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Review Article

Molecular Biology of the two Less Common Vascular Brain Neoplasms in Adults – A Comprehensive Review

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Abstract

Brain neoplasms are a significant cause of morbidity and mortality worldwide, affecting individuals across an extensive range of demographics. In adults, the most common primary intracranial tumors are gliomas, whereas less common vascular brain neoplasms include hemangioblastomas (HBs) and primary central nervous system lymphomas (PCNSLs). HB is a highly vascular tumor comprising 3% of all Central Nervous System (CNS) tumors. Approximately 25% of these cases are hereditary, resulting from von Hippel-Lindau (VHL) disease - an autosomal dominant disorder - whereas the remainder develop sporadically. These tumors are characterized by a remarkably high prevalence of recurrent somatic mutations (50%) and Loss of Heterozygosity (LOH) at the gene locus on chromosome 3p (72%). Mutations in ARID1B have also been revealed in HB cases. PCNSL is typically a diffuse large B-cell lymphoma (DLBCL). Several genomic alterations have been detected, including the expression of BCL2 and BCL6, mutations in genes encoding p53, ATM, and MYD88, as well as chromosomal deletions, repeated losses, and insertions. Its molecular biology remains a complex field where basic research is essential to meet clinical expectations regarding antitumor efficacy. Modern investigations have focused on understanding the biology and pathogenesis of these tumors to develop new agents for personalized, targeted molecular treatment. The current study presents a comprehensive review of contemporary knowledge regarding the molecular features of these neoplasms. It focuses on the primary intracellular signaling pathways involved in their pathogenesis, genomic and epigenetic characteristics, and the predictive value of molecular indices according to the 2021 WHO classification.

Key Words: brain neoplasms; hemangioblastoma; primary central nervous system; lymphoma; molecular biology; genetics; epigenetics

Introduction

Brain neoplasms affect a wide diversity of individuals and result in significant morbidity and mortality worldwide. Among these, two less common vascular brain neoplasms in adults are hemangioblastomas (HBs) and primary central nervous system lymphomas (PCNSLs). PCNSL is typically a diffuse large B-cell lymphoma (DLBCL) [1]. It primarily affects elderly individuals, with a median age of 66-67 years, whereas it is rare in young individuals [2] and infrequent in the pediatric population [3]. PCNSL accounts for less than 5% of all primary brain tumors and typically affects the brain, spinal cord, leptomeninges, and eyes [4]. The cellular origin remains to be elucidated, as it is unclear whether PCNSL originates within the CNS or is a systemic lymphoma

that escapes from the host's immune system to proliferate in the CNS "sanctuary" [5].

Various genomic alterations have been identified in PCNSL, such as the expression of BCL2, BCL6 [6-8], and IRF4/MUM1 [5], as well as non-synonymous somatic mutations in MYD88, PIM1, and BTG2 [5,9-14]. Non-conservative mutations have also been recorded in the TP53, ATM, PTEN, JAK3, and PIK2CA loci [5,15]. Structural alterations include deletions at chromosomes 6p21 and 6q21-23 [16,17], affecting PRDM1, PTPRK, and A20/TNFAIP3, recurrent chromosomal losses at 9p21 [16], and insertions on chromosome 12q, harboring CDK4, MDM2, STAT6, and GLI1 [16-20], as well as insertions on the long arms of chromosomes 1, 7, and 18 [18].

Other genomic alterations include CARD11 [5,9-13,21] and MALT1 [22] mutations and overexpression. Copy number alterations (CNAs) and translocations on chromosome 9p24, involving the programmed death-ligand 1 (PD-L1) and 2 (PD-L2) loci [23], are frequent. Homozygous loss of HLA class II genes and CDKN2A [24], recurrent BCL6 translocations [25,26], and TBL1XR1 variations [27] are also common. PCNSL biology is mediated by the JAK/STAT signaling pathway [8,23,28,29]. Furthermore, micro-RNAs (mi RNAs) play a critical role, tumor-suppressive miRNAs, such as miR-193b, miR199a, miR-145, and miR-214, are often downregulated [30], whereas miR-17-5p is notably upregulated [30,31].

Epigenetic silencing via DNA hypermethylation has been detected at loci including MGMT, DAPK, and RFC, as well as the CDKN2A (p16 INK4a/p14ARF) locus [32,33], alongside promoter methylation of CDKN1B and RB1 [18,20]. In cases localized to the splenium, TERT promoter mutations are present [34,35]. Inflammatory markers also play a role, as BCA-1 (CXCL-13) is highly expressed [36-38], and Interleukin (IL)-4 signaling may be critical for pathogenesis and progression [8]. HB is a highly vascular, benign tumor accounting for 3% of all CNS tumors, 1-2.5% of all primary intracranial tumors [39], 7-8% of posterior cranial fossa tumors [40], and 7-10% of spinal cord tumors. Its pathology is characterized by neoplastic "stromal" cells embedded within a dense network of vascular channels [41,42]. HBs develop either sporadically or as a manifestation of von Hippel-Lindau (VHL) disease, an autosomal dominant disorder, in approximately 25% of cases [40]. While 75% of HBs are sporadic, the majority of these cases do not carry observable germline VHL alterations. Sporadic cases typically present as solitary lesions, whereas VHL patients tend to develop multiple HBs [43-45].

