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NRP1 as a potential molecular target for medulloblastoma

NRP1 como potencial alvo molecular para meduloblastoma

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ABSTRACT

Introduction: Medulloblastoma is a malignant, highly aggressive and fast-growing tumor that arises in the cerebellum or the floor of the fourth ventricle and brain stem, especially in children. Even with advances in therapy, morbidity and mortality remains a major challenge. Therefore, new treatments are needed to reduce these outcomes.

Objective: To review the relationship NRP1 (neuropilin 1) and medulloblastoma as a potential therapeutic target and, also, with overall survival.

Method: This is a narrative review carried out in the PubMed and Scielo databases. The search used the following keywords: "neuropilins, medulloblastoma, brain tumors, pediatrics". The inclusion criteria were review articles, experimental studies, pre-clinical and clinical research, in English and Portuguese, and available in full text. The selected articles were analyzed based on the technologies covered, future perspectives and challenges mentioned, diseases mentioned and the central idea of the article.

Result: 30 articles were included.

Conclusion: Medulloblastomas have high transcriptional levels of neuropilin (NRP1) and their low levels are related to lower overall survival, especially in SHH. In this sense, NRP1 and its complex action system appear as a potential target for oncological therapies for brain tumors.

KEYWORDS: Neuropilin-1. NRP1. Medulloblastoma. Pediatric câncer. Brain tumor.

RESUMO

Introdução: Meduloblastoma é tumor maligno, altamente agressivo e de rápido crescimento que surge no cerebelo ou no assoalho do quarto ventrículo e tronco cerebral, especialmente em crianças. Mesmo com avanços na terapia, a morbimortalidade permanece grande desafio. Por isso, novos tratamentos são necessários para reduzir esses desfechos.

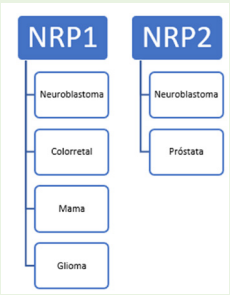
Objetivo: Revisar a relação NRP1 (neuropilina 1) e meduloblastoma como potencial alvo terapêutico e, também, com sobrevida global.

Método: Trata-se de revisão narrativa realizada nas bases de dados PubMed e Scielo. A busca utilizou as seguintes palavras-chave: "neuropilinas, meduloblastoma, tumores cerebrais, pediatria". Os critérios de inclusão foram artigos de revisão, estudos experimentais, pesquisas pré-clínicas e clínicas, em inglês e português, e disponíveis em texto completo. Os artigos selecionados foram analisados com base nas tecnologias abordadas, perspectivas futuras e desafios mencionados, doenças referidas e ideia central do artigo.

Resultado: Foram incluídos 30 artigos

Conclusão: Os meduloblastomas possuem altos níveis transcricionais de neuropilina (NRP1) e seus baixos níveis relacionam-se com menor sobrevida global, especialmente nos SHH. Nesse sentido, a NRP1 e seu complexo sistema de atuação aparece como potencial alvo de terapias oncológicas para tumores cerebrais.

PALAVRAS-CHAVE: Neuropilinas. Meduloblastoma. Tumores Cerebrais. Pediatria.



Expression of neuropilins in tumor cells

Central Message

Brain tumors are the leading cause of death among childhood neoplasms. Among them is medulloblastoma, a malignant, highly aggressive and fast-growing germ cell tumor. It is the most common brain tumor in childhood. It has heterogeneous behavior, both from a clinical and biological point of view. Thus, it is pertinent to review the relationship between NRP1 (neuropilin 1) and medulloblastoma as a potential therapeutic target, as well as in relation to overall survival.

Perspective

Medulloblastomas have high transcriptional levels of neuropilin (NRP1). In addition, its low levels are related to lower overall survival. In this sense, NRP1 and its complex system of action appear as a potential target for oncological therapies for brain tumors, and further studies are needed to qualify this hypothesis.

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INTRODUCTION

Brain tumors are the leading cause of death among childhood neoplasms.[1] Among them is medulloblastoma, which is a malignant, highly aggressive and fast-growing germ cell tumor that originates in the cerebellum or midline of the brain stem. It is the most common brain tumor in the pediatric population, accounting for approximately 20% of all primary CNS tumors in children.[2,3] It has heterogeneous behavior, both from a clinical and biological point of view.[4] It usually presents with signs and symptoms of increased intracranial pressure, such as headache, vomiting, and cranial nerve palsy. Other signs such as neurological deficits, gait ataxia, and dilatation of the ventricular system (hydrocephalus) may be present, depending on the size and location of the tumor.

