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Original Research Article

The P53 and P75^{ntr} Expression Status in Medulloblastomas: An Insight

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Abstract:

Introduction: Medulloblastomas (MBs) are primitive neuroectodermal tumors (PNETs) located in the cerebellum. They are the most common malignant brain tumors in children, but their origin remains a mystery. MB cells express various neuronal and glial markers, suggesting they arise from different stages of neural development.

Materials and Methods: In this study, we used immunohistochemistry to examine the expression patterns of the tumor suppressor gene p53 and the common low-affinity neurotrophin receptor p75NTR in 42 MB samples.

Results: We found that 7 out of 42 medulloblastomas (16.6%) were positive for p53, with no significant difference observed between different subtypes. P75NTR expression was detected in 3 out of 16 desmoplastic nodular medulloblastomas (18.7%) and 2 out of 26 classic medulloblastomas. Interestingly, our study found a slightly higher p53 expression rate (16.6%) compared to previous reports (0-10%).

Conclusion: While p75NTR may be upregulated in a subset of MBs, further investigation with larger studies is needed to confirm this association. Additionally, our findings regarding p75NTR expression differ from prior studies that reported 100% positivity in desmoplastic medulloblastomas.

Keywords: Meduloblastoma, primitive neuroectodermal tumors, p53 gene, p75 neurotrophin receptor.

Introduction

Medulloblastomas are a type of pediatric cerebellar embryonal tumor and account for roughly 25% of all childhood intracranial tumors. These highly malignant tumors are classified as WHO grade IV. Histologically, they are characterized by sheets of immature cells. The current WHO classification system recognizes several medulloblastoma subtypes, including classic, desmoplastic, nodular, large cell, and melanotic medulloblastomas. [1]

Extensive cytogenetic and molecular research has revealed frequent chromosomal abnormalities in medulloblastomas. These include isochromosome 17q, monosomy 17p, trisomy 17q, and loss of heterozygosity (LOH) in chromosomes 17p, 10, and 21. [3-5] However, studies investigating oncogene over expression and amplification patterns haven't identified any consistently predictive changes for medulloblastoma. [6-7]

While other studies have identified an additional locus telomeric to 17p13, loss of heterozygosity (LOH) for chromosome 17p has been reported in approximately 45% of the limited number of medulloblastomas investigated [3-5]. This has allowed for the tentative localization of a potential medulloblastoma tumor suppressor gene to 17p13 [3]. The co-localization of the LOH region at 17p13 with the p53 gene suggests a potential role for p53 in medulloblastoma biology [7,8]. Mutations and deletions of the p53 gene are well-documented in numerous adult cancers, including brain tumors, colon cancer, lung cancer, breast cancer, and soft tissue sarcomas [9-12]. In the case of gliomas, p53 mutations have been linked to the clonal expansion of mutant cells, promoting progression from low-grade to high-grade tumors [12].

The p53 gene encodes a DNA-binding protein of approximately 53 kDa (kilodaltons) [13]. This protein regulates the transcription of genes involved in cell proliferation and cell cycle progression, such as IMP dehydrogenase [15] and the cdk2 inhibitor protein p21 (CIP1/WAF1) [16]. p53 controls the G1-S phase transition in proliferating cells [14]. Most mutant p53 alleles lack this ability, leading to the loss of p53-mediated cell cycle arrest, which is crucial for DNA repair and maintaining genome integrity [18].The p53 protein can also regulate its own activity by controlling the expression of the mdm2 gene [19]. The mdm2 gene encodes a protein that binds to p53, inactivating its function [20].

Amplification of the mdm2 gene has been observed in sarcomas [20, 21] and can sometimes occur as part of a larger amplified region including the cdk4 gene and, less frequently, the gli gene [22]. Mdm2 amplification provides another mechanism for p53 inactivation in tumors that lack p53 gene mutations.

Studies have shown a high frequency of p53 mutations [23, 24] or mdm2 gene amplification [20, 21] in rhabdomyosarcoma and osteogenic sarcoma, while Wilm's tumor, neuroblastoma, and hepatoblastoma exhibit a lower frequency of these alterations [25]. This suggests significant variation in the frequency of p53 mutations and mdm2 amplification across different childhood solid tumors.

Only a few studies have investigated the p53 gene in medulloblastomas, and these studies involved a small number of cases [11,26,27]. Their findings suggest a low prevalence of p53 gene alterations in this tumor type.

Neurotrophic factors and their receptors play a critical role in the differentiation and maintenance of developing neuronal progenitor cells. Physiologically, the growth and differentiation of cerebellar granular cells are regulated by the neurotrophins BDNF and NT-3, along with the coordinated expression of their specific receptors, TrkB and TrkC, respectively [28].

The p75 neurotrophin receptor (p75NTR), previously known as the low-affinity nerve growth factor receptor, belongs to the tumor necrosis factor receptor family. It contains a death domain and is involved in both the survival and apoptosis of neural cells [29,30]. While p75NTR has been detected in the external germinal layer (EGL) of the developing cerebellum in rodents [31,32] and humans [33,34], its specific role in cerebellar development remains unclear.

In this study, we analyzed the expression and distribution patterns of p53 and p75NTR in a series of medulloblastomas using immunohistochemistry. We further investigated the correlation between p53 and p75NTR expression with histological features, differentiation status, and patient age.

Material and Methods

This study was conducted between October 2006 and September 2008. Out of 65 cases of medulloblastoma diagnosed during this period, only 42 were eligible for inclusion. The remaining 23 cases were excluded due to unavailable tissue blocks or insufficient tissue in the blocks for immunohistochemistry.