The histogenesis of HBs remains uncertain. It has been hypothesized that they originate from embryologically arrested "hemangioblast" stem cells [41,46]. Consequently, the WHO classification categorizes HB as a "neoplasm of uncertain histogenesis" [47,48]. These tumors are primarily diploid with few chromosomal abnormalities [49,50]. The presence of VHL mutations has been estimated at10% to 44% in sporadic HB cases [51]. The frequency of chromosome 3 aneuploidy ranges from 18% to 69% in these sporadic tumors [49,50]. Mutations in the VHL tumor suppressor gene, located on chromosome 3p25.3 appear to play a role in both sporadic and VHL disease-related tumors [52-54], however the genetic factors explaining the clinical heterogeneity of the HBs remain unknown. Despite CNA in a small subset of cases [53], the HBs exome is remarkably simple, lacking additional oncogenic driver mutations [52,54]. HBs are characterized by a notably high prevalence of recurrent somatic mutations (50%) and LOH of the gene locus on chromosome 3p (72%). These genomic alterations are responsible for biallelic VHL inactivation in 47% of cases, and an inactivating alteration in at least one allele in 78% of sporadic HBs [52]. Mutations in the ARID1B gene have also been recorded. This gene acts as a tumor suppressor in various types of cancers [55,56].

Further analysis is needed to determine whether such subclonal variations are functionally essential in supporting the sporadic development of HBs [57]. Epigenetic alterations in sporadic and VHL-associated HBs were detected through the molecular characterization of the VHL promoter [53], raising the possibility that DNA methylation patterns could lead to the identification of relevant biological subgroups. Over the past decade, notable progress in genomic research has improved the classification and management of brain tumors. However, despite these molecular advancements, improvements in overall survival rates and quality of life remain suboptimal. This article provides a comprehensive review of the molecular features of HB and PCNSL, focusing on intracellular signaling pathways, genomic and epigenetic characteristics, and their roles in pathogenesis.

PCNS Lymphoma

Epidemiological data and Classification

PCNSL accounts for 4-6% of all extranodal lymphomas, approximately 2% of all CNS tumors, and up to 1% of all lymphomas [58]. Moreover, its overall incidence rate is 0.5 cases per 100,000-person years, representing 3% to 4% of all newly diagnosed intracranial neoplasms [59]. The median age at diagnosis is 65 years old. The tumor is frequently detected in individuals with acquired immune deficiencies, such as AIDS or post-transplant conditions in immuno-compromised patients, in which the tumor cells are typically Epstein-Barr virus (EBV)-positive [60]. It is also associated with congenital immune deficiencies, such as X-linked lymphoproliferative syndrome, Wiskott-Aldrich syndrome, or ataxia telangiectasia [61]. Approximately 90% of PCNSL cases are diffuse large B cell lymphomas (DLBCLs), and their immunohistochemical analysis typically demonstrates a non-germinal center B-cell-like (non-GCB) immunophenotype [62-64]. In contrast, a small subcategory of patients is diagnosed with T-cell, marginal zone, Burkitt, or lymphoblastic lymphomas [65].

According to gene expression profiling, tumor cells are most closely related to late GC (exit) B-cells [6]. Currently, the 2021 WHO Classification categorizes PCNSLs primarily as DLBCL, as previously mentioned, without further grading, in contrast to other common primary brain tumors [1].

PCNSL histogenetic origin

Under normal circumstances, the CNS is an immunologically privileged site devoid of B-cells. Therefore, the cellular origin of PCNSL remains to be elucidated. One proposed mechanism suggests that a malignant B-cell clone arising systemically might express specific adhesion molecules that facilitate homing to the CNS. There, the tumor cells proliferate and undergo additional mutations in the absence of modulatory control by the host's immune system. It remains unknown whether PCNSL originates within the CNS or is part of a systemic lymphoma that escapes the immune system to multiply in the CNS 'sanctuary' [5]. B-cells recruited to the brain during an inflammatory response may remain for extended periods and eventually undergo malignant transformation while localized within the CNS. Alternatively, B-cells may transform into a malignant state outside the CNS, for example, during a GC response in a secondary lymphoid organ [5].

It is possible that both mechanisms play a role. However, the selective homing of a malignant B-cell solely to the brain cannot be easily explained and remains difficult to validate experimentally. To date, no specific cell adhesion molecule, chemokine or cytokine has been identified that predicts selective B-cell homing to the brain in PCNSL, nor have significant differences in adhesion molecule expression been found between PCNSL and systemic lymphomas [18].

The B-cell differentiation process may provide insights into the histogenetic origin of PCNSL. The primary phase involves the assembly of the V, D, and J sections of the immunoglobulin (Ig) heavy and light chain genes in the bone marrow [9]. Following successful assembly, naïve B-cells exit the bone marrow for the next phase of maturation, where they interact with antigens in the GCs of secondary lymphoid organs, to

improve their B-cell receptor (BCR) binding affinity. The process of somatic hypermutation (SHM) in the first 1.5-2.0 kb of the V region genes is regulated within the GCs [10]. This process and affinity maturation require specific antigens, antigens-presenting cells (APC) and T- cells, and the presence of BCL6 [11]. SHM may either increase or decrease BCR affinity, leading to the selection of B-cell clones for further rounds of SHM. Eventually, these cells either undergo apoptosis or exit the GCs [12]. After SHM, B-cells may undergo Ig class-switch recombination, substituting the BCRμ constant region with downstream regions to generate various antibody classes [5].