Treatment usually consists of a surgical procedure, chemotherapy and radiotherapy, and the prognosis is reserved in many cases. For this reason, it is important to research new proteins involved in carcinogenesis with the objective of developing new drugs.

Neuropilin-1(NRP1), a protein encoded by the NRP1 gene, acts as a VEGFR coreceptor and plexin receptors involved mainly in neoangiogenesis and tumor progression and may represent a potential prognostic molecular target for cancer. In medulloblastoma (MB), NRP1 is associated with the promotion of survival and favors undifferentiated phenotype in tumor cells.

The objective of this review was to verify the relationship between NRP1 (neuropilin 1) and MB as a potential therapeutic target, and its relationship with overall survival.

METHOD

This is a narrative review carried out in the PubMed and Scielo databases. The search used the following keywords: "neuropilins, medulloblastoma, brain tumors, pediatrics". The inclusion criteria were review articles, experimental studies, preclinical and clinical research, in English and Portuguese, and available in full text. The selected articles were analyzed based on the technologies addressed, future perspectives and challenges mentioned, diseases referred to and the central idea of the article. 31 articles were included

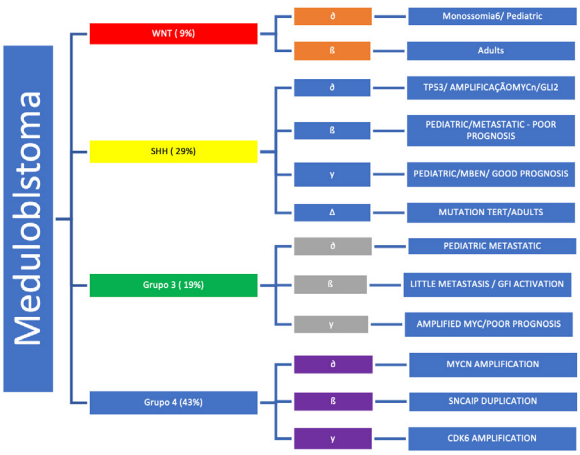
DISCUSSION

MB is the most frequent solid tumor of the central nervous system in childhood, affecting one in five children with brain tumors. Classically it is located in the posterior fossa – where about half of intracranial tumors occur in this age group – causing symptoms of intracranial hypertension and cranial nerve injury. Even though it is malignant and has a high capacity for metastatic implantation through the cerebrospinal fluid route, its mortality has drastically reduced with the standard treatment that combines surgery, chemotherapy and radiotherapy. However, this reduction was at the expense of poorer quality of life due to neurological lesions and the emergence of secondary neoplasms.[5] In addition, the behavior of this type of disease is heterogeneous both clinically and pathologically. In this sense, MB continues to be a challenge for neurosurgery, in which maintaining quality survival is the goal to be achieved.

Although it is found in all age groups, it is in the first decade of life that its peak incidence (5-9 years) is in the first decade of life. Also, there is a higher 2:1 ratio for boys. Preferably, it affects the cerebellar vermis and has no correlation with family history. Also, it can be associated with some syndromes, such as Li-Fraumeni, Turcot, and Gorlin.[6]

Pathophysiology

MB has very undifferentiated cells. It was believed to come from a cell called "meduloblast". Matsuo et al.[4] reported that MB derives from precursor residual granular cells located in the outer granular layer of the medullary velum of the cerebellum.[3] One of the ways of classifying these tumors is histological, with 4 subtypes: classic, desmoplastic/nodular, anaplastic/large cell, and extensive nodularity.[7] The classic type is the most frequent, and the anaplastic and extensive nodularity type have the worst prognosis.[8] However, the behavior of tumors of the same histological type is heterogeneous, both in terms of treatment and pathological. In this sense, stratification by other methods was necessary. Thus, molecular biology, through the knowledge of the developmental signaling pathways of oncogenesis, classifies it into several subtypes. Early gene expression profiling classified MBs into 4 distinct major molecular subtypes: 2 with mutations in developmental pathways, Sonic Hedgehog (SHH) and Wingless (WNT), and 2 others: group 3 (G3) characterized by MYC amplification in 17% of cases, and group 4 (G4) which occurs in the largest number of patients, with a low level of genetic alterations and a higher rate of metastases. Also, from this classification, there are different subtypes of MB (Figure 1).[9] It demonstrates the difference in behavior in relation to biomolecular alterations with protein amplification, as well as in clinical behavior, such as prognosis and greater chance of developing metastases.



