Aberrant signaling pathways in medulloblastomas

A stem cell connection

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ABSTRACT

Medulloblastoma is a highly malignant primary tumor of the central nervous system. It represents the most frequent type of solid tumor and the leading cause of death related to cancer in early childhood. Current treatment includes surgery, chemotherapy and radiotherapy which may lead to severe cognitive impairment and secondary brain tumors. New perspectives for therapeutic development have emerged with the identification of stem-like cells displaying high tumorigenic potential and increased radio- and chemo-resistance in gliomas. Under the cancer stem cell hypothesis, transformation of neural stem cells and/or granular neuron progenitors of the cerebellum are though to be involved in medulloblastoma development. Dissecting the genetic and molecular alterations associated with this process should significantly impact both basic and applied cancer research. Based on cumulative evidences in the fields of genetics and molecular biology of medulloblastomas, we discuss the possible involvement of developmental signaling pathways as critical biochemical switches determining normal neurogenesis or tumorigenesis. From the clinical viewpoint, modulation of signaling pathways such as TGFβ, regulating neural stem cell proliferation and tumor development, might be attempted as an alternative strategy for future drug development aiming at more efficient therapies and improved clinical outcome of patients with pediatric brain cancers.

Key words: medulloblastoma, neurobiology, signal transduction, stem cells, transforming growth factor beta, biological therapy.

Vias de sinalização aberrantes no meduloblastoma: uma conexão com célula-tronco

RESUMO

Meduloblastoma é um tumor maligno do sistema nervoso central (SNC). Na infância, representa o tumor sólido mais frequente e a principal causa de morte relacionada ao câncer. Tratamentos atuais incluem cirurgia, quimioterapia e radioterapia, que podem trazer prejuízos cognitivos e desenvolvimento de tumores secundários. Novas perspectivas terapêuticas surgem com a identificação de células-tronco em gliomas, as quais apresentam alto potencial tumorigênico e maior resistência à radioterapia e quimioterapia. A hipótese das células-tronco tumorais sugere que a transformação de células-tronco e/ou progenitores neurais do cerebelo está envolvida no desenvolvimento do meduloblastoma. Portanto, analisar alterações genéticas e moleculares envolvidas nesse processo é de grande importância na pesquisa básica e aplicada ao câncer. Nesse sentido, discutimos o possível envolvimento de vias de sinalização bioquímica críticas a ambos os processos de

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neurogênese normal ou tumorigênese, com base em evidências atuais na área de genética e biologia molecular dos meduloblastomas. Do ponto de vista clínico, a modulação de vias de sinalização como a do TGFβ, regulando proliferação de célula-tronco neural e desenvolvimento tumoral, pode ser uma estratégia alternativa para o desenvolvimento de novos medicamentos objetivando-se terapias mais eficientes e melhora do prognóstico dos pacientes pediátricos com câncer de SNC.

Palavras-chave: meduloblastoma, neurobiologia, transdução de sinal, células-tronco, fator transformador de crescimento beta, terapia biológica.

Medulloblastoma is a malignant embryonic neuroepithelial tumor that account for approximately 16% of all pediatric brain tumors[1]. In the United States, about 540 new cases are registered each year, with incidence peaking between five and ten years of age[2,3]. According to criteria established by the World Health Organization (WHO) in 2007, medulloblastomas are classified in five histological subtypes: classic, desmoplastic, medulloblastoma with extensive nodularity, anaplastic, and large-cell medulloblastoma. The latter two types are highly aggressive tumors with similar molecular features and clinical outcomes[4]. The classic symptoms include headaches, vomits and nauseas, irritability and ataxia[1,3]. The five-year survival rate for medulloblastoma depends on clinical prognostic criteria, standing around 40% and 70% for "high risk" and "standard risk" patients, respectively[5].