Sequence analysis of Ig variable region genes in PCNSL has detected high frequencies of somatic mutations. These findings indicate that PCNSLs originate from mature B-cells that have been exposed to antigens and have undergone T-cell-dependent affinity maturation within a GC microenvironment [66]. Morphologically, PCNS cells resemble Centro blasts, and the presence of SHMs in rearranged Ig segments demonstrates their prior involvement in a GC reaction [13].

Expression of B cell markers such as CD19, CD20, and CD79a, is present in almost all PCNSLs. CD10 is present in 10-20% of cases, while plasma cell markers (CD38, CD 138) are generally absent. Further immunophenotype characterization has shown that these tumors process overlapping features of GC and activated B-cell differentiation. Specifically, immunohistochemical analyses have demonstrated that the majority of brain lymphomas express MUM-1, an activated B-cells marker, and BCL-6, a GCs marker [40], as previously confirmed [8]. BCL-2 and BCL-6 are expressed in 56%-93% and 60%-80% of PCNSL cases, respectively [6]. BCL-6 serves as the dominant regulator of the GC reaction and suppresses the exit of B-cells exit from the GCs [23]. Strong IRF4/MUM1 expression is observed in approximately 90% of PCNSLs, indicating that the tumor cells are transitioning out of the GC. Since IRF4/MUM1 expression is more frequently associated with memory B-cells than with GC-B cells, the CD10-BCL6+IRF4/MUM1+ phenotype suggests that further B-cell maturation is impaired. This corresponds to a late GC exit phenotype and is associated with a poor prognosis [5].

Biological analyses have demonstrated that PCNSL is at the late B-cell GC exit phase and exhibits constitutive Nuclear Factor-kB (NF-kB) activity. This activity is driven by mutations in BCR pathway genes, the Toll-like receptor (TLR) pathway (notably MYD 88), and CARD11 [5, 9-13]. Recently, DLBCL has been categorized into distinct molecular clusters. PCNSL has been closely associated with the MCD subtype (defined by the co-occurrence of MYD88L265P and CD79B mutations) or the cluster 5 (C5) DLBCL. Both classifications converge on the presence of recurrent MYD88L265P, PIM1, CD 79B, and BTG2 mutations, as well as Ig heavy locus (IgH)-BCL6 translocations. Other hallmarks include copy number gains at 3q12.3 and 9p24. (involving PD-L1/PD-L2) and copy losses at 6p21-22 (human leukocyte antigen, HLA, locus), 6q21, and 9p21.3 (CDK N2A biallelic loss) [5,26]. Although recent reports have suggested a significant role for the tumor microenvironment in PCNSL pathogenesis, a comprehensive survey examining its interaction with mutation and methylation events is currently lacking [5,14-17].

PCNSL genomic alterations

During SHM phases, B-cell differentiation requires DNA double-strand breaks, consequently, the failure to accurately repair these breaks may lead to the emergence of malignant cells. PCNSL cells frequently harbor translocations affecting Ig and Ig-related genes, most notably BCL6 [23]. Constitutive BCL-6 activity, often caused by mutations in its promoter, can exert significant tumorigenic effects. The Cancer and Leukemia Group B (CALGB) 50202 trial demonstrated that BCL-6 overexpression is associated with poorer survival and refractory disease status [27]. Although these findings have been supported by other studies [67], various retrospective analyses have yielded conflicting results [5,8].

Next-Generation Sequencing (NGS) has revealed that over 80% of non-conservative mutations occur within loci encoding proteins such as TP53, ATM, PTEN, JAK3, PIK2 CA, PTPN11, CTNNB1, and KRAS [15]. Specifically, mutations in the TP53 and ATM genes may be critically involved in the PCNSL molecular pathophysiology. Furthermore, non-synonymous somatic mutations in MYD88, PIM1, and Btg2 have been detected at high frequency via whole-exome sequencing in PCNSL samples [14]. Deletions and insertions of genetic material are highly frequent in PCNSL. Comparative genomic hybridization (CGH) has identified several critical genetic abnormalities. The most common genomic alteration involves the deletion of the chromosome 6p21 region, which harbors the HLA locus [17]. Deletions on chromosome 6q are also frequent, particularly at the 6q21-23 [16] locus. This region contains PTPRK, a protein tyrosine phosphatase implicated in cell adhesion signaling, PRDM1, a tumor suppressor and regulator of B-cell differentiation, and A20 (TNFAIP3), a negative regulator of the NF-kB signaling pathway.

While 6q deletions are associated with adverse outcomes in follicular lymphoma [68], they are present in 66% of PCNSL specimens. Reduced expression of PTPRK, a candidate tumor suppressor, is associated with 6q22-23 deletion, suggesting its role in PCNSL progression. LOH analysis has also shown that 6q aberrations predict shorter survival. Recurred chromosomal losses have also been recorded at the 9p21 locus [16], which contains CDKN2A and other genes involved in cell cycle regulation.