Source: Menyhart[9]

FIGURE 1 — Molecular stratification of medulloblastoma

Stratified classification demonstrates prevalence. Also, classification of subtypes associated with molecular alterations related to the profile, greater chance of metastases and prognosis.[9]

Classification

In the last review of neuropathology, published in 2021, Louis DN10 presented an update to this classification due to heterogeneous clinical and biological behavior. The WNT and SHH MBs were maintained, but the latter were divided in relation to TP53 (mutant or wild). In addition, types 3 and 4 were replaced by non-WNT/non-SHH (Table 1).[7]

TABLE 1 — MB Classification according to the World Health Organization[10]

Classification of medulloblastoma
Medulloblastomas, molecularly defined
Medulloblastoma, WNT-activated
Medulloblastoma, SHH-activated and TP53-wild
Medulloblastoma, SHH-activated, and TP53-mutant
Medulloblastoma, non-WNT/non-SHH
Medulloblastomas, histologically defined

Treatment

Treatment usually includes surgical resection, radiation therapy, and chemotherapy11. The goal of surgery is to resect as much of the tumor as possible without causing neurological damage. Radiation therapy is often used to reduce the risk of recurrence and improve the chances of long-term survival. Chemotherapy helps eliminate remaining cancer cells and reduce the risk of recurrence.[11,12] In the case of MBs, the overall survival is 45%13 and the deleterious effects of the treatment are frequent. Thus, the treatment is complex, and, despite the advances, the quality of life continues to be a challenge and constant concern for professionals in this area. Therefore, a multidisciplinary team and new therapies related to NRP1 can play an important role in your therapy.

Neuropilins

Neuropilins are multifunctional transmembrane glycoproteins involved in physiological and pathological processes.[14] First identified as the part responsible for the formation of the CNS through neuronal migration activity, neuropilins – NRP1/NRP2 – also have importance in angiogenesis, through stimulation of endothelial growth factors and in the modulation of endothelial cells.[15] Neuropilin 1 (NRP1) acts on tumor growth and dissemination by participating in the stimulation of tumor growth factors, acting especially through 2 different ligands: semaphorin class 3 and an endothelial growth factor isoform, VEGF.[16,17] In this sense, through bonds and coreceptors, semaphorins, VEGF(R) and plexins18 They participate in different pathophysiological processes, such as cell survival, migration, and proliferation. The semaphorin3/NRP1/plexinA1 complex is related to neuronal migration, inhibiting axonal orientation signals for projection neurons, apoptosis, and tumor suppression (Figure 2). When associated with vascular endothelial growth factors (VEGF), NRP1 enhances interaction with its receptors (VEGFR) by stimulating the process of angiogenesis and lymphangiogenesis17. Plexins are binding agents between NRP1 and semaphorins that influence the process of this molecular pathway.

Allied to this, they play an important role in the regulation of the immune response through dendritic cells where they participate in the process of adhesion of these with other defense cells such as T lymphocytes, providing a response from both the innate and the adaptive immune system.[19] Some studies have shown a correlation between increased levels of neuropilins in tumor vessels, which suggests a relationship with tumor progression12. Pan et al.[15] demonstrated that by blocking the function of both proteins, NRP1 and VEGF, in tumor models, there was a reduction in their growth. Some specific types of tumors are identified and related to these proteins (Table 2, Figure 2)18. In pediatric brain tumors, there are already relationships between increased NRP1 expression and worse prognosis.[20] In addition, several studies have demonstrated the overexpression of NRP1 in all types of brain tumors, regardless of type or grade, being an isolated prognostic factor (Figure 4).[20-23]

