptor phosphorylation; (3) CBL acting on the degradation of the cytokine receptors.[56] The activation and negative regulation of JAK/STAT pathway are demonstrated in Figure 1. The latest studies have shown that aberrant activation of JAK/STAT pathway may also participate in pathogenesis of PCNSL. High levels of interleukin-10 (IL-10), which signals via the JAK/STAT pathway, have been reported in CSF and correlate with adverse prognosis.[57,58] Another B-cell growth factor IL-4, also signaling via the JAK/STAT pathway, has been shown to be expressed by tumor vasculature and tumor cells in PCNSL.[59] A cohort study of 33 PCNSLs conducted by Liu *et al.* reported that aberrant methylation of SHP1 promoter occurred in 87.9% of PCNSLs, and was correlated with decreased expression and phosphorylation of SHP1 protein, as well as increased expression of STAT3 protein; thus, it was concluded that attenuation of the biological functions of SHP1 protein resulted from aberrant methylation of the SHP1 promoter contributed to the constitutive activation of the JAK/STAT signaling pathway in the pathogenesis of PCNSL.[60]

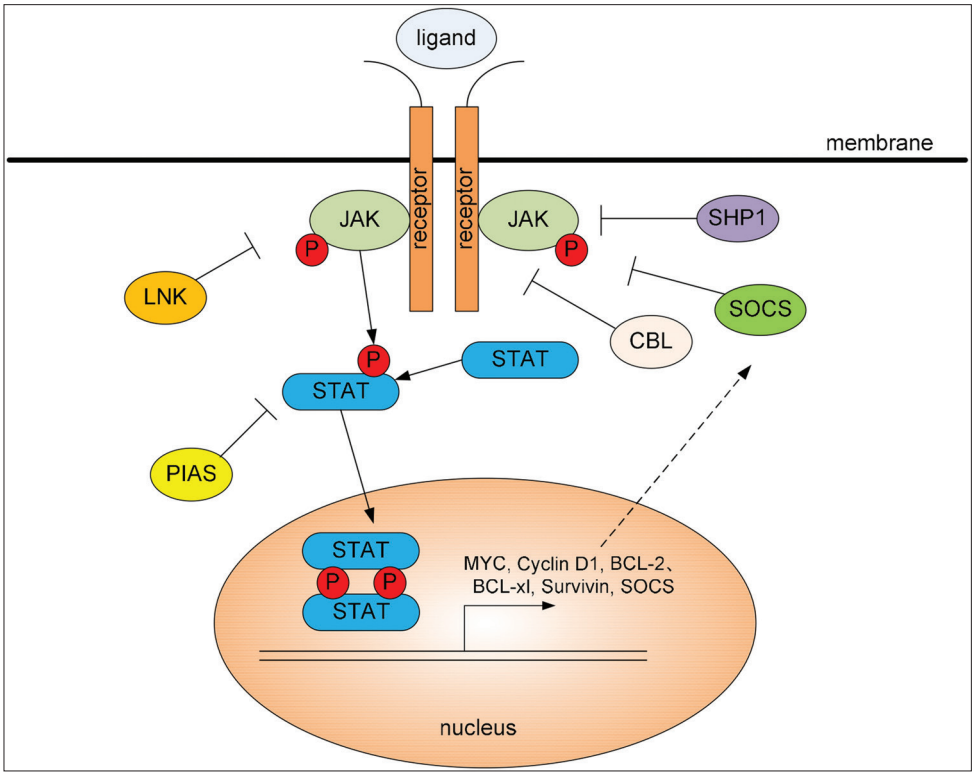

Figure 1: The activation and negative regulation of the JAK/STAT pathway.

Conclusion

From the above scientific research, we can summarize that tumor cells of PCNSL derive from a distinct cell of origin and exhibit a unique immunophenotype. Besides, some molecular and genetic alteration may contribute to malignant transformation, including aberrant somatic hypermutations of proto-oncogenes, DNA methylation of tumor suppressor genes, gains and losses of genetic material, as well as activation of the NF-κB and JAK/STAT signaling pathway. However, we are still confused about the integrated molecular mechanisms involved in pathogenesis of PCNSL, as well as whether PCNSL initially arising inside or outside of the CNS. It is anticipated that these problems will be solved soon as multicenter collaboration and molecular techniques are better implemented.

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Conflicts of interest

There are no conflicts of interest.

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