Chromosomal gains on chromosome 12 are very common, specifically at the 12q locus harboring CDK4, MDM2, STAT6, and GLI1 [16,18-20]. Distinct alterations also occur on the long arms of chromosomes 1, 7, and 18 [18], whereas DNA copy number losses are frequently found on chromosome 6 and the short arms of chromosomes 17 and 18. CNAs and translocations on chromosome 9p24, involving the PD-L1 and -2 genes, are frequent, suggesting that immune escape is critical to PCNSL pathophysiology [23]. Homozygous loss of HLA class II [24] and CDKN2A, along with TBL1XR1 variants, are common features that align PCNSL with the recently described [27] “MCD”, “C5”, or “MYD 88-like” subtypes, which are hypothesized to originate from long-lived memory B-cells [27,69-71].

Less research has been conducted on molecular pathogenesis of PCNSL compared with systemic. A molecular aberration in PCNSL that has been reproducibly detected is homozygous deletion or promoter hypermethylation of the CDKN2A gene, which is responsible for P14ARF production. Growth arrest mediated by P14ARF is p53-dependent as p14ARF binds to MDM2, a mediator of p53 stabilization.TP53 mutations are infrequent genomic events in PCNSL, in contrast to systemic lymphomas in which TP53 gene inactivation may be observed in 20% to 40% of tumors. These findings indicate that early alterations of CDKN2A in PCNSL contribute to tumor development and reduce the selective pressure for secondary TP53 mutations [19]. Deletion of CDKN2A, CDKN1B, and RB1 have also been reported in PCNSL cases [18,19].

The Janus kinase (JAK/STAT) signaling pathway plays a central role in the biology of PCNSL, according to molecular analyses. Transcript and protein levels of Il-4 and Il-10 which act as mediators of the JAK/ STAT intracellular signaling pathway and promote B cell proliferation, are upregulated in the tumor microenvironment, as well as in the vitreous and cerebrospinal fluid (CSF) [8]. These cytokines have been associated with tumor response and disease progression [8,28]. The upregulation of Il-4 and Il-10 and activation of downstream JAK/STAT signaling are linked to aberrant MYD88 activation, which is involved in TLR signaling [29]. Increased intratumoral levels of JAK1 transcripts have also been observed in PCNSL [23,28]. Approximately 55% of PCNSL cases harbor mutations within the Toll/IL-1 receptor (TIR) domain of MYD 88, most commonly the L265P mutation, which results from a leukine-to-proline

at position 265 and contributes to lymphomagenesis, particularly in PCNSL and activated DLBCL [72].

A L265P substitution in MYD88 is observed in 38%-50% of PCNSL cases, and CD79B is mutated in approximately 20% of cases [17]. Other studies have reported MYD88 mutation frequencies ranging from 38% and 94% in PCNSL cases [27,73,74], which may reflect selection bias due to small cohort sizes, given the rarity of the disease. MYD88 encodes a signaling adaptor protein that regulates NF-kB activation and the JAK/STAT3 signaling pathway following stimulation of TLRs, Il-1/Il-18 receptors, and Interferon-β (IFN-β) production. The MYD88 L265P mutation and loss of CDKN2A have been identified as early mutational events in PCNSL [75]. Although TP53 alterations play a relatively minor role in PCNSL pathogenesis, the CDKN2A/B locus encodes multiple proteins that regulate key cell-cycle control pathways, including the p53 pathway (via p14 ARF) and the RB1 pathway (via p16 INK4a), underscoring the importance of p53-associated mechanisms in PCNSL biology [76].

The CD 79B gene encodes a subunit of the BCR complex that is essential for BCR signaling, and subsequent NF-kB activation. Approximately 40% of PCNSL cases harbor mutations within the immunoreceptor tyrosine-based activation motif of CD79B, most commonly at tyrosine 196 (Y196), leading to chronic active BCR signaling and sustained NF-kB pathway signaling activation [77]. In contrast, systemic DLBCL exhibits lower frequencies of MYD88 and CD79B in the active B-cell (ABC) subtype, with reported rates of 8%-37% for MYD88 and 12%-22% for CD79B mutations [29,78].

The BCR pathway transmits its signals to the CARD11-BCL10-MALT1 (CBM) signalosome complex. Less common mutations as well as overexpression of CARD11 [21] and MALT1 [22] have also been observed in PCNSL cases. Bruton tyrosine kinase (BTK) serves as a key mediator linking BCR and TLR signaling pathways to downstream NF-kB activation. In more than 90% of PCNSL tissue samples, components of the BCR, TLR, or NF-kB signaling pathways are altered. The BCR and TLR pathways, along with their downstream target NF-kB, are frequently affected by SHM, particularly in genes encoding MYD88 and CD79B. NF-kB signaling appears to be the dominant pathway involved in PCNSL pathogenesis [26,79,80], playing a critical role in transcriptional regulation and cell survival. Constitutively activation of NF-kB promotes cellular proliferation, inhibits apoptosis, and sustains the viability of activated ABC DLBCL [80]. NF-kB activity is further enhanced by mutations or deletions of tumor necrosis factor alpha induced protein 3 (TNFAIP3) [73]. The majority of PCNSLs are of the non-GCB-DLBCL subclass and share many genetic aberrations with non-CNS ABC-DLBCL within the same signaling pathways. SHM has been reported to contribute to PCNSL pathogenesis, with a higher mutational load than in systemic DLBCL [13]. SHM targets identified in PCNSL include proto-oncogenes such as PIM1, PAX5, BTG2, and OSBPL10 [13,26].