TABLE 2 — Neuropilin expression in tumor cells

	Neuroblastoma	Colorectal	Breast	Glioma	Prostate
NRP1	X	X	X	X	
NRP2	X				X

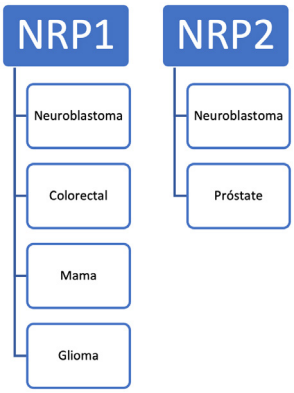
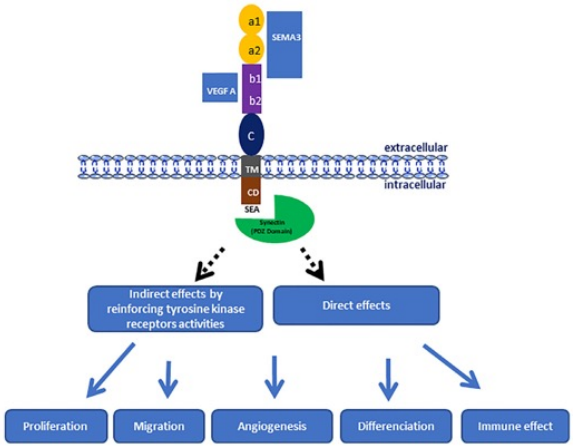


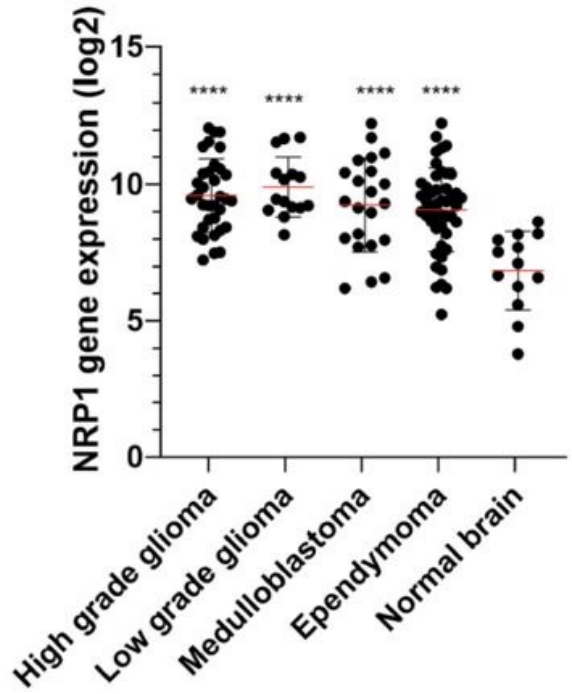
FIGURE 2 — Expression of neuropilins in tumor cells: NRP1 is present in frequent tumors such as the breast and also in those of the CNS

Schematic representation of the NRP1 neuropilin structure indicates the binding regions of natural ligands and their involvement in the progression of pediatric brain tumors through the control of different biological processes (Figure 3).[20]



Source: Douyere M.[20]

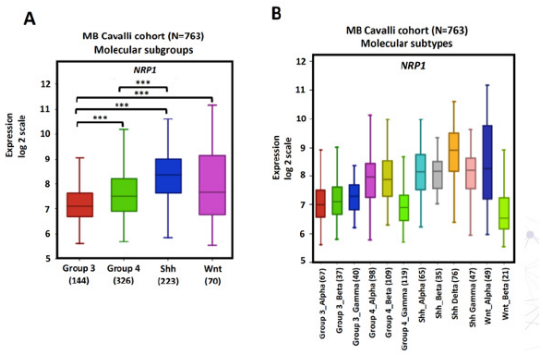
FIGURE 3 — Schematic representation of the NRP1 structure with its ligands and involvement in tumor progression



Source: Douyere M[20]

FIGURE 4 — Expression (log 2) of NRP1 in different pediatric tumor cells and normal brain