The choice of treatment modality depends on the age of the patient, volume of the remaining tumor, and presence of metastasis, being based mainly on tumor resection, craniospinal radiotherapy, and conventional cytotoxic therapies. However, the main limitation of current treatments is the lack of specificity which often elicits long-term adverse effects that include secondary tumors, as well as hearing, cognitive, endocrinal and vascular impairment[6]. Hence, understanding the cellular and molecular alterations involved in medulloblastoma pathogenesis is a critical step toward clinical improvements.

Despite great advances in the knowledge of medulloblastoma biology, the origin of this type of primitive neuroectodermal tumor is not yet well established. Pediatric medulloblastoma typically originates in the midline of the cerebellum, growing and compressing the fourth ventricle at the beginning of the disease progression. There is a clear genetic component in its development. Several techniques including karyotyping, fluorescence *in situ* hybridization, and comparative genomic hybridization have been used to identify chromosome alterations not only in medulloblastomas but also in other types of embryonic brain tumors[7]. One common genetic alteration in medulloblastoma is a deletion involving the short arm of chromosome 17, which is detected in 40-50% of primary tumors[8,9]. However, whether this type of deletion correlates with poor clinical prognosis still needs to be confirmed[10].

More recently, an increasing amount of studies have suggested that medulloblastomas may originate from genetic alterations affecting neural stem cells (NSC) and/or granule neuron progenitor cells from the cerebellum[4,5,11], involving aberrant signaling pathways critical to neurogenesis[12,13]. This new interplay between cancer and stem cell biology opens new avenues for studying the molecular events underlying tumorigenesis. The primitive nature of medulloblastomas makes them excellent models for such type of studies, with potential applications in oncology.

Medulloblastoma stem Cells

In the central nervous system (CNS), stem cells self-renew themselves and give rise to transient proliferating progenitors that eventually differentiate into mature neurons and glial cells. All these cellular processes are genetically regulated by a complex network of molecular interactions. In cancer, it has been postulated that genetic alterations in stem cells causing dysfunctional patterns of self-renewal and/or differentiation may lead to neoplastic stem cells and ensuing tumor development[14,15].

One of the first evidence supporting this cancer stem cell (CSC) model of tumorigenesis was reported in acute myeloid leukemia (AML)[16]. After implanting into immunodeficient mice a subset of leukemic cells with typical normal hematopoietic stem cell phenotype, the authors observed development of secondary AML that phenotypically resembled the original tumor cells found in the patient.

In solid tumors, CSC were first identified in breast cancer[17] based on the expression of CD44, a marker associated with normal mammary ductal stem cells. As observed in AML, when a small subpopulation of CD44+ cells was injected in immunodeficient mice, new tumors with histopathological features similar to the original specimen were developed. The secondary tumors were comprised by both CD44– and CD44+ cells. In contrast, no tumors were observed in animals injected with CD44– breast tumor cells.

Soon after the report of CSC in breast cancer, the CSC hypothesis was also proposed for the origin of high grade tumors from the CNS such as glioblastoma mul-

tiforme[18] and medulloblastoma[15]. Singh and colleagues[19] were the first to identify and isolate populations of CSC in medulloblastomas. Intracranial injection of medulloblastoma cells expressing the transmembrane glycoprotein CD133 were capable of generating new tumors in immunodeficient mice[15]. As little as 100 CD133+ cells were enough to develop new tumors with anatomo-pathological characteristics that closely resembled those of the original tumor. On the other hand, injections of up to 10^5 CD133– cells did not have the same tumor initiating capability. Since then, CD133 has been used as a marker of human CSC in brain tumors[15,19], in addition to being one of the hallmarks of normal neural stem cells.

Another hypothesis for the origin of medulloblastomas involves fully differentiated and mature cells acquiring a primitive, multipotent phenotype during neoplastic transformation. Thus far, no data supporting this hypothesis has been provided for embryonal brain tumors[11]. However, the recent discovery of iPS cells (induced pluripotent stem cells) demonstrated that ectopic expression of a few pluripotency-related genes is sufficient to generate embryonic stem-like cells from fibroblasts, which do become undifferentiated and tumorigenic[20], supporting the above concept.