Despite extensive genetic studies of PCNSL [5,26,75,81], reports on global gene expression profiling remain limited. Available studies indicate that PCNSL exhibit distinct gene expression profiles, which differentiate them from systemic ABC-DLBCL. These differences are particularly evident in the expression of Ig constant genes, highlighting the role of B-cell maturation in the classification of PCNSL and other lymphomas, similar to approaches used in leukemia and multiple myeloma [82].

MYC, a transcription factor commonly upregulated in DLBCL via translocation, drives cell proliferation and regulates cell development, differentiation, and apoptosis, partly through downregulation of BCL2 [83,84]. In PCNSL, microRNAs associated with the MYC signaling pathway have been reported, with tumor-suppressor microRNAs such as miR-193b, miR-199a, miR-145, and miR-214 being downregulated [30].

Epigenetic alterations in PCNSL

Epigenetic silencing through DNA methylation is also involved in the pathogenesis of PCNSL. DNA hypermethylation has been found in various loci such as CDKN2A, p16 INK4a, DAPK, p14ARF, MGMT, and RFC [32,33]. Array-based DNA methylation profiling identified 194 distinctively methylated genes when comparing PCNSL patients to controls. A significantly enriched CpG content was also observed in these differentially methylated genes. However, no differences in methylation patterns between PCNSL and systemic DLBCL cases were recorded [85]. Additionally, promoter methylation of RB1 and CDKN1B has been found in PCNSL cases [18,20].

PCNSL are highly proliferative neoplasms [86]. TERT activation leads to unlimited proliferation, and activating TERT promoter mutations are frequent in various human cancers [34]. Mutations at two hotspot positions (-124G>A and -146G>A) result in enhanced TERT promoter activity. Bruno et al. have found that these TERT promoter mutations were present in PCNSL located in the splenium [35].

MicroRNAs may also play a critical role in the PCNSL pathogenesis as they do in other malignant neoplasms. MiR-17-5p, which targets the proapoptotic gene E2F1, was significantly upregulated in nine PCNSL cases compared with nodal DLBCL cases [87]. It has also been reported that miRNA upregulation is associated with overexpression induced by inflammatory cytokines (miR-155), inhibition of terminal B cell differentiation (miR-30b/c, miR-9), or the MYC pathway (miR-92, miR-17-5p, miR-20a) [30].

Nevertheless, Deckert et al. [5] reported contradictory outcomes. Specifically, they observed that miR-155 exhibited the lowest expression level compared with other mi-RNAs implicated in PCNSL. CSF analysis from PCNSL patients demonstrated that miR-19, miR-21, and miR-92 were expressed at significantly higher levels than in controls with inflammatory CNS diseases, highlighting the potential of these miRNAs as clinical bio-markers [31].

The role of tumor microenvironment in PCNS pathogenesis

Under normal conditions, the brain is immunologically “quiet”, whereas some PCNSL specimens exhibit signs of inflammatory reactions, included activated macrophages and reactive T-cell infiltration. In the CNS perivascular area, T cells residing near blood vessels may interact with perivascular antigen-presenting macrophages. Subsequent invasion of the CNS parenchyma requires antigen stimulation. In the absence of antigen, T cells may remain confined to the perivascular region [88]. Activated perivascular infiltration by CD8 T cells may be associated with favorable outcomes, suggesting the potential efficacy of immunotherapy in enhancing T-cell-mediated immune-surveillance [89].

Inflammatory activation may precede or accompany PCNSL [90]. Chemokines regulate leukocyte trafficking, proliferation and adhesion, contributing to the organization of normal lymphoid structures. A recent study reported high expression of the B-cell-attracting chemokine BCA-1(CXCL-13) in PCNSL. This chemokine promotes B-cell homing to secondary lymphoid organs. BCA-1 binds to its receptor, CXCR5, which is also expressed by B-cells in PCNSL, and may facilitate the extranodal localization of CNS lymphomas. Although BCA-1 is expressed by lymphoma cells, it is not produced by tumor endothelia in PCNSL and therefore, does not contribute to the angiotropic growth pattern of these tumors [36].

Mechanisms underlying the intracerebral tropism and dissemination of lymphoma cells are central to PCNSL pathogenesis and may involve chemokines such as CXCL-13, and CXCL12 (SDF-1). The diagnostic relevance of Il-10 and CXCL-13 concentration in CNS lymphomas has been demonstrated [37,38]. Elevated CFS levels of CXCL-13 and Il-10 are also associated with poor prognosis in PCNSL patients [36,91].