Araujo, M. A. et al.[24] analyzed datasets derived from 763 samples of primary patient MBs subgrouped by molecular characteristics revealed high levels of mRNA content of the NRP1 target gene in all molecular subgroups. The Shh subgroup (n = 223) had significantly higher transcriptional levels than Group 3 (n = 144) and Group 4 (n = 326). Stratifying the samples by molecular subtypes, they observed a significant increase in NRP1 levels, especially in Shh α, β, Δ and γ tumors compared to the other subtypes. NRP1 expression in MB samples showed that low expression was related to reduced overall survival of patients in all subgroups. The analysis of the correlation of overall survival with transcriptional levels of NRP1 in the subgroups analyzed separately showed that low transcriptional levels were associated with lower survival in the subgroups Group 3 (p = 0.047) and Shh (p = 0.031). This study was carried out through a sample of a public database - Medulloblastoma Advanced Genomics International Consortium (MAGIC)[12] - which contains approximately 2000 in silico samples of registered MBs from several centers specialized in neurosurgery in the world. The classification of the subgroups and the number of patients in each one was performed according to the availability of stratification in each database. All subgroups were compared using. Overall survival was measured from the time of the date of initial diagnosis to death or the date of the last follow-up, using it combined with gene expression data according to the availability of each database (Figure 5).



Source: Araujo, MA et al.[24]

FIGURE 5 — Analysis of correlation between NRP1 expression and overall survival in MB (n = 763)

In addition, these authors revealed high levels of mRNA content of the target gene NRP1 in all molecular subgroups of MB. Stratifying the samples by molecular subtypes, a significant increase in NRP1 levels was observed, especially in Shh α, β, Δ and γ tumors compared to the other subtypes. NRP1 expression was related to reduced overall survival of all subgroups analyzed together; its correlation with the transcriptional levels of NRP1 analyzed separately demonstrated that low transcriptional levels are associated with lower survival.

Advances in the therapy of this type of neoplasm have provided a significant increase in survival. Wide surgical resection has an important prognostic factor, as well as the age of diagnosis and the presence of metastases. However, deleterious effects of the treatment occur frequently and produce cranial nerve lesions, cardiac and pulmonary dysfunctions, gonadal hypofunction, growth and reproductive dysfunction, behavioral changes, neuroendocrine disorders, and new neoplasms.[25] These effects act in a way that compromises the quality of life and remain challenging.[11] In addition, despite survival between 42-50%[13]. At 5 years, most recurrences occur in the first 2 years after surgery, which requires constant surveillance in these patients. In this sense, when the diagnosis is made early, and the patient does not have metastases, this survival reaches 70-80% in 5 years.[11] This demonstrates that therapeutic interventions and early diagnostic methods are necessary for a better prognosis and reduction of these deleterious effects.

The role of neuropilins (NRP1/NRP2) in tumor development is not yet well defined. Its most diverse forms of action through multiple agents (VEGFs/semaphorins/TGF/PIGF) are present in several tumor types and seem to play an important role in their development.[20] The role of NRP1 in the immune regulatory activity seems to be important, because through a laboratory study with rats with low expression of NRP1 the response to autoimmune disease such as multiple sclerosis related to encephalomyelitis was worse compared to rats with overpressure.[26] In addition, it has been shown that blocking the function of both NRP1 and VEGF in tumor samples results in effective growth reduction and helps in tumor suppression.[15] The relationship between NRP1 and endothelial growth factors also demonstrates importance in tumor angiogenesis and nutrition.[16] Several studies suggest this relationshi[14,20,27] inferring an important role in the appearance of brain neoplasms. Zhang et al.[28] demonstrated that NRP1 acts to produce genetic transcription mediating tumor progression, invasion and proliferation in gliomas. Others reveal high levels of neuropilins in neoplasms such as leukemias.[29] In neuroblastomas, elevated NRP1 expression levels are related to longer survival30, and this is in line with what was published by Ishizuka et al30 who also demonstrated this finding by adding that silencing NRP1 acts in the promotion of tumor migratory invasive activities. In a divergent way, Snuderl et al.[27] described that high levels of the PIGF/NRP1 complex are correlated with a worse prognosis in MBs. In the same sense, Douyere et al20 they also linked high transcriptional levels of neuropilin1 in childhood brain tumors with a worse prognosis.[20] Solomon et al,26 demonstrated the relationship between NRP1 and the immune response of T cells, which are directly linked to tumor progression and inflammatory response produced in the CNS.[31]

CONCLUSION

Medulloblastomas have high transcriptional levels of neuropilin (NRP1). In addition, their low transcriptional levels are related to lower overall survival, especially in SHH. In this sense, NRP1 and its complex system of action appear as a potential target for oncological therapies for brain tumors, and further studies are needed to qualify this hypothesis.