Cases were evaluated histologically and reclassified according to the 2007 WHO classification. The following parameters were reviewed: age, sex, tumor location, histological subtypes, and anaplasia. Paraffin blocks were retrieved, and immunohistochemistry was performed for p53 (using DAKO monoclonal antibody, DO-7 clone) and p75NTR.

For p53 staining evaluation, a labelling index was calculated by counting a minimum of 1,000 nuclei. The index was determined as follows:

P53 Labeling Index [%] = (Number of positive nuclei / Total number of nuclei) x 100

A minimum of 5% of cells exhibiting nuclear positivity was considered positive for p53. Positive controls were used for both p53 and p75NTR: tissue sections from a developing brain were used for p75NTR, and positive control tissue was used for p53 (reference not provided).

Results

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Discussion

Medulloblastoma is the most common embryonal tumor of the central nervous system. It primarily occurs in children and has the potential to differentiate along a variety of histogenetic lineages. Although neuronal differentiation is most frequent, glial, melanotic, or even mesenchymal differentiation can be observed [1]. Several histological variants of medulloblastoma have been recognized, including classic, large cell/anaplastic, and desmoplastic subtypes. [1]

While this neoplasm most commonly affects children, 15-36% of cases are reported in adults. [35] Some histological subtypes exhibit distinct

behaviors in children. For example, desmoplastic medulloblastoma with extensive nodularity has a predilection for young children and may have a better prognosis. [36] Conversely, the large cell subtype has a much poorer prognosis with an increased tendency to spread to the leptomeninges. [37]

This study presents a detailed histopathological review of 42 medulloblastoma cases. Additionally, immunohistochemistry was used to analyze the tumor suppressor gene p53 and nerve growth factor receptor p75NTR in various medulloblastoma subtypes. The frequency and age distribution of medulloblastomas were documented for both childhood and adult cases.

Our study found that 61.9% of the medulloblastomas displayed classical histology. The mean age of patients with childhood medulloblastoma was 9.4 years, and 70.8% had classical histology, similar to the findings of Ferrante et al. [38] and Sarkar et al. [39] who also reported a high frequency of classical medulloblastoma in the pediatric population. In contrast to adult series, where the desmoplastic variant is often seen in 25-40% of cases, [40] the majority (80.7%) of classical medulloblastomas in our study were located in the midline. This frequent midline location of classical medulloblastoma may support the hypothesis of its origin from persistent pluripotent cells in the roof of the fourth ventricle, as proposed by Rorke et al. [41] Conversely, laterally located tumors, which were frequently desmoplastic histology (62.5%) and more common in adults, might originate from the persistent external granule cell layer of the fetal cerebellum. [42] Consistent with these findings, our study observed a higher prevalence (70.8%) of classical histology in childhood tumors. Out of 16 desmoplastic medulloblastomas 9 showed typical morphology of desmoplastic variant in our series. In children 3 out of 7 desmoplastic medulloblastomas were desmoplastic medulloblastoma with extensive nodularity (DMEN). In recent years this distinct morphological variant has been found to have been found to have favourable prognosis compared with the classical variant. [41] Till date there are 24 reported cases of MBEN in literature and largest series was reported by Giangaspero et al. [36]

Neurotrophic factors and their receptors play a critical role in the differentiation and maintenance of developing neuronal progenitor cells in both the central and peripheral nervous systems. The effects of neurotrophins are mediated by two receptor classes: the Trk family of receptor tyrosine kinases (TrkA, TrkB, and TrkC) and the enigmatic p75NTR receptor. Neurotrophins are multifunctional, influencing neuronal proliferation, differentiation, and programmed cell death. [42]

Bühren et al. [43] demonstrated p75NTR expression in medulloblastomas with a significant desmoplastic component. Their study found that 17% of classic medulloblastomas were p75NTR-positive compared to 71% of medulloblastomas with a desmoplastic component. In our study, p75NTR was positive in 3 out of 16 desmoplastic nodular medulloblastomas. Interestingly, one of the patients expressing p75NTR remained recurrence-free for 7 years.

The exact significance of p75NTR in medulloblastoma remains unclear. During development, p75NTR can induce apoptosis and promote neural differentiation. It is present in the proliferative EGL (external germinal layer) but absent in post-mitotic neurons. Bühren et al. [43] also observed a negative correlation of p75NTR expression in classic medulloblastomas, suggesting a more immature nature of this variant.

The most common cytogenetic abnormalities observed in medulloblastoma are rearrangements of chromosome 17 and the presence of double minute chromosomes. Alterations of the p53 gene/protein are relatively uncommon in this tumor type.

Loss of heterozygosity (LOH) for sequences on chromosome 17p is often associated with p53 tumor suppressor gene mutations in various cancers. However, Cogen et al. reported p53 mutations in only two out of 20 medulloblastoma specimens, [44] and Saylors et al. [45] did not detect any p53 mutations in their study of 12 medulloblastomas. In our current series, 7 out of 42 medulloblastomas (16.6%) showed p53 positivity by immunohistochemistry, with no statistically significant difference observed between subtypes. These findings are consistent with the similar frequency of p53 positivity reported by Pramanik et al. [46]

Therefore, the exact role of p53 in medulloblastoma development remains unclear. While p75NTR expression may be up regulated in a subset of medulloblastomas, further studies are needed to confirm a definitive association.

Conclusion

In summary, the present study demonstrates p53 expression in medulloblastomas, which is consistent with previous studies, although we observed a slightly higher percentage of positive cases.Our findings regarding p75NTR expression are noteworthy. We observed p75NTR expression in a subset of medulloblastomas, particularly the desmoplastic variant. However, this contradicts previous studies who reported p75NTR expression in 100% of desmoplastic medulloblastomas.

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