Furthermore, ectopic expression of the B-cell growth factor Il-4 was also detected in PCNSL [8]. Il-4 may function as an autocrine growth factor for lymphoma cells and as a paracrine factor due to its unique expression

by tumor-associated endothelia in PCNSL. Il-4 is not expressed in the normal brain vasculature or in malignant astrocytic neoplasms. These findings support the hypothesis that Il-4 play a critical role in PCNSL pathogenesis and progression and may contribute to the angiotropic growth pattern of lymphoma cells within the CNS. Additionally, the activated form of the transcription factor STAT6, a mediator of Il-4-dependent gene expression, is expressed by tumor cells and tumor-associated endothelia in PCNSL, providing further evidence for the functional significance of Il-4 signaling in PCNSL [92].

Hemangioblastoma

Epidemiological data

Hemangioblastoma (HB) is a highly vascular tumor, accounting for 3% of all CNS tumors, 1-2.5% of primary intracranial tumors [39], 7-8% of posterior cranial fossa tumors [40], and 7-10% of spinal cord tumors. It is generally benign, characterized by neoplastic "stromal" cells embedded with in a dense network of vascular channels [41]. Cystic HBs are more commonly located in the cerebellar hemispheres and, more broadly, in a limited subset of CNS regions, including retina, brainstem, and spinal cord [39-41].

HBs may arise sporadically or as part of von Hippel-Lindau (VHL) disease, an autosomal dominant disorder, which accounts for approximately 25% of cases [40]. About 75% of HBs are sporadic, and somatic VHL mutations have been detected in only a small subset of these tumors [42]. In contrast to familial VHL disease, most sporadic HBs do not exhibit detectable germline or somatic alterations in VHL [43,44]. Sporadic cases typically present as solitary lesions, whereas VHL patients often develop multiple HBs [45]. Two possible explanations have been proposed for the difference in VHL mutation frequency between familial and sporadic HBs. The first suggests that sporadic HBs may arise from alterations in hypoxia-sensing pathway other than VHL, producing a histologically-identical phenotype with excessive angiogenesis. A candidate gene is TCEB1, which encodes. VHL-binding partner belonging C. Genomic sequencing of clear cell renal carcinoma has shown somatic mutations in TCEB1 in a minority of cases lacking VHL mutations. The second explanation is that earlier bulk sequencing techniques were technically limited and may have underestimated the full extent of VHL inactivation [93]. Despite their classification as benign WHO grade 1 tumor [94], HBs are associated with significant morbidity due to the cumulative effects of the primary tumor or development of peritumoral cysts, which are often large [95]. In some cases, tumor recurrence or progression may occur [96] and, more rarely, leptomeningeal dissemination has been reported [97].

HB cell of origin

It remains unclear whether HBs originate from an embryologically arrested "hemangioblast" stem cell that has subsequently differentiated into the distinct cellular component supporting the tumor architecture [41,46]. A series of immunohistochemical and ultrastructural studies have failed to clarify the origin of the stromal cells. Consequently, HBs remain classified as tumors of ''uncertain histogenesis'' [47]. Decades ago, it was hypothesized that HBs arise from a ''congenital anlage", with histologic features reflecting an "embryologic type of the tumor cell [48]. Stein et al. [98] suggested an Angiomesenchymal origin for HB, based on developmental biology observations originally described by Sabin [99]. Sabin [99] and Murray [100] investigated the morphologic evolution of embryonic Angio mesenchymal tissue into hemangioblasts. However, the hemangioblast itself remained an ''hypothetical'' cell until Choi et al. [101] reported the identification of a common precursor for hematopoietic and endothelial cells. The generation of hemangioblasts from embryonic stem cells [101] enabled detailed analysis of gene and protein expression during embryonic hematopoiesis and vasculogenic.

Consequently, several proteins have been identified that are directly associated with pre-mesangioblast and hemangioblastic differentiation [102]. These include growth factors, transcription factors and transmembrane receptors such as brachyury, Scl, Csf-1R, Gata-1, Flk-1, and Tie-2 [103]. Various hypotheses regarding HB histogenesis have been proposed implicated glial, endothelial, arachnoid, neuroendocrine, fibro-histiocytic cells, embryonic choroid plexus, neuroectodermal cells, or heterogeneous cell populations [104]. These unresolved interpretations have led to the current WHO classification of HBs as neoplasms of ''uncertain histogenesis'' [47]. Although earlier immunohistochemical studies were unable to definitively identify the origin of stromal cells, the complex immunophenotype combined with their unique morphology may suggest that these cells lack a direct cytologic counterpart in mature brain tissue or in tissues outside the CNS.

Other investigators, based on the morphologic heterogeneity of HBs, have focused on the cytogenetic relationship between stromal and vascular cells. Some studies [105,106] have suggested differentiation of stromal cells into vascular cells, whereas others detected no transition of stromal cells into 'Vasoformative' elements and suggested that vascular and stromal cells represent distinct cytologic components [107,108]. However, another report identified ultrastructural evidence of Weibel-Palade body formation within the cytoplasm of stromal cells, suggesting vascular differentiation potential of these cells [109].