Authors' contributions

Conceptualization: Moisés Augusto de Araujo
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Supervision: Gustavo Rassier Isolan
Writing (original draft): All authors
Writing (proofreading and editing): All authors

REFERENCES

1. Pollack IF. Brain tumors in children. N Engl J Med. 1994;331(22):1500-7. Doi: 10.1056/NEJM199412013312207
2. Schepke E, Tisell M, Kennedy C, Puget S, Ferroli P, Chevignard M, et al. Effects of the growth pattern of medulloblastoma on short-term neurological impairments after surgery: results from the prospective multicenter HIT-SIOP PNET 4 study. J Neurosurg Pediatr. 2020;17:1-9. Doi: 10.3171/2019.11.peds19349
3. Cho YJ, Tsherniak A, Tamayo P, Santagata S, Ligon A, Greulich H, et al. Integrative genomic analysis of medulloblastoma identifies a molecular subgroup that drives poor clinical outcome. J Clin Oncol. 2011;29(11):1424-30. Doi: 10.1200/jco.2010.28.5148
4. Matsuo S, Takahashi M, Inoue K, Tamura K, Irie K, Kodama Y, et al. Thickened area of external granular layer and Ki-67 positive focus are early events of medulloblastoma in Ptch1(+)/(-) mice. Exp Toxicol Pathol. 2013;65(6):863-73. Doi: 10.1016/j.etp.2012.12.005
5. Ning MS, Perkins SM, Dewees T, Shinohara ET. Evidence of high mortality in long term survivors of childhood medulloblastoma. J Neurooncol. 2015;122(2):321-7. Doi: 10.1007/s11060-014-1712-y
6. National Cancer Institute. Childhood Medulloblastoma and Other Central Nervous System Embryonal Tumors Treatment (PDQ®)–Health Professional Version. 2023. Disponível em: https://www.cancer.gov/types/brain/hp/child-cns-embryonal-treatment-pdq
7. Li KK, Lau KM, Ng HK. Signaling pathway and molecular subgroups of medulloblastoma. Int J Clin Exp Pathol. 2013;6(7):1211-22.
8. Gajjar A, Chintagumpala M, Ashley D, Kellie S, Kun LE, Merchant TE, et al. Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): long-term results from a prospective, multicentre trial. Lancet Oncol. 2006;7(10):813-20. Doi: 10.1016/s1470-2045(06)70867-1
9. Menyhart O, Gyorffy B. Molecular stratifications, biomarker candidates and new therapeutic options in current medulloblastoma treatment approaches. Cancer Metastasis Rev. 2020;39(1):211-33. Doi: 10.1007/s10555-020-09854-1
10. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncol. 2021;23(8):1231-51. Doi: 10.1093%2Fneuonc%2Fnoab106
11. Quinlan A, Rizzolo D. Understanding medulloblastoma. JAAPA. 2017;30(10):30-6. Doi: 10.1097/01.jaa.0000524717.71084.50
12. Cavalli FMG, Remke M, Rampasek L, Peacock J, Shih DJH, Luu B, et al. Intertumoral Heterogeneity within Medulloblastoma Subgroups. Cancer Cell. 2017;31(6):737-54. Doi: 10.1016/j.ccell.2017.05.005
13. Dufour C, Beaugrand A, Pizer B, Micheli J, Aubelle MS, Fourcade A, et al. Metastatic Medulloblastoma in Childhood: Chang's Classification Revisited. Int J Surg Oncol. 2012;2012:245385. Doi: 10.1155/2012/245385
14. Chaudhary B, Khaled YS, Ammori BJ, Elkord E. Neuropilin 1: function and therapeutic potential in cancer. Cancer Immunol Immunother. 2014;63(2):81-99. Doi: 10.1007/s00262-013-1500-0
15. Pan Q, Chanthery Y, Liang WC, Stawicki S, Mak J, Rathore N, et al. Blocking neuropilin-1 function has an additive effect with anti-VEGF to inhibit tumor growth. Cancer Cell. 2007;11(1):53-67. Doi: 10.1016/j.ccr.2006.10.018
16. Vieira JM, Schwarz Q, Ruhrberg C. Selective requirements for NRP1 ligands during neurovascular patterning. Development. 2007;134(10):1833-43. Doi: 10.1242%2Fdev.002402
17. Eichmann A, Makinen T, Alitalo K. Neural guidance molecules regulate vascular remodeling and vessel navigation. Genes Dev. 2005;19(9):1013-21. Doi: 10.1101/gad.1305405
18. Kreuter M, Bielenberg D, Hida Y, Hida K, Klagsbrun M. Role of neuropilins and semaphorins in angiogenesis and cancer. Ann Hematol. 2002;81(Suppl 2):S74.
19. Roy S, Bag AK, Singh RK, Talmadge JE, Batra SK, Datta K. Multifaceted Role of Neuropilins in the Immune System: Potential Targets for Immunotherapy. Front Immunol. 2017;8:1228. Doi: 10.3389/fimmu.2017.01228
20. Douyere M, Chastagner P, Boura C. Neuropilin-1: A Key Protein to Consider in the Progression of Pediatric Brain Tumors. Front Oncol. 2021;11:665634. Doi: 10.3389%2Ffonc.2021.665634
21. Latil A, Bieche I, Pesche S, Valeri A, Fournier G, Cussenot O, et al. VEGF overexpression in clinically localized prostate tumors and neuropilin-1 overexpression in metastatic forms. Int J Cancer. 2000;89(2):167-71. Doi: 10.1002/(sici)1097-0215(20000320)89:2%3C167::aid-ijc11%3E3.0.co;2-9
22. Bachelder RE, Crago A, Chung J, Wendt MA, Shaw LM, Robinson G, et al. Vascular endothelial growth factor is an autocrine survival factor for neuropilin-expressing breast carcinoma cells. Cancer Res. 2001;61(15):5736-40.