Although the cellular nature of medulloblastomas is still in dispute, it is known that some molecular pathways activated during neurogenesis are genetically al-tered in CNS tumors[21]. Moreover, evidences based on aberrant cerebellar development indicate that populations of granule neuron precursor cells and the cellular signaling pathways that regulate their development might be involved in the formation of different subtypes of medulloblastomas[4,5].

Molecular pathways and tumorigenesis

Normal neural development depends on the activation of membrane receptors by growth factors and subsequent transduction of these messages through intracellular signaling pathways. Some of these pathways, for instance, control the expansion of granular neurons during normal embryonic and early post-natal development of the cerebellum[4]. There are several studies in the literature reporting a possible role of these same pathways in the development of CNS neoplasias, including embryonic tumors[7] (Figure).

Studies carried out with murine models of medulloblastoma suggest that tumors may be originated from precursors of granular cells known as granular cell progenitors (GCP). During normal development, Purkinje cells signal GCP to initiate proliferation through Sonic hedgehog (SHH) glycoprotein secretion. Afterwards, GCP exit cell cycle and are directed to the inner portion of external granular layer (EGL) where differentiation and migration through Bergmann's glia fibers are initiated to constitute
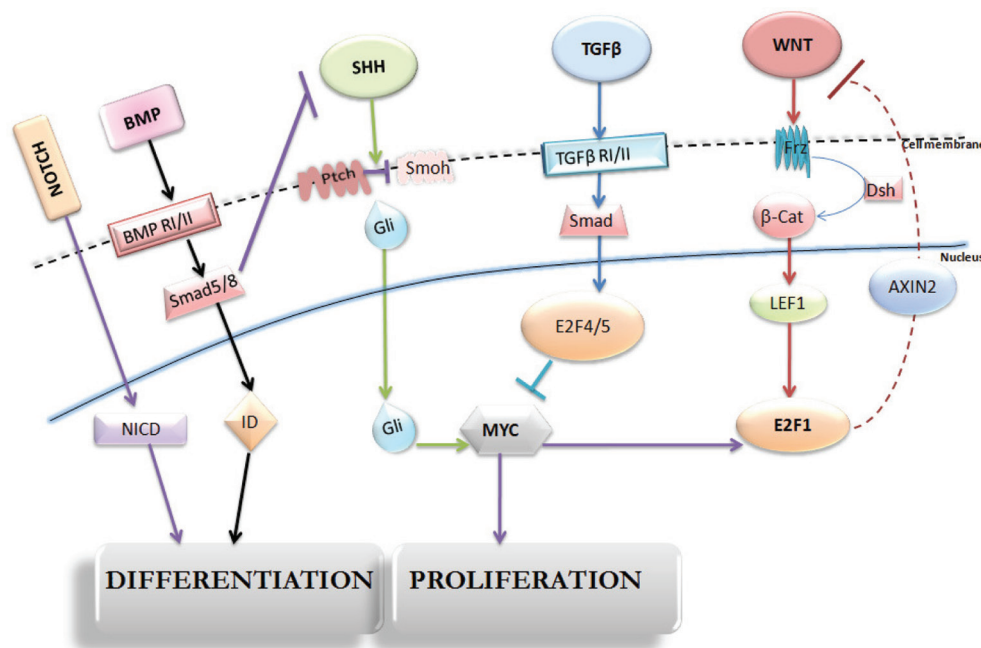

Figure. Main signaling pathways involved in medulloblastoma development. The SHH, NOTCH, WNT and TGFβ pathways are highly active during neurogenesis. Under pathological conditions, aberrant signaling may disrupt the delicate balance among GCP proliferation, migration, and differentiation processes, contributing to tumorigenesis.

the internal granular layer (IGL). All these steps in granular cell development are orchestrated by different and interacting molecular pathways. Under pathological conditions, aberrant signaling disrupting this delicate balance of GCP proliferation, migration, and differentiation may contribute to medulloblastoma development[21-23].