Proteins expressed during early hemangioblast differentiation have recently identified, including Scl, also known as Tal-1, which regulates proliferation and self-renewal of multipotent hematopoietic cells [110] and acts as a regulator of erythroid cells differentiation [111], as well as brachyury, a transcription factor essential for posterior mesoderm formation, differentiation, and axial development in vertebrates [103]. Additional proteins involved to vasculogenesis, Flk-1 and Tie-2, and hematopoiesis, Csf-1R and Gata-1, have also been associated with hemangioblast development [103]. Flk-1, also known as kdr, is a receptor tyrosine kinase whose ligand is Vascular Endothelial Growth Factor (VEGF), a key mediator of endothelial cell differentiation. The Tie-2 receptor tyrosine kinase plays an important role in angiogenesis, particularly in vascular network formation. Csf-1R is a transmembrane protein tyrosine kinase receptor for Csf-1, a macrophage-specific growth factor. Gata-1 is a tissue-specific transcription factor essential for erythroid and megakaryocytic development [112]. Notably, these proteins were consistently expressed in HB stromal cells, an observation that strongly supports the hypothesis that embryonic progenitor cells with hemangioblastic differentiation potential represent the cytologic counterpart of the stromal cell population.

Another model suggests that stromal cells are genetically distinct due to VHL deficiency and promote reactive angiogenesis by recruiting normal endothelial cells through pseudo-hypoxia-mediated paracrine signaling. This model contrasts with the alternative hypothesis of an embryologically arrested, heritable "hemangioblast" clone that transdifferentiates into the diverse cellular components comprising the tumor [46,113]. Accordingly, it has been suggested that HBs are primarily comprised of developmentally arrested hemangioblastic stem cells with the capacity to differentiate into primitive vascular structures and RBCs, analogous to embryonic angioblastic mesenchyme [39].

In areas of blood island differentiation within HBs, co-expression of Erythropoietin (Epo) and its receptor (Epo-R) has been demonstrated [114]. Epo-R is expressed during early embryonic blood island formation in mice between embryonic days 8.0 to 9.5 [115] and is upregulated during early blood island differentiation [115]. Epo is a HIF target protein and is upregulated following HIF activation in VHL-deficient stromal cells. Consequently, it has been suggested that the concurrent expression of developmental proteins and HIF target proteins may establish autocrine and paracrine signaling loops that promote tumor growth. Following the observation of consistent Tie-2 expression in stromal cells, co-expression of Ang-1, another HIF target protein was investigated [116].

These findings led to the identification of a potential Tie-2/Ang-1 autocrine/paracrine loop in HB stromal cells. This discovery was preceded by the demonstration of three additional potential autocrine/paracrine loops, transforming growth factor-α (TGF-α), another HIF target protein [117], and its receptor [118], Flk-1 and its HIF-regulated ligand VEGF [119], and stromal cell-derived factor-1 (SDF-1) with its receptor CXCR4 [120]. Moreover, the Tie-2/Ang-1 autocrine/paracrine loop has also been identified in other human neoplasms [121].

Molecular Biology of HB

Despite the presence of CNAs in a small subset of cases [53], the HB exome is notably simple and lacks additional oncogenic driver mutations [52,54]. These tumors are largely diploid with few chromosomal abnormalities [49,50], and have served as prototypic lesions for studying genomic drivers of hypoxia-mediated metabolism in cancer [42]. VHL mutations are detected in approximately 10% to 44% of sporadic HBs [51]. The reported frequency of chromosome 3 aneuploidy in sporadic tumors ranges from 18% to 69% [49,50]. However, only one report identified concurrent somatic VHL mutation and LOH of VHL in one of 13 sporadic HBs [50], while another detected missense mutation with VHL deletion by comparative genomic hybridization in two of 16 sporadic HB cases [49]. These findings may be explained by low VHL mutant allele fractions restricted to the neoplastic "stromal" cell population in sporadic HBs, in contrast to familial tumors, which are characterized by heterozygous germline VHL mutations.

Mutations of the VHL tumor suppressor gene, located on chromosome 3p 25.3 appear to play a role in both sporadic and VHL disease-associated tumors [52-54]. However, the genetic determinants underlying the clinical heterogeneity of HBs remain largely unknown. Loss of chromosome 3p or the entire chromosome 3 represents the most common cytogenetic abnormality in HBs. Other recurrent abnormalities include losses of chromosome regions 1p11-p31, chromosome 9,12 (q24.13), and 18q, as well as gains of chromosome regions 1 (p36.32), 7 (p11.2), and chromosome 19 [122].

Transcriptomic and lipidomic analyses of cystic and solid HBs have identified dysregulation of lipid metabolism-related genes in cyst-forming tumors [123], however the underlying molecular mechanisms remain unclear. In a recent study by Takayanagi et al., molecular characterization of the VHL promoter revealed epigenetic differences between sporadic and VHL-associated HBs [53], raising the possibility that DNA methylation alterations may define biologically relevant subgroups.

Mutations in ARID1B, a tumor suppressor gene implicated multiple cancer types [55,56], have also been reported. Further studies are required to determine whether these subclonal variants are functionally significant in driving sporadic HB development [57]. HBs are composed of vascular and ''stromal'' cells. The neoplastic "stromal" cells account for approximately 10-20% of the total tumor cell population, while the remainder consists of vascular endothelial cells, pericytes, and other nucleated cells, such as lymphocytes, present within the vascular channels [104]. LOH analyses of micro dissected stromal cells have demonstrated that these cells represent the neoplastic, VHL-deficient component of HBs [104,114,124].