23. Beierle EA, Dai W, Langham MR, Jr., Copeland EM, 3rd, Chen MK. Expression of VEGF receptors in cocultured neuroblastoma cells. J Surg Res. 2004;119(1):56-65. Doi: 10.1016/j.jss.2004.01.002

24. de Araújo MA, Malafaia O, Ribas-Filho JM, Fratini L, Roesler R, Isolan GR. Low Expression of the NRP1 Gene Is Associated with Shorter Overall Survival in Patients with Sonic Hedgehog and Group 3 Medulloblastoma. Int J Mol Sci. 2023;24(14):11601. Doi: 10.3390/ijms241411601

25. Zahnreich S, Schmidberger H. Childhood Cancer: Occurrence, Treatment and Risk of Second Primary Malignancies. Cancers (Basel). 2021;13(11):2607. Doi: 10.3390/cancers13112607

26. Solomon BD, Mueller C, Chae WJ, Alabanza LM, Bynoe MS. Neuropilin-1 attenuates autoreactivity in experimental autoimmune encephalomyelitis. Proc Natl Acad Sci U S A. 2011;108(5):2040-5. Doi: 10.1073/pnas.1008721108

27. Snuderl M, Batista A, Kirkpatrick ND, de Almodovar CR, Riedemann L, Walsh EC, et al. Targeting placental growth factor/neuropilin 1 pathway inhibits growth and spread of medulloblastoma. Cell. 2013;152(5):1065-76. Doi: 10.1016/j.cell.2013.01.036

28. Zhang G, Chen L, Sun K, Khan AA, Yan J, Liu H, et al. Neuropilin-1 (NRP-1)/GIPC1 pathway mediates glioma progression. Tumour Biol. 2016;37(10):13777-88. Doi: 10.1007/s13277-016-5138-3

29. Piechnik A, Dmoszynska A, Omiotek M, Mlak R, Kowal M, Stilgenbauer S, et al. The VEGF receptor, neuropilin-1, represents a promising novel target for chronic lymphocytic leukemia patients. Int J Cancer. 2013;133(6):1489-96. Doi: 10.1002/ijc.28135

30. Ishizuka Y, Koshinaga T, Hirano T, Nagasaki-Maeoka E, Watanabe Y, Hoshi R, et al. NRP1 knockdown promotes the migration and invasion of human neuroblastoma-derived SK-N-AS cells via the activation of beta1 integrin expression. Int J Oncol. 2018;53(1):159-66. Doi: 10.3892/ijo.2018.4397

31. Buffon VA, Conti BP, Beltrame CM, Sobral ACL, Simm EB, Bark SA. Perfil epidemiológico de tumores intracranianos metastáticos submetidos à neurocirurgia. BioSCIENCE. 2022;80(2): Doi: 100-5. 10.55684/80.2.23