The Sonic Hedgehog-Patched (SHH-PTCH) pathway is the major mitogenic regulator of cerebellar EGL cells[24]. During cerebellar development, SHH glycoprotein is mainly produced by Purkinge neurons. Secreted SHH binds to PTCH receptor expressed in EGL precursor cells. After release of Smoothened (SMOH) inhibition, the pathway is activated resulting in transcription of target genes such as those encoding the PTCH and GLI transcription factors. In mice, blockage of SHH signaling pathway with antibodies reduces the amount of differentiated granular cells[25]. Although, cell proliferation is normal in the cerebellum of Gli1 knockout mice, medulloblastoma can be induced by exogenous SHH[26].

The role of SHH in granular cell proliferation is directly connected to cell cycle control, since SHH was shown to induce the expression of CYCLIN D1 and D2 during development[27]. This effect is mediated by MYCN[28], which is expressed in EGL cells during clonal expansion *in vivo* and is up-regulated *in vitro* following SHH treatment. On the other hand, MYCN specific inactivation in progenitor neural cells leads to a smaller and disorganized cerebellum with reduced cellular density in the IGL[29].

Mutations in genes encoding key mediators of the SHH-PTCH pathway (PTCH, SUFU, and SMOH) were described in 25% of sporadic human medulloblastomas[30]. PTCH mutation in germ line cells leads to a Gorlin's syndrome, familial disorder characterized by occurrence of medulloblastomas, basal cell carcinomas, and rhabdomyosarcomas[31,32]. Recently, Yang et al.[33] provided direct evidences that aberrant SHH signaling in stem cells can originate medulloblastomas. PTCH deletion in knockout Ptc[c/c] mouse pluripotent stem cells induces its expansion. Interestingly, only stem cells that differentiate into the granular cell lineage continue cell division until tumor development. The increased production of granular neuron progenitors during pos-natal development leads to a rapid tumor formation, with 100% of animals succumbing to medulloblastoma within three to four weeks.

In addition to SHH, NOTCH and WNT are other examples of proteins that modulate pathways controlling proliferation and differentiation of cerebellar granular cells. Both pathways are highly active during cerebellum development[21]. About 15% of medulloblastomas present mutations affecting the WNT transduction signal[31,34]. Mutations in WNT pathway genes have also been identified in sporadic medulloblastomas related to tumor incidence in Turcot syndrome, a familial syndrome of brain tumors[35].

TGF β: a new player in medulloblastoma development?

Transforming growth factor beta (TGFβ) and its signaling pathway is frequently involved in cell growth, embryogenesis, differentiation, morphogenesis, extracellular matrix formation, wound healing, immune response and apoptosis in a wide variety of cells. This pathway also regulates homeostasis and wound repair in adult tissues, including the CNS[36,37].

The TGFβ superfamily consists of more than 100 different proteins, such as activins and inhibins, bone morphogenetic proteins (BMP), veg-1, the Drosophila decapentaplegic complex, and Mullerian-inhibiting substance. Thus far, more than 40 members of this superfamily have been described in mammals[38,39] as being involved in various physiological and pathophysiological processes of the brain. All three isoforms TGFβ1, TGFβ2 and TGFβ3 are expressed in neurons and glial cells[36]. The respective TGFβ receptors are expressed in almost every mammalian cells, including cancer cells[40,41].

In adult healthy CNS, TGFβ2 and TGFβ3 are ubiquitous and usually co-expressed in the CNS[42]. TGFβ1 expression, however, is lower and predominantly found in the meninges and choroid plexus. This particular member of the TGFβ superfamily plays a central role in coordinating complex cellular responses in the injured CNS and has been associated with beneficial as well as detrimental activities regarding tissue repair[43].