As previously discussed, the high prevalence of recurrent somatic VHL mutations (approximately50%) and LOH at the chromosome 3p (approximately 72%) leads to biallelic VHL inactivation in 47% of sporadic HBs and inactivation of at least one VHL allele in 78% of cases [52]. Biallelic VHL loss results in impaired degradation of HIF-1α, which subsequently drives aberrant transcription of hypoxia-responsive genes, including VEGF and PDGFB [125]. Consequently, the tumor mass is composed predominantly of non-neoplastic endothelial cells and surrounding pericytes, with only a minor fraction consisting of neoplastic "stromal" cells that harbor the driver genetic alterations. Thus, HB tumorigenesis appears to be consisted of a small subpopulation of neoplastic stromal cells that recruit and interact with various non-neoplastic cellular components to generate the characteristic tumor architecture [39,126].

The Notch signaling pathway appears to be involved in HB pathogenesis [127]. Additional candidate genes implicated in HB development include EGFR, PTCH, RB1, PTPN11, FLT3, IRF4, FGFR1, CHEK2, PRDM16, MKL1, GPHN, FOXP1, GPC3, IKZF1, HOXA9, HOXA11, HOXC13, HOXC11, HOXD11, and HOXD13 [122]. Copy number gains involving miR-551a (located within the PRDM16 locus), as well as gains of miR-196a-2 and miR-196b, have also been identified in HB samples [122].

Conclusion

PCNSL and HB constitute a complex group of diseases characterized by marked genomic, biological and clinical heterogeneity. Neoplastic subtypes harboring alterations in genes that play critical roles in CNS development have been identified, and murine models based on several of these findings have been established. Significant progress has been made in elucidating the molecular pathogenesis of PCNSL leading to the clinical use of targeted therapeutic agents, including those aimed at inhibiting NF-kB pathway activation. However, further investigation is required to clarify the spectrum and functional significance of molecular alterations responsible for uncontrolled cell proliferation in the majority of these neoplasms.

Hemangioblastoma	Molecular alterations
Tumor suppressor genes inactivation	VHL (located on chromosome 3p25-26) [52-57]
Functional VHL protein (pVHL) loss	Overproduction of VEGF [112, 119], PDGFB [124,125], Epo [114,115]
Copy Number Variations (CNVs)	Chromosome 12q (including PTPN11 gene), 1p11-p31, 3p13 (FOXP1), 6q, 8p11.22 (FGFR1), 12q24.13,13q12.2 (FLT3),18q,22q13.1 (MKL1), 22q12.1 (CHEK2) loss [122], Chromosome 1p36.32 and 7p11.2 gains (inclu-ding EGFR gene) [59], chromosome 19, 2q31.1 (HOXD11, HOXD13, HOXD1, 1HOXD13) 9q22.32 (PTCH),12q13.13 (HOXC 13, HOXC11), Xq26.2 (GPC3) gain [122]
Loss of Heterozygosity (LOH)	Chromosome 6q (sometimes concurrent with 3p loss, possible involvement of ZAC1 tumor sup-pressor gene) [107,114,123]
Gene mutations	ARID1B gene [55-57]
Signaling pathways alterations	EGFR overexpression [122], Notch receptor/ effector expression (especially NOTCH1, NOTCH4, HES1, HESS5) [127]
Candidate genes genomic aberrations	PRDM16, PTPN11, HOXD11, HOXD13, FLT3, FGFR1, FOXP1, GPC3, HOXC13, HOXC11, MKL1, IRF4, GPHN, IKZF1, RB1, HOXA9, HOXA11 and several microRNA, including hsa-miR-196a-2, and miR-551a [122]

Table 1: Molecular alterations in Hemangioblastoma

Primary Central Nervous System Lymphoma	Molecular alterations
Point mutation (non-Somatic Hypermutation (SHM)/a (aberrant) SHM	Genes coding for ATM, TP53, PTEN, PIK3CA, JAK3, CTNNB1, PTPN11, KRAS [5,15], PIM1, BTG2 [5,13, 14, 26], MYD88 [5,10-14], CD79B [29,77,78], MALT1 [22], CARD11 [5,9-13,21], OSBPL10 [13,26]
SHM/aSHM	BCL6 promoter substitution [6-8], PIM1, PAX5 [35, 36,39,79], RhoH/TTF, MYC proto-oncogene activation [90,91], IGH (Immunoglobulin Heavy) locus translocation [90,99]
Genetic material gain	12q (STAT6, MDM2, CDK4, MDM2, GLI1) [16-20], 1q, 7q, 18q [18] leading to NF-kB activation
Genetic material loss	6p21 (HLA) immune escape [16,17], 9p21 (CDKN2A) proliferation [5,16,25,26], 6q21-23 [5,16,17,26] (PRDM1 tumor activation, A20 (TNFAIP3 NF-kB activation) [75,82]
DNA hypermethylation	CDKN2A [19,25,32,33,84-86], DAPK, $p14^{ARF}$, $p16^{INK4A}$, RFC, MGMT no expression [32,33], CDKN1B, RB1 [18- 20], TERT promoter mutations [34,35]
Deletion	CDKN2A [18,19,25,32,33,84,85], RB1, CDKN1B [18-20]

Table 2: Molecular alterations in Primary Central Nervous System Lymphoma

Accessibility's

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