Up-regulation and activation of TGFβ1 pathway in the CNS have been reported after lesions caused by acute insults such as stroke and traumatic brain injury or events leading to neurodegeneration[42]. Accordingly, TGFβ1 expression in the brain tends to increase with aging[44] and is up-regulated in some neurological disorders such as Alzheimer[45], Parkinson[46] and Creutzfeldt-Jacob diseases[47], amyotrophic lateral sclerosis[48], in addition to autoimmune disorders such as multiple sclerosis. Under such conditions, TGFβ1 could either be involved in gliosis or protection of mature neurons at the expense of generating new ones[49].

Acute up-regulation of TGFβ1 after brain injury may be beneficial due to its positive effect on neurogenesis[50,51]. However, when TGFβ1 expression levels remain chronically elevated, it may affect the cell cycle of neural progenitor cells and inhibit neurogenesis by prolonging G1 and/or increasing cell cycle exit[49,52].

A similar effect on neurogenesis occurs during normal mammalian CNS development, when TGFβ has been reported to inhibit neural stem cell proliferation. In cancer, however, this TGFβ mediated cell growth control seems to be bypassed[39]. Resistance to growth inhibition can be detected in malignant glioma cells with functionally active TGFβ receptors[53]. Moreover, silencing of TGFβ ex-

pression by interfering RNA has been reported to inhibit glioma cell migration and invasiveness and extinguish glioma cell tumorigenicity *in vivo*[54]. Indeed, TGFβ may act as an oncogene during tumor progression. In medulloblastoma, the effects of TGFβ have been associated with mitogenic stimulation[55]. Stimulation of the TGFβ signaling pathway can further promote metastasis through its role in the epithelial-to-mesenchymal transition[56]. Furthermore, TGFβ is well known by its anti-inflammatory and immunosuppressive properties and might as well favor tumor growth by inhibiting the immune surveillance against cancer cells[22]. Indeed, both TGFβ1 and TGFβ2 have been reported to be involved in development and progression of high-grade gliomas[57].

Due to its pro tumorigenic properties, modulation of TGFβ signaling pathway is currently under investigation as a therapeutic strategy in gliomas[58]. Noteworthy, there is some evidence that BMPs exert anti-proliferative effects in medulloblastomas. Production of BMP2 after stimulation with retinoids has been demonstrated to cause apoptosis in medulloblastoma cells[59]. In addition, Rios et al.[60] reported that BMP2 is able to suppress SHH-induced proliferation of granule cell precursors, which are considered as putative cells of origin in some cases of medulloblastoma. Therefore, in addition to inhibiting TGFβ, stimulation of BMPs could also be explored as a therapeutic approach in medulloblastomas. However, as members of the TGFβ superfamily play important roles in a wide variety of biological processes, attempts to modulate TGFβ signaling in medulloblastomas still require extensive studies in experimental models before clinical testing.

CONCLUSION

Cumulative findings in the fields of cancer genetics and cell biology support a close connection between signaling pathways controlling stem cell biology and tumorigenesis. The role of SHH, NOTCH, WNT, and TGFβ pathways in normal neurogenesis and development of primary brain tumors illustrates this concept. Indeed, primitive malignant embryonic tumors such as medulloblastomas constitute one practical study subject to understand mechanisms by which cancer stem cells are generated. Identification of genetic alterations leading to neoplastic transformation of neural stem cells and knowledge of critical regulators determining the intrinsic properties of medulloblastoma stem cells should be of great value. It could help refine the development of new cancer drugs and enhance the efficiency of molecular therapy and tumor targeting strategies. Under the cancer stem cell hypothesis context, the dual role of TGFβ signaling in neural stem cell growth control and medulloblastoma development makes it an interesting pathway to be further investigated along this clinical development